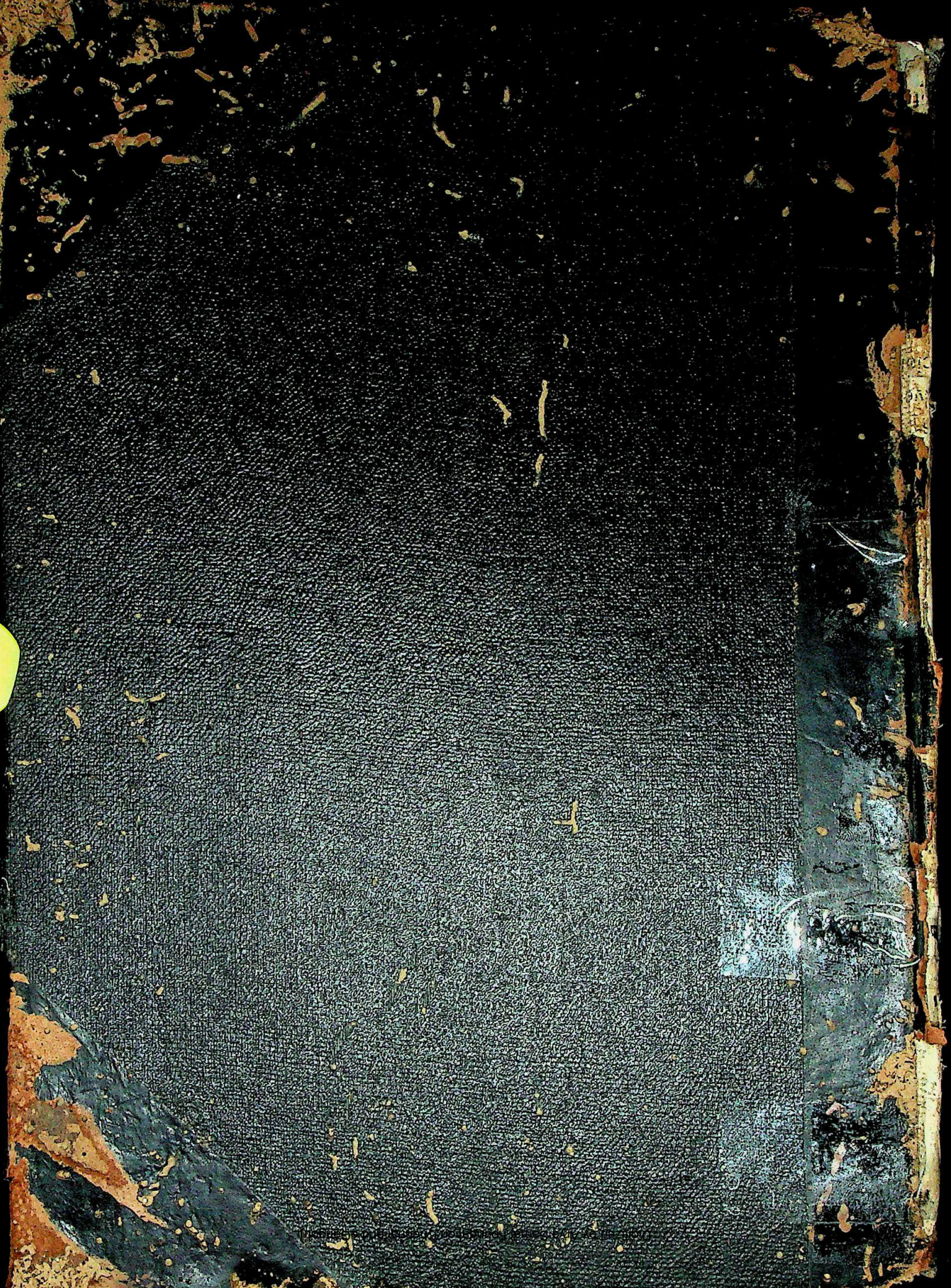

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Form of Presentation.—There should be one or more introductory paragraphs setting forth the occasion, significance and main objectives of the investigation and the method of attack. This should be followed by the experimental results and a discussion of them, either *seriatim* or at their conclusion. Finally, there should be a brief summary of the main achievements of the investigation. Sometimes, particularly when the subject matter is involved and there are many details which, though essential for a successful repetition of the experiments, are unnecessary for the main account of the investigation, these details can with advantage be relegated to an appendix or supplement, just preceding the Summary. In intermediate cases it is often advisable to retain a single, straightforward presentation but to intercalate sections in fine print giving the experimental details of procedure. This has the great advantage of keeping the experimental details close to the more general statements based upon them and yet at the same time permitting the reader if he wishes to pass over this section without inconvenience.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

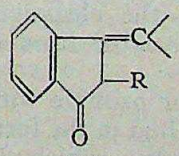
Some 2,3-Disubstituted Indones

BY ROBERT L. FRANK, HENNING EKLUND, JOHN W. RICHTER, CLINTON R. VANNEMAN AND ARNOLD N. WENNERBERG

2,3-Disubstituted indones have been reported to be activators for alcoholic fermentation. According to Pirrone,[1] 2-ethyl-3-phenylindone, 2-methyl-3-phenylindone and 2,3-diphenylindone increase the rate of alcoholic fermentation by as much as 18%. The present research was undertaken in the hope of discovering other compounds that would produce this effect. Nine 2,3-disubstituted indones have been synthesized in which the substituents are alkyl, aryl or substituted aryl groups.

The indones in which the substituent on the 2-position is aromatic were prepared by the addition of excess Grignard reagent to 2-substituted indanediones according to the method employed by Jacobi[2] and by Koelsch[3] (I–IV). Those in which the substituent on the 2-position is aliphatic were prepared by the Reformatsky reaction followed by simultaneous dehydration and ring closure by means of concentrated sulfuric acid (V–VI–IV). This method has been carried out successfully by de Fazi.[4]

When the substituent in the 3-position is a primary or secondary aliphatic group, it is possible for the dehydration of the β-hydroxy ketone (III) to take place in such a way as to form the indone (IV) or the isomeric alkylidene indanone (VII).



VII

Weiss and Alberti[5] have shown that both types of dehydration products form when 2-phenylindane-1,3-dione is treated with benzylmagnesium chloride and the resulting product is dehydrated.

To establish definitely the structures of the indones of this type, the position of the double bond in 3-ethyl-2-phenylindone was determined by ozonolysis.

Ozonization in acetic acid yielded two crystalline products. One of these was colorless and gave the correct combustion analysis for the ozonide (VIII). The other was yellow and had the composition of *o*-propionylbenzil (IX). This compound could only arise from the indone (IV) and not from the alkylidene indanone (VII).

(1) Pirrone, *Ann. chim. appl.*, **22**, 501 (1932); *C. A.*, **27**, 159 (1933).

(2) Jacobi, *J. prakt. Chem.*, **129**, 55 (1931).

(3) Koelsch, THIS JOURNAL, **58**, 1331 (1936); **65**, 1639 (1943).

(4) de Fazi, *Gazz. chim. ital.*, **45**, II, 143 (1915).

(5) Weiss and Alberti, *Monatsh.*, **59**, 220 (1932).

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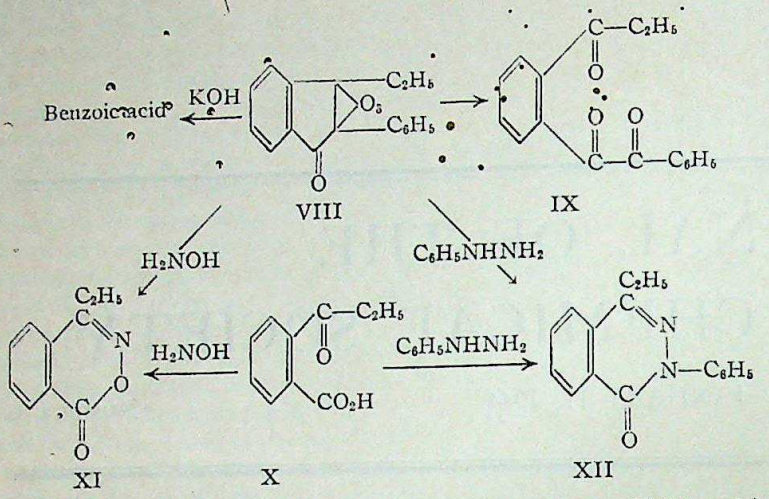

The ozonide from 3-ethyl-2-phenylindone was a remarkably stable compound, melting at 93° with no decomposition. It burned evenly and did not explode when heated in a flame. Treatment with hydrogen and platinum oxide for a long period did not alter it. These properties are perhaps due to the hindrance which might be expected from the groups around the double bond in 3-ethyl-2-phenylindone. Boiling with water converted the ozonide to a yellow oil, presumably due to the formation of the triketone (IX).

Alkaline hydrolysis of the ozonide yielded benzoic acid in 95% yield assuming the formation of one mole from each mole of ozonide. No *o*-propionylbenzoic acid (X), a product which might be expected from the cleavage of the ozonide (VIII), could be isolated from the reaction mixture.

Treatment of the ozonide with hydroxylamine hydrochloride resulted in the formation of a colorless crystalline product which showed no depression in melting point when mixed with a sample of the known 4-ethyl-1-keto-2,3,1-benzoxazine (XI).[6] The latter was obtained by the method of Daube[7] from hydroxylamine and *o*-propionylbenzoic acid (X). *o*-Propionylbenzoic acid (X) can be derived from the indone (IV) but not from the alkylidene indanone (VII).

The ozonide was also heated with phenylhydrazine and a crystalline product was isolated. The same product was obtained when *o*-propionylbenzoic acid (X) was heated with phenylhydrazine. The compound is evidently 1-ethyl-3-phenylphthalazone (XII), although it melts at 111–112°, whereas Gottlieb[8] reported a melting point of 102°.

Ultraviolet absorption spectra also indicate the structure IV rather than VII for these compounds. The spectrum of -3-ethyl-2-phenylindone shows a maximum at 255 mμ ($\log \epsilon = 4.765$ in 95% ethanol), very near the maximum of 259 mμ ($\log \epsilon = 4.702$ in 95% ethanol) in the spectrum of 2,3-diphenylindone, in which the double bond is definitely fixed.

Tests on these compounds as activators for alcoholic fermentation are being carried out by Dr. F. M. Clark of the Department of Bacteriology of this University and the results will be reported elsewhere.

Experimental

2-Phenylindane-1,3-dione.—This compound was prepared by the method of Nathanson[9] from 66 g. (0.30 mole) of benzalphthalide and 9 g. (0.39 mole) of sodium dissolved in 600 cc. of absolute methanol. The yield was 63.0 g. (95%), m. p. 144–145°.

2-Anisyl- and 2-Veratrylindane-1,3-diones.—2-Anisylindane-1,3-dione was prepared by the method of Koelsch[3] using 85 g. (0.634 mole) of phthalide, 85 g. (0.625 mole) of anisaldehyde and 20.5 g. (0.891 mole) of sodium dissolved in 400 cc. of absolute ethanol. The yield of product melting at 153–154° was 54.5 g. (34.6%).

2-Veratrylindane-1,3-dione was prepared in a similar manner from 100 g. (0.746 mole) of phthalide, 120 g. (0.723 mole) of veratric aldehyde and 20.5 g. (0.891 mole) of sodium in 400 cc. of absolute ethanol. The yield of light yellow needles, m. p. 188–190°, was 68.0 g. (33.4%).

Anal.[10] Calcd. for $C_{17}H_{14}O_3$: C, 72.33; H, 5.00. Found: C, 72.60; H, 5.21.

Preparation of Indones by Addition of Grignard Reagents to Indanediones.—The indones prepared by this means are the first seven in Table I, in which the substituent on the 2-position (IV) is aromatic.

The Grignard reagents were prepared in amounts of 0.15 to 0.25 mole in three-necked round-bottomed flasks equipped with efficient stirrers. Equimolar amounts of magnesium and the organic halide were used in 200–400 cc. of anhydrous ether. The indanediones, dissolved in 200–400 cc. of anhydrous benzene or toluene, were added in one-fourth to one-third the molar amounts of Grignard reagent and the solutions were refluxed for one to two hours. It was necessary to use large amounts of benzene or toluene to dissolve the indanediones and also to keep the reaction mixture homogeneous during the addition. In the preparation of 3-ethyl-2-veratrylindone, for example, it was necessary to use a liter of dry benzene for 15 g. of 2-veratrylindane-1,3-dione. The color of the solutions became deep red as the indanediones were added, but this color disappeared as the reactions proceeded. The reaction mixtures were usually pink or colorless before they were worked up.

The Grignard complexes were decomposed by cold dilute sulfuric acid and the benzene (or toluene) layers were washed with dilute sodium carbonate solution and with water. The solvent was then removed by distillation and the residues were subjected to steam distillation for several hours. The taffy-like residues after steam distillation were separated by decantation and crystallized from ethanol or glacial acetic acid.

An alternate method of purification was distillation of the indones under reduced pressure rather than by steam distillation of the impurities. The products were then obtained as clear colored resins and could be crystallized.

Considerable variation in the ease of purification was encountered in the products. 3-Cyclohexyl-2-phenylindone, in particular, was obtained pure only after eight crystallizations from ethanol and methanol.

The phenylhydrazone or oxime of each indone was prepared and recrystallized from ethanol. The melting points and analyses are included in Table I.

(6) Patterson and Capell, "The Ring Index," Reinhold Publishing Corporation, New York, N. Y., 1940, No. 950.
(7) Daube, *Ber.*, **38**, 206 (1905).
(8) Gottlieb, *ibid.*, **32**, 958 (1899).
(9) Nathanson, *ibid.*, **26**, 2576 (1893).
(10) The microanalyses reported in this paper were carried out by Miss Margaret McCarthy and Miss Theta Spoor.

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TABLE I

2,3-DISUBSTITUTED INDONES

Product Formula IV R	R′	Description	M. p., °C.	Yield, %	Molecular formula	Calcd., % C	H	N	Found, % C	H	N
Phenyl	Methyl	Yellow-orange plates	67–68	40 (I-IV)	$C_{16}H_{14}O$	87.25	5.48		87.20	5.45	
(Phenylhydrazone)		Golden needles	120		$C_{22}H_{18}N_2$			9.03			9.15
Phenyl	Ethyl	Yellow-orange needles	97–98	42 (I-IV)	$C_{17}H_{14}O$	87.14	6.02		87.18	5.89	
(Phenylhydrazone)		Yellow needles	96–97		$C_{23}H_{20}N_2$			8.63			8.67
(2,4-Dinitrophenylhydrazone)		Orange needles	206–207		$C_{23}H_{18}N_4O_4$			13.52			13.16
Phenyl	Cyclohexyl	Yellow-orange needles	163–164	10 (I-IV)	$C_{21}H_{20}O$	87.46	6.99		86.99	7.07	
(Phenylhydrazone)		Yellow needles	166–167		$C_{27}H_{26}N_2$			7.40			7.48
Phenyl	Phenyl	Red plates	152–153[a]	48 (I-IV)							
(Phenylhydrazone)		Yellow plates	175–176[b]								
Anisyl	Ethyl	Orange rhombs	119–120	42 (I-IV)	$C_{18}H_{18}O_2$	81.79	6.10		81.97	5.98	
(Phenylhydrazone)		Yellow-orange granules	156–157		$C_{24}H_{22}N_2O$			7.91			7.93
Anisyl	Isopropyl	Yellow-orange needles	138–139	23 (I-IV)	$C_{19}H_{18}O_2$	81.99	6.52		81.98	6.48	
		(b. p. 198–203° (2 mm.))									
(Phenylhydrazone)		Golden plates	166–168		$C_{25}H_{24}N_2O$			7.61			7.60
Veratryl	Ethyl	Scarlet needles	111–112	27 (I-IV)	$C_{19}H_{18}O_3$	77.53	6.16		77.73	5.97	
		(b. p. 192–195° (4 mm.))									
(Phenylhydrazone)		Golden needles	188–190		$C_{25}H_{24}N_2O_2$			7.29			7.27
Ethyl	Phenyl	Yellow-orange rhombs	92–93[c]	22 (V-VI-IV)							
(Oxime)		Yellow needles	179–180[d]								
n-Propyl	Phenyl	Golden rhombs	72.5–73	50 (V-VI-IV)	$C_{18}H_{16}O$	87.06	6.50		87.18	6.55	
(Phenylhydrazone)		Brown needles	107–108		$C_{24}H_{22}N_2$			8.28			8.44

[a] de Fazi [*Gazz. chim. ital.*, 45, I, 554 (1915)] recorded 151–153°. [b] Orekhoff [*Bull. soc. chim.*, [4] 25, 597 (1919)] recorded 175–176°. [c] de Fazi[4] recorded 92–93°. [d] de Fazi[4] recorded 182–183°.

All of the indones prepared give a deep green color with concentrated sulfuric acid, as described by de Fazi.[4]

2-Ethyl-3-phenylindone.—This compound was prepared by the method of de Fazi[4] from 6.8 g. (0.104 mole) of powdered zinc (purified by washing successively with 10% hydrochloric acid, water, alcohol, acetone, ether and anhydrous ether and dried at 100° *in vacuo*), 20 g. (0.110 mole) of benzophenone and 20 g. (15.1 cc.; 0.103 mole) of ethyl α-bromobutyrate in 60 cc. of dry benzene. The resulting white tufts were dissolved in 40 cc. of cold concentrated sulfuric acid and the green solution was allowed to stand for six hours and carefully diluted with ice water. The yield of yellow-orange crystals, recrystallized from ethanol, was 5.1 g. (22%), m. p. 92–93°.

3-Phenyl-2-*n*-propylindone.—α-Bromovaleric acid was prepared by the method of "Organic Syntheses"[11] for the preparation o α-bromocaproic acid from 50 g. (0.49 mole) of valeric acid and 78 g. (0.49 mole) of bromine, using 3 cc. of phosphorus trichloride as catalyst. The crude product was esterified by refluxing with absolute ethanol for five hours. The alcohol was then removed by evaporation and the residual liquid, after drying over "Drierite," was fractionally distilled, yielding 55.0 g. (54%) of ethyl α-bromovalerate, b. p. 92–94° (25 mm.); $n^{20}D$ 1.4496.

3-Phenyl-2-propylindone was prepared by the method of de Fazi[4] from 20 g. (0.110 mole) of benzophenone, 20.8 g. (0.099 mole) of ethyl α-bromovalerate and 9 g. (0.138 mole) of purified zinc powder in 60 cc. of dry benzene. Recrystallization of the intermediate product from high-boiling petroleum ether yielded 6.0 g. of white tufts, m. p. 112–113°.

Anal. C, 75.15, 75.18; H, 7.20, 7.26.

This analysis corresponds to the empirical formula of neither the β-hydroxy ester nor the α,β-unsaturated ester, but the compound nevertheless undergoes cyclization to the desired indone.

This material was cyclized by means of concentrated sulfuric acid in the same manner as the ethyl homolog. The yield of yellow-orange needles of 3-phenyl-2-propylindone was 5.6 g. (23%, based on ethyl α-bromovalerate), m. p. 72.5–73°. The analysis and phenylhydrazone are included in Table I.

Ozonization of 3-Ethyl-2-phenylindone

In Acetic Acid.—Eight-tenths of a gram (0.0034 mole) of 3-ethyl-2-phenylindone dissolved in 65 cc. of glacial acetic acid was treated with 3% ozone for two hours at room temperature. It was then diluted with 65 cc. of water, causing a cloudy precipitate. After the addition of 0.24 g. of powdered zinc the mixture was allowed to stand in the icebox overnight, whereupon it became yellow. It was then diluted with water to 300 cc. and neutralized with sodium hydroxide, after which the neutral solution was extracted with one 50-cc. portion and three 25-cc. portions of benzene. The benzene solution was evaporated under an air jet to a yellow oil which was dissolved in ethanol. Two compounds crystallized from the ethanol solution on standing overnight. One of these formed large yellow tabular crystals (60 mg.) and the other formed an equal amount of large white rhombohedra. The crystals were separated by hand with the aid of a magnifying glass, and each compound was recrystallized from ethanol. The yellow compound melted at 93° and gave the correct combustion analysis for *o*-propionylbenzil (IX).

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.82; H, 5.30.

The white compound melted at 92–93° and gave the correct combustion analysis for the ozonide (VIII) of 3-ethyl-2-phenylindone.

Anal. Calcd. for $C_{17}H_{14}O_4$: C, 72.33; H, 5.00. Found: C, 72.39; H, 4.81.

A mixture of the yellow and white crystals melted at 67–72°.

This experiment was repeated several times, but the yellow compound was obtained in crystalline form only in the one case described here.

In Chloroform.—Four grams (0.017 mole) of 3-ethyl-2-phenylindone dissolved in 100 cc. of dry chloroform was ozonized at 0° with 3% ozone. At the end of one and one-half hours the color became pale yellow and the reaction was stopped. Water was then added (100 cc.) and the chloroform was removed by boiling. The ozonide remaining in the water was then removed by ether extraction. The ether extract was evaporated and the resulting oil was crystallized from alcohol, yielding 4.0 g. (83%) of the white ozonide (VIII), m. p. 92–93°.

Attempted Hydrogenation of the Ozonide.—A mixture of 1.75 g. (0.0062 mole) of the ozonide with 125 mg. of platinum oxide catalyst in 200 cc. of ethanol was treated with two atmospheres of hydrogen at room temperature for fifteen hours. The ozonide was recovered and identified by mixed melting point.

(11) Clarke and Taylor, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., second edition, 1941, p. 115.

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Reaction of the Ozonide with Potassium Hydroxide.—One gram (0.0035 mole) of the ozonide was refluxed for two hours in 50 cc. of 10% alcoholic potassium hydroxide. The mixture was poured into water, acidified with hydrochloric acid, and extracted with ether. The ether layer was extracted with sodium hydroxide solution and this was then acidified with hydrochloric acid. "Darco" was added and the water was heated and filtered. Benzoic acid crystallized from the filtrate, yielding 0.40 g., m. p. 121–122°.

Reaction of the Ozonide with Hydroxylamine.—One gram (0.0035 mole) of the ozonide was refluxed for two hours with 1 g. (0.014 mole) of hydroxylamine hydrochloride, 10 cc. of pyridine and 10 cc. of absolute ethanol. The solvents were removed by evaporation under an air jet and the residual crystals were triturated with water. The product (XI) was recrystallized from ethanol, forming 0.36 g. (58%) of fine white needles, m. p. 117–119°.

Anal. Calcd. for $C_{10}H_9N_2O$: N, 8.00. Found: N, 7.82.

Reaction of the Ozonide with Phenylhydrazine.—One gram (0.0035 mole) of the ozonide was heated at 235–240° for two hours with 4 cc. (0.041 mole) of phenylhydrazine. The reaction mixture was poured into dilute acetic acid and the resulting oil was separated and twice crystallized from ethanol. The yield of product, m. p. 110–112°, was 0.03 g. (2.5%).

Anal. Calcd. for $C_{16}H_{14}N_2O$: C, 76.80; H, 5.60; N, 11.20. Found: C, 76.86; H, 5.74; N, 11.36.

***o*-Propionylbenzoic Acid (X).**—The method was that of Gottlieb,[8] in which 66 g. (0.625 mole) of freshly fused sodium propionate, 130 g. (1.0 mole) of propionic anhydride and 100 g. (0.675 mole) of phthalic anhydride were refluxed at 170° for two and one-half hours. The product, ethylidene phthalide, was obtained as an oil (97 g.). Of this 46 g. (0.29 mole) was refluxed with 10% aqueous sodium hydroxide. The yield of *o*-propionylbenzoic acid was 23.4 g. (44%), m. p. 96–97°.

4-Ethyl-1-keto-2,3,1-benzoxazine (XI).[6]—The method of Daube[7] was used, starting with 3 g. (0.017 mole) of *o*-propionylbenzoic acid, 3 g. (0.043 mole) of hydroxylamine hydrochloride and 10 cc. of 10% potassium hydroxide solution. The yield of product, m. p. 115–117°, was 1.9 g. (64%).

The melting point was not lowered when this compound was mixed with the reaction product of the ozonide with hydroxylamine.

1-Ethyl-3-phenylphthalazone (XII).[8]—One gram (0.0056 mole) of *o*-propionylbenzoic acid was refluxed with 4 cc. (4.4 g.; 0.041 mole) of phenylhydrazine at 235–240° for two hours. The reaction mixture was poured into dilute acetic acid, whereupon crystals formed. These were recrystallized from ethanol, forming 0.35 g. (40%) of long white needles, m. p. 111–112°.

The same product was formed when *o*-propionylbenzoic acid was treated with phenylhydrazine according to the directions of Shriner and Fuson[12] for preparing phenylhydrazones.

The melting point was not lowered when this compound was mixed with the reaction product of the ozonide with phenylhydrazine.

Summary

1. Seven new 2,3-disubstituted indones are described.

2. The dehydration products after the addition of the Grignard reagents of primary and secondary alkyl halides to 2-substituted indanediones have been shown to be indones rather than alkylidene indanones.

(12) Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., second edition, 1940, p. 64.

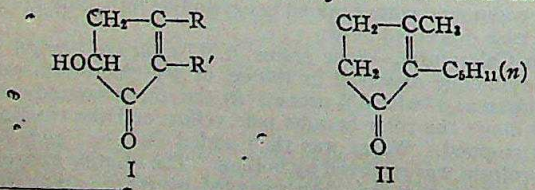
URBANA, ILLINOIS RECEIVED JULY 9, 1943

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Preparation of Cyclopentenones from Lactones[1]

BY ROBERT L. FRANK, PETER G. ARVAN, JOHN W. RICHTER AND CLINTON R. VANNEMAN

A method for preparing substituted cyclopentenones has been reported by Plattner and St. Pfau[2] which consists in the removal of the elements of water from γ,δ-unsaturated acids or the corresponding lactones. This reaction has also been reported in the patent literature[3] and has been studied recently by Bryusova and Osipova.[4] It was thought that if the yields for this transformation on a laboratory scale could be improved, it might afford a means of preparing hydroxycyclopentenones similar to pyrethrolone (I, R = CH_3; R′ = C_5H_7), the alcohol portion of the pyrethrins, by the sequence of reactions shown on the following page.



Such compounds could be used in studies relating chemical structure to pyrethrin-like insecticidal activity.

In order to investigate the reaction, γ-methyl-γ-decanolactone (III) was prepared in 28–31% yields by the addition of *n*-hexylmagnesium chloride or bromide to ethyl levulinate. The lactone was formed directly in this reaction due to the splitting out of ethoxymagnesium halide from the Grignard complex.[5] An attempt to prepare the lactone by the use of *n*-hexylzinc chloride was unsuccessful.

The use of phosphorus pentoxide as the dehydrating agent caused the transformation of γ-methyl-γ-decanolactone (III) to dihydrojasmone

(1) Presented before the Organic Division at the Pittsburgh meeting of the American Chemical Society, September 6–10, 1943.

(2) Plattner and St. Pfau, *Helv. Chim. Acta*, **20**, 1474 (1937).

(3) Maschmeijer, French Patent 765,515 (June 12, 1934); I. G. Farbenindustrie, A.-G., French Patent 785,540 (Dec. 8, 1935); English Patent 453,518 (Aug. 20, 1936); Givaudan and Co., German Patent 639,455 (May 12, 1936).

(4) Bryusova and Osipova, *Sintezy Dushistykh Veshchestv, Sbornik Statei*, 295 (1939); *C. A.*, **36**, 3789 (1942).

(5) Grignard, *Compt. rend.*, **135**, 627 (1902).

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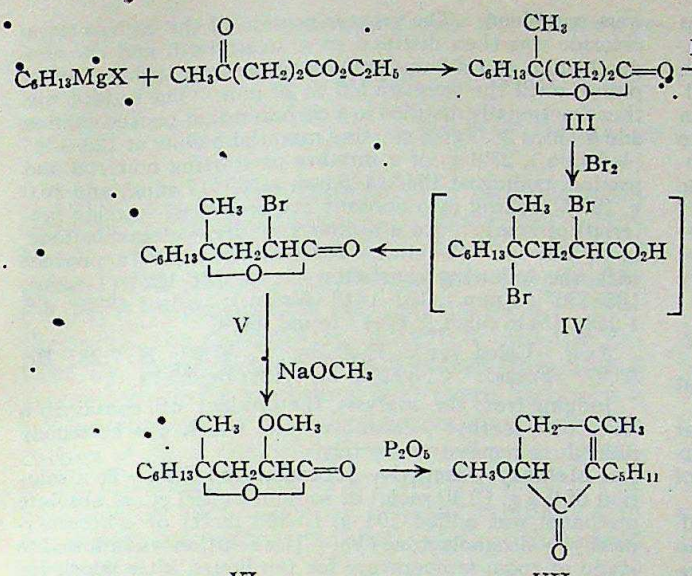


(II)[6] to take place smoothly in yields of 50%. The product was identified by boiling point, density, refractive index, formation of its semicarbazone and its ultraviolet absorption spectrum. The spectrum, measured in 95% ethanol at a concentration of 2.5×10^{-5} moles per liter, showed a maximum at 235 mμ (log $\epsilon = 4.33$) (Gillam and West[7] reported 237 mμ). While Plattner and St. Pfau mentioned the formation of dihydrojasmone (II) from γ-methyldecylenic acid, they did not give details of the transformation.

In order to apply this reaction to the preparation of the methoxycyclopentenone (VII) it was first necessary to prepare α-methoxy-γ-methyl-γ-decanolactone (VI). This was successfully accomplished by bromination of γ-methyl-γ-decanolactone (III) and subsequent treatment of the bromolactone (V) with sodium methoxide.

When the bromination product of γ-methyl-γ-decanolactone (III) was distilled, copious amounts of hydrogen bromide were evolved, with much foaming, even if the reaction mixture was first washed with sodium bicarbonate solution. It seems likely that this was due to the formation of α,γ-dibromo-γ-methylcapric acid (IV), which was then dehydrobrominated and cyclized to the desired product (V) during the distillation. This type of reaction is known to occur when γ-valerolactone is treated with hydrogen bromide.[8] The bromolactone (V), once obtained, showed no tendency to undergo dehydrobromination in subsequent distillations.

The reaction of the methoxylactone (VI) with phosphorus pentoxide did not yield the desired methoxycyclopentenone (VII).

(6) Treff and Werner, *Ber.*, **66**, 1521 (1933).
(7) Gillam and West, *J. Chem. Soc.*, 671 (1942).
(8) Emmert, *Ber.*, **40**, 912 (1907); Fittig and Fränkel, *Ann.*, **255**, 31 (1889).

Twenty-three grams (0.112 mole) of the methoxylactone (VI) was poured onto 28.4 g. (0.20 mole) of phosphorus pentoxide in a 250-cc. Claisen flask connected to a receiver cooled by dry-ice. Heat was at once evolved and the contents turned black. The product was then distilled under reduced pressure, yielding 10.2 g. of a dark viscous liquid. This final product from three runs, totaling 19.0 g., was combined and redistilled in a 50-inch Podbielniak column.[9] Eleven fractions were collected varying in weight from 0.8 g. to 2.1 g.

Fraction 2, b. p. 74–82° (3–5 mm.), analyzing C, 87.72; H, 10.51; n^{20}D 1.5190, was evidently an impure hydrocarbon and was found to decolorize both bromine and potassium permanganate.

Fraction 8, b. p. 112–115° (3–5 mm.), which showed the lowest refractive index of all the products, namely, n^{20}D 1.4720, gave saponification equivalents 178 and 180 (seven hours of refluxing with 0.68 *N* sodium hydroxide was necessary).

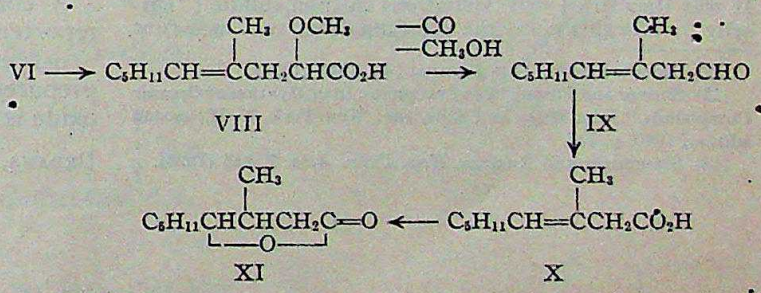
Anal.[10] Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 71.04, 71.05; H, 11.18, 10.02.

It is suggested that Fraction 8 may be β-methyl-γ-pelargonolactone (XI), which could conceivably result from the following transformations (oxidation of the aldehyde (IX) could have taken place during the distillation).

The loss of two carbon atoms to form a lactone in this reaction is evidence that the bromine atom and methoxyl group in the bromolactone (V) and the methoxylactone (VI), respectively, are indeed in the expected *alpha* position.

Experimental Preparations

Ethyl Levulinate.—Five hundred eighty-one grams (5.0 moles) of levulinic acid, 583 cc. (460.7 g., 10.0 moles) of 95% ethanol, 500 cc. of benzene and 5 cc. of concentrated sulfuric acid were refluxed for fifteen hours in a 3-liter, round-bottomed flask equipped with a continuous water



extractor and a reflux condenser. The reaction mixture was then fractionally distilled to yield 583 g. (81%) of product, b. p. 93–94° (18 mm.); n^{20}D 1.4212.

γ-Methyl-γ-decanolactone (III).—A solution of *n*-hexylmagnesium chloride was prepared in the usual manner from 48.6 g. (2.0 moles) of magnesium turnings, 278 cc. (241.2 g.; 2.0 moles) of *n*-hexyl chloride (Sharples) and 500 cc. of anhydrous ether. It was then transferred to a 1-liter dropping funnel and added dropwise to a solution of 288.0 g. (2.0 moles) of ethyl levulinate in 700 cc. of anhydrous benzene and 200 cc. of anhydrous ether contained in a 3-liter, three-necked, round-bottomed flask fitted with the aforementioned dropping funnel, a stirrer and a reflux

(9) Podbielniak, *Ind. Eng. Chem., Anal. Ed.*, **3**, 177 (1931).
(10) The microanalyses reported in this paper were carried out by Miss Theta Spoor, Miss Margaret McCarthy and Miss Dorothy Schneider.

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condenser. During the addition of the Grignard reagent a voluminous white precipitate formed in the yellow solution. Stirring and reflux were continued overnight, after which the mixture was cooled in an ice-bath and iced dilute sulfuric acid was added. The ether-benzene layer was then washed with water, dried over anhydrous calcium sulfate ("Drierite") and fractionally distilled in a carborundum-packed column. The first fraction after removal of the solvent consisted of 25.1 g. of ethyl levulinate, b. p. 63–70° (5 mm.); $n^{20}D$ 1.4234. The desired product boiled at 120–125° (4–5 mm.) and the yield was 103.2 g. (28%, based on *n*-hexylchloride), $n^{20}D$ 1.4487; d^{20}_4 0.950; [M]D calcd.,[11] 52.5; found, 52.0. It had a peach-like odor.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.59; H, 11.27.

A quantity of residue somewhat greater than the amount of product was left after the fractional distillation.

When *n*-hexyl bromide was used in the same molar amounts instead of the chloride and the reaction was carried out as described above, repeated runs gave yields of 113 g. (31%) of γ-methyl-γ-decanolactone.

Dihydrojasmone (II).—Into a glass-jointed, round-bottomed flask containing 28 g. (0.20 mole) of phosphorus pentoxide was poured 50 g. (0.27 mole) of γ-methyl-γ-decanolactone (III). The contents heated at once and turned black. The flask was quickly attached to a modified Widmer column and evacuated, whereupon 21.0 g. (50%) of product distilled in high purity, b. p. 91° (2 mm.); $n^{20}D$ 1.4785; d^{20}_{20} 0.920.

The semicarbazone, prepared according to the directions of Shriner and Fuson,[12] melted at 173–174° (Staudinger and Ruzicka[13] reported 175–176°).

α-Bromo-γ-methyl-γ-decanolactone (V).—To 60 g. (0.33 mole) of the lactone (III) and 75 cc. of dry carbon tetrachloride in a 500-cc., three-necked, round-bottomed flask equipped with a mechanical stirrer, a 125-cc. dropping funnel and a reflux condenser to which was attached a gas trap was added 55 g. (0.34 mole) of bromine, dried with concentrated sulfuric acid. The mixture was stirred for five hours at room temperature after which it was heated at 70–75° for two hours. A mercury-vapor lamp was placed so that the maximum amount of light fell on the reaction vessel (ordinary white light gave much lower yields). The flask was cooled to room temperature and the contents washed successively with dilute aqueous sodium bisulfite, 5% aqueous sodium bicarbonate and water. It was then dried with anhydrous calcium sulfate ("Drierite"). At this point the solutions from two such runs were combined. The greater portion of the carbon tetrachloride was then distilled on a steam-bath and the residue heated at 150° under reduced pressure, using a water pump, until the pressure fell to 20 mm. The residue was then fractionally distilled in a carborundum-packed column and yielded 26.0 g. of starting material boiling at 128–134° (4–5 mm.), 27.0 g. of a mixture of starting material and product boiling at 134° (4–5 mm.)–160° (7 mm.), and 36.0 g. (27%, taking into account the recovered starting material) of nearly pure α-bromo-γ-methyl-γ-decanolactone, b. p. 160–165° (7 mm.). Redistillation gave a product with the following constants: b. p. 121–122° (1 mm.), 135–136° (3 mm.), 151–154° (5 mm.); $n^{20}D$ 1.4890; d^{20}_4 1.243; [M]D calcd.,[11] 60.4; found, 60.9.

Anal. Calcd. for $C_{11}H_{19}O_2Br$: C, 50.20; H, 7.28; Br, 30.37. Found: C, 50.98; H, 7.12; Br, 30.11.

Judging from the analysis, the product still contained a trace of γ-methyl-γ-decanolactone, which was extremely difficult to remove completely.

α-Methoxy-γ-methyl-γ-decanolactone (VI).—To a solution of 9.2 g. (0.40 mole) of sodium in 250 cc. of absolute methanol was added 104 g. (0.396 mole) of α-bromo-γ-methyl-γ-decanolactone (V). The solution was allowed to stand at room temperature for ten hours, after which the precipitated sodium bromide was removed by filtration and the excess methanol by distillation *in vacuo*. The residue was poured into 1 liter of water and this was then extracted with two 500-cc. portions of ether. The ether extract was dried over anhydrous calcium sulfate and fractionally distilled in a modified Widmer column to give 64 g. of material boiling at 105–115° (3 mm.). This was redistilled to give 55 g. (65%) of product, b. p. 107–108° (3 mm.); $n^{20}D$ 1.4408; d^{20}_{20} 0.964; [M]D calcd.,[11] 58.6; found, 58.7; saponification equivalent, calcd., 214; found, 216.

Anal. Calcd. for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 67.94; H, 10.01.

In some runs the yields were lower and small amounts of a higher-boiling isomer were obtained, b. p. 151–170° (3–4 mm.); $n^{20}D$ 1.4710; D^{20}_4 1.020; [M]D calcd.,[11] 58.6; found, 58.8; saponification equivalent, calcd., 214; found, 203.

Anal. Calcd. for $C_{12}H_{22}O_3$: C, 67.25; H, 10.35. Found: C, 66.93; H, 9.85.

Summary

A convenient synthesis of dihydrojasmone is reported.

α-Methoxy-γ-methyl-γ-decanolactone has been prepared and its reaction with phosphorus pentoxide is discussed.

URBANA, ILLINOIS RECEIVED AUGUST 12, 1943

(11) Swientoslawski, THIS JOURNAL, **42**, 1945 (1920).

(12) Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., second edition, 1940, p. 142.

(13) Staudinger and Ruzicka, *Helv. Chim. Acta*, **7**, 245 (1924).

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[COMMUNICATION NO. 938 FROM THE KODAK RESEARCH LABORATORIES]

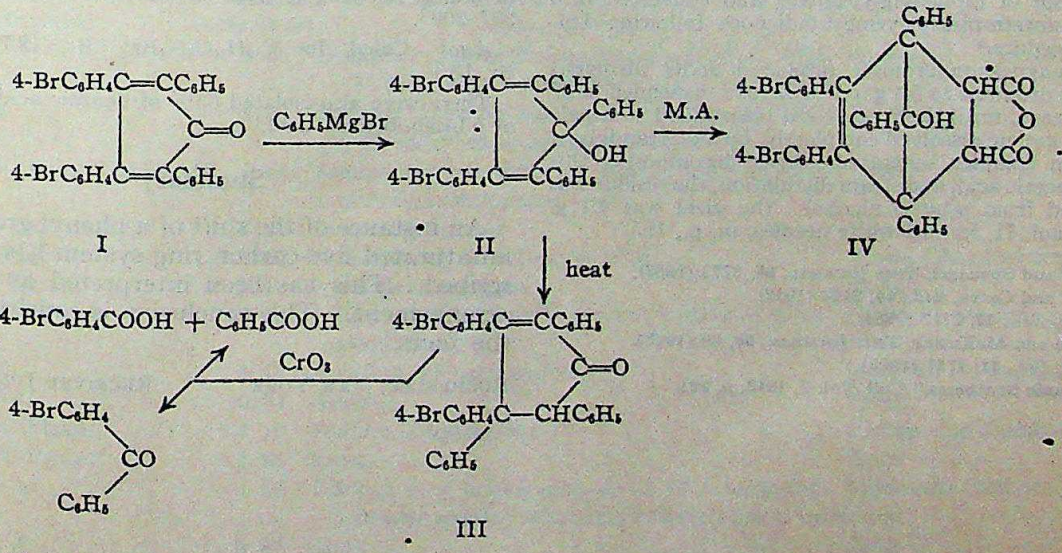
On the 1,3-Rearrangement of a Phenyl Group

BY C. F. H. ALLEN AND J. VANALLAN

The action of phenylmagnesium bromide upon tetraphenylcyclopentadienone gives either a carbinol, formed by 1,2-addition to the carbonyl group, or a ketone, resulting from 1,4-addition to the α,β-unsaturated carbonyl system.[1] Furthermore, the carbinol is converted into the ketone by being heated. This isomerization was accounted for by assuming that there had been a 1,3-rearrangement of the phenyl radical from the carbon atom of the original carbonyl group to one in the β-position of the unsaturated system. The evidence for such a change was the production of benzophenone upon oxidation of the isomerized substance.

All attempts to synthesize this rearranged product were unsuccessful. The use of *p*-methoxyphenylmagnesium bromide, with a view to obtaining *p*-methoxybenzophenone by degradation of the substance resulting from a rearrangement was likewise unsuccessful.[1]

What appears to amount to a positive proof has finally been secured, making use of the known 4,4′-dibromotetraphenylcyclopentadienone, I.[2] The phenyl carbinol, II, which was formed by the action of phenylmagnesium bromide in benzene, was rearranged by heating at 260–265° to the cyclopentenone, III.



The evidence that the carbinol II and ketone III have the structure indicated is important, since rearrangements are assumed to have occurred. The bromine-free pentaphenylcyclopentadienol, to which type II belongs, was first described and its structure proved by Ziegler.[3] In our previous paper,[1] were added the significant data (1) that it adds maleic anhydride, and (2) that it shows one active hydrogen in the Grignard machine. These two observations, plus the formation of a characteristic deep red color, on treatment with concentrated sulfuric acid, afford convenient experimental means for confirming this type of structure. When considering the interaction of a Grignard reagent and tetraphenylcyclopentadienones, it is only necessary to distinguish between 1,2 and 1,4 or 1,6-additions. Since the dibromo carbinol II was obtained by this standard reaction, shows one active hydrogen and no addition, adds maleic anhydride IV, and gives a deep red halochromism with sulfuric acid, there is no reasonable doubt as to its structure. The fact that it is rearranged by heating to form a ketone is also analogous to the behavior of Ziegler's carbinol.[1]

By similar analogies to the corresponding halogen-free ketone,[1] the structure III is assigned to the ketone resulting from the rearrangement. It was formed from the same type of compound by the same sort of reaction. A highly-hindered carbonyl group, such as the one present in the ketone III, is best detected by the Grignard machine, in which it shows one addition. The new ketone III has no active hydrogen, but shows one addition; it also exhibits a yellow halochromism with concentrated sulfuric acid. Upon oxidation by chromium trioxide in acetic acid, it gives 4-bromobenzophenone, 4-bromobenzoic and benzoic acids; this means that in the ketone a phenyl and a 4-bromophenyl are attached to the same carbon atom.

Since the carbinol has been isomerized to a ketone, the phenyl group originally attached to this particular carbon atom must have moved else-

(1) Allen and VanAllan, THIS JOURNAL, 65, 1384 (1942).
(2) Dilthey, Trösken, Plum and Schömmer, *J. prakt. Chem.*, 141, 1346 (1934).
(3) Ziegler and Schnell, *Ann.*, 445, 277 (1925).

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where. But a phenyl group has turned up on the carbon atom originally containing only a 4-bromophenyl group, three carbons away. Hence, it is reasonable to assume that there has been a 1,3-rearrangement of a phenyl.

It may be suggested that the phenyl has undergone two 1,2-shifts, but this means twice as many assumptions. There does not appear to be any certain way of determining whether any 1,3-shift is actually such, or proceeds by two 1,2-rearrangements, but since 1,3-shifts have been generally accepted in other instances, there is no reason why a phenyl group should be an exception.

This is the first instance which appears to be a direct proof for a 1,3-rearrangement of a phenyl group. We have previously pointed out several reactions that appeared to admit of no other interpretation. In addition to the cyclopentadienol mentioned above,[1] there are the bimolecular products formed by the action of acidic dehydrating agents upon anhydracetonebenzil and many of its substitution products,[4,5] and the formation of 2-phenylquinoline from cinnamalaniline.[6]

The *para*-alkylation of benzoyldurene[7] which the authors suggested might be a case of the rarely-observed 1,6-addition of a Grignard reagent to a conjugated system, could equally well be an analogous case—an instance of the common 1,4-addition to the α,β-unsaturated system, followed by a 1,3-shift of the alkyl group.

Experimental

The necessary 4,4′-dibromobenzil was secured by the bromination[8] of diphenylglyoxalone[9] and converted into the dibromotetraphenylcyclopentadienone following Dilthey's procedure.[2]

Phenylmagnesium bromide (prepared under nitrogen) was added dropwise to 5.4 g. of the ketone suspended in 27 cc. of benzene, until the intense red color faded to a pale pink; the ketone dissolved completely, but, on standing, a magnesium complex separated. After decomposing this with iced acetic acid, and steam distillation, the residue was crystallized from *n*-butyl alcohol: the yield was 4.1 g. The carbinol, II, formed white needles, m. p., 195°.

(4) Allen and Spanagel, This Journal, **55**, 3773 (1933).
(5) Allen and Gates, *ibid.*, **64**, 2123 (1942).
(6) Peine, *Ber.*, **17**, 2117 (1884).
(7) Fuson and McKusick, This Journal, **65**, 60 (1943).
(8) Biltz, *Ber.*, **41**, 1761 (1908).
(9) "Organic Syntheses," Coll. Vol. 2, 1943, p. 231.

Anal. Calcd. for $C_{35}H_{24}OBr_2$: Br, 25.8. Found: Br, 25.8.

In the Grignard machine it showed one active hydrogen, but no addition. It gives a deep red color with concentrated sulfuric acid.

The maleic anhydride addition product IV was readily formed on heating a mixture of 1 g. of each component at 200° for five minutes, cooling and triturating with methanol. After recrystallization from xylene it melted at 222°.

Anal. Calcd. for $C_{39}H_{26}O_4Br_2$: Br, 22.3. Found: Br, 21.9.

The rearrangement product, the ketone III, was obtained by heating 11 g. of the carbinol at 260–265° (14 mm.) for two hours, cooling, taking up in ether, adding alcohol, and allowing it to stand overnight. A little floating solid matter was removed, and ether added. A new crystalline material soon separated; after filtration, the filtrate was diluted by ligroin—it soon became full of the solid ketone. The analytical sample was recrystallized from *n*-propyl alcohol and, finally, from acetic acid. The yield was 6.1 g., m. p. 178°; it gives a yellow color with concentrated sulfuric acid. (The change in color from red to yellow affords a convenient qualitative method for following the rearrangement.)

Anal. Calcd. for $C_{25}H_{24}OBr_2$: C, 67.8; H, 3.9; Br, 25.8. Found: C, 67.7; H, 3.9; Br, 25.9.

In the Grignard machine it showed no active hydrogen and one addition.

The oxidation was carried out by adding chromium trioxide in small portions to an acetic acid solution of the ketone; the reaction was vigorous. Since some unoxidized material was left after thirty minutes, the whole was refluxed for eight hours. It was then diluted and the ketone steam-distilled. After appropriate manipulation a 53.5% yield of *p*-bromobenzophenone was obtained. It had a melting point of 77–78° after recrystallization from methanol; the mixed melting point with an authentic specimen was 78–79°. The 2,4-dinitrophenylhydrazone separated in orange-red leaflets from dioxane–ethyl alcohol, m. p. 207–209°.

Anal. Calcd. for $C_{19}H_{13}O_4N_4Br$: Br, 12.7. Found: Br, 13.1.

There were also isolated 63% of benzoic acid and 32% of *p*-bromobenzoic acid.

Summary

An instance of the shift of a phenyl group in an unsaturated five-carbon ring system has been described. This has been interpreted as a 1,3-rearrangement. This conclusion is consistent with the facts.

Rochester, New York Received June 14, 1943

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STANFORD UNIVERSITY]

Solubilization and the Colloidal Micelles in Soap Solution

BY J. W. MCBAIN AND K. E. JOHNSON

Solubilization is the power which even dilute aqueous solutions of soaps, detergents and other colloidal electrolytes possess of bringing into thermodynamically stable[1] colloidal solution hydrocarbons, dyes and other substances insoluble in water. The commercial importance of this phenomenon has long been known, but it is only recently that its mechanism has been established as consisting of sorption upon and incorporation within colloidal micelles.[2,3,4]

Conversely, a study of solubilization may now be utilized to throw light upon the nature of the micelles and solutions of colloidal electrolytes. The results here to be presented show that solubilization cannot be accounted for by solution in the hydrocarbon portion of the micelles, and they therefore show that assumed structures such as spherical micelles, in which this is the only mechanism so far proposed, are wholly inadequate. On the other hand, they lend further support to the conception that the solubilized material is placed in layers within the lamellar micelles.

Materials and Method

The dye and methods used were the same as those described in references 3 and 4, namely, 1-*o*-tolylazo-2-naphthol; F. D. and C. orange no. 2; Orange OT, in the form of well-developed crystals. The potassium soaps were prepared by neutralization of Kahlbaum purest fatty acids with Kahlbaum, washed, carbonate-free potassium hydroxide. These were made up in boiled-out distilled water and contained 0.4 equivalent per cent. excess of potassium hydroxide to suppress hydrolysis. Dye was added in only slight excess and the mixture was gently agitated in closed containers in a thermostat until equilibrium was reached. This required at least sixteen to twenty-four hours for more dilute solutions and from seven to ten days for more concentrated solutions of soap. When approaching equilibrium from supersaturation, much longer times were required, presumably on account of the effect of protective action upon the dye separating out. The liquid was then kept motionless in a thermostat for twenty-four hours, or until examination in a strong light showed that all dye particles had settled. Analysis was made by diluting a portion of the liquid with a mixture of acetone and water in such proportion as to keep the dye in solution, and measuring in a Klett–Summerson photoelectric colorimeter with a B-420 blue filter, calibrated against known benzene solutions of dye. The latter gave similar results to dye solubilized in aqueous Aerosol OT.

Some Results with Commercial Detergents

Data for many detergents have been published in reference 4. We may supplement these by the results in Table I.

TABLE I

THE SOLUBILIZATION IN MILLIGRAMS OF DYE PER HUNDRED CC. OF SOLUTION, MADE BY TAKING ONE GRAM OF COMMERCIAL DETERGENT IN ONE HUNDRED CC. OF WATER

Detergent	Mg. of dye	Type of detergent	Manufacturer
Aerosol 18	2.60	Disodium monosulfostearylsuccinamide, 35%, + 65% water and slight turbid impurities	American Cyanamide and Chemical Co.
Aerosol OS	3.65	Sodium isopropyl naphthalene sulfonate, 95% active alkyl naphthalene sulfonate—fairly pure	Same
Ammonium salt of Aerosol OT	1.44	Ammonium salt of dioctyl (2 ethyl hexanol) ester of sodium sulfosuccinic acid	Same
Zinc salt of Aerosol OT	6.56	Zinc salt of above	Same
Alronol (100%)	3.00	Non-electrolytic detergent with	Alrose Chemical Co.
Alronol (90%)	3.4	trivalent nitrogen	Same
Nacconol NRSF	3.23	Sodium alkyl aryl sulfonate, not a sulfated fatty alcohol	National Aniline and Chemical Co.
Nopco 1067	1.17	An alkyl aromatic sulfonate	National Oil Products Co.
Nopco 1086-C	0.44	Same	Same
Orvus W. A. Flakes	3.70	Sodium lauryl sulfate	Procter and Gamble
Orvus W. A. Paste	1.85	Same	Same
Santomerse 1	1.25	Belongs to a homologous series of substituted aromatic sodium sulfonates (alkylated aryl sulfonate)	Monsanto Chemical Co.
Santomerse S	0.95	Same	Same
Sodium tetradecyl sulfate	0.13	Specially purified	E. I. du Pont de Nemours Co.
Triton W-30	0.57	A sulfonated aromatic ether alcohol	Röhm and Haas

The Solubilization of Dye in a Homologous Series of Pure Potassium Soaps Containing from Eight to Fourteen Carbon Atoms.—The lowest members of the homologous series of potassium salts of fatty acids, such as potassium acetate, propionate and butyrate, are ordinary strong electrolytes, whereas colloid appears in con-

(1) J. W. McBain and M. E. L. McBain, THIS JOURNAL, 58, 2610 (1936).

(2) J. W. McBain, "Solubilization and other Factors in Detergent Action," Advances in Colloid Science I, 99–142, Interscience Publishers Company, Inc., New York, 1942.

(3) R. C. Merrill, Jr., and J. W. McBain, *J. Phys. Chem.*, 46, 10 (1942).

(4) J. W. McBain and R. C. Merril l Jr., *Ind. Eng. Chem.*, 34, 915 (1942).

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centrated solutions of potassium hexoate, and in progressively less concentrated solutions of the higher soaps. Since solubilization of dye is a manifestation of the presence of micelles, it is of great interest to compare the solubilization of dye by various concentrations of typical homologs both to show in how far these are colloidal electrolytes, and also to throw light upon the nature of the colloidal micelles present in different concentrations of different homologs.

Measurements are therefore presented in Tables II, III, IV and V for the solubilization of Orange OT in potassium octoate, decylate, dodecylate and tetradecylate containing the added alkali sufficient to suppress hydrolysis. The results are also shown graphically in Fig. 1. To ensure attainment of the reversible equilibrium from both sides, the measurements with laurate and with myristate are approached from the side of undersaturation and also, by first heating the solution to cause more dye to dissolve, from the side of supersaturation. It is seen from the graphs how closely the corresponding values came together in the time allotted. We may therefore be sure that the true solubilization was actually measured.

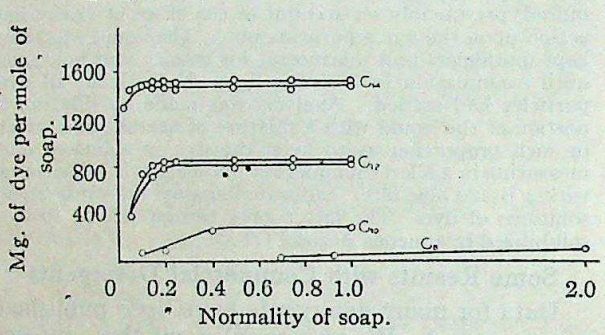

Fig. 1.—The solubility of orange OT in various molalities of aqueous solutions of a homologous series of pure potassium soaps at 25°.

TABLE II

THE SOLUBILITY OF ORANGE OT IN VARIOUS MOLALITIES OF AQUEOUS SOLUTIONS OF POTASSIUM CAPRYLATE (KC_8) AT 25°

	From undersaturation		From oversaturation	
m soap	Mg. dye/ 100 cc.	Mg. dye/ mole KC_8	Mg. dye/ 100 cc.	Mg. dye/ mole KC_8
0.700	2.73	39.0	3.18	45.4
0.924	4.90	53.0	..	..
2.00	23.0	115.2	26.7	133.7

TABLE III

THE SOLUBILITY OF ORANGE OT IN VARIOUS MOLALITIES OF AQUEOUS SOLUTIONS OF POTASSIUM CAPRATE (KC_{10}) AT 25°

	From undersaturation		From oversaturation	
m soap	Mg. dye/ 100 cc.	Mg. dye/ mole KC_{10}	Mg. dye/ 100 cc.	Mg. dye/ mole KC_{10}
0.1	1.81	181	1.49	149
.2	3.72	186	...	...
.4	10.33	258	11.26	282
1.0	29.21	292	28.98	290

TABLE IV

THE SOLUBILITY OF ORANGE OT IN VARIOUS MOLALITIES OF AQUEOUS SOLUTIONS OF POTASSIUM LAURATE (KC_{12}) AT 25°

	From undersaturation		From oversaturation	
m soap	Mg. dye/ 100 cc.	Mg. dye/ mole KC_{12}	Mg. dye/ 100 cc.	Mg. dye/ mole KC_{12}
0.05	1.94	388.0	1.95	390
.10	6.90	690	7.43	743
.15	10.74	716	12.16	811
.20	15.65	782	16.79	840
.25	20.87	835	21.03	841
.50	39.54	791	42.77	855
.75	59.59	795	65.10	868
1.00	83.15	832	85.44	854
2.00	164.5	822		

TABLE V

THE SOLUBILITY OF ORANGE OT IN VARIOUS MOLALITIES OF AQUEOUS SOLUTIONS OF POTASSIUM MYRISTATE (KC_{14}) AT 25°

m soap	Mg. dye/ 100 cc.	Mg. dye/ mole KC_{14}	Mg. dye/ 100 cc.	Mg. dye/ mole KC_{14}
0.025	3.26	1306	...	..
.05	7.23	1445	7.24	1448
.10	14.87	1487	15.17	1517
.15	22.03	1468	22.73	1515
.20	29.27	1463	30.39	1520
.25	36.20	1448	37.76	1510
.50	73.09	1462	76.04	1521
.75	108.4	1445	114.1	1521
1.00	147.4	1474	152.3	1523

It will be seen from the tables and Fig. 1 that the amount of dye solubilized by one mole of each of these four successive homologs of even carbon number stand in the proportions of 1 to 2.34 to 6.77 to 12.04, when the concentration is sufficiently high to ensure full colloidality of the soap. In other words, the solubilizing power per soap molecule in a micelle increases enormously with relatively small increase in the number of carbon atoms in the molecule.

Nevertheless, the soap solutions are strictly comparable because, as Brady has shown,[5] the osmotic coefficients of all straight chain colloidal electrolytes actually coincide when they are plotted on a diagram in which the unit of concentration is in each case taken as the molality at which the osmotic coefficient, g, equals 0.5. The significance of these data will be discussed in a later section.

Next of interest was to ascertain the solubilizing power of equimolar solutions of laurate and myristate. The data given in Table VI and Fig. 2 show that the solubilizing power of the mixture lies not quite midway between that for the two pure soaps separately, namely, 9.09 times the solubilizing power of the caprylate.

In addition to these data for 25°, measurements at 50°, given in Table VII and plotted in Fig. 2, show the very high temperature coefficient of solubilization.

(5) J. W. McBain and A. P. Brady, THIS JOURNAL, 65, 2072 (1943).

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TABLE VI

THE SOLUBILITY OF ORANGE OT IN VARIOUS MOLALITIES OF AN EQUIMOLAR MIXTURE OF POTASSIUM LAURATE AND POTASSIUM MYRISTATE AT 25°

m soap	From undersaturation Mg. dye/ 100 cc.	From undersaturation Mg. dye/ mole soap	From oversaturation Mg. dye/ 100 cc.	From oversaturation Mg. dye/ mole soap
0.05	5.10	1019	5.17	1370
.10	10.58	1058	10.89	1519
.15	16.91	1127	17.14	1657
.20	22.58	1129	22.99	1741
.25	27.61	1105	29.21	1764
.50	55.07	1102	57.17	1746
.75	82.92	1106	84.83	1759
1.00	112.3	1123	114.2	1751

TABLE VII

SOLUBILITY OF ORANGE OT IN VARIOUS MOLALITIES OF SOAPS AT 50°

m soap	Mg. dye/100 cc. soln. C_{12}	Mg. dye/100 cc. soln. $C_{12}+C_{14}$	Mg. dye/100 cc. soln. C_{14}	Mg. dye/mole soap C_{12}	Mg. dye/mole soap $C_{12}+C_{14}$	Mg. dye/mole soap C_{14}
0.025	...	...	4.94	..	..	1796
.05	5.27	6.85	10.93	1054	1370	2185
.10	11.82	15.19	23.37	1182	1519	2337
.15	...	24.86	34.47	..	1657	2298
.20	...	34.81	46.34	..	1741	2319
.25	33.30	44.10	58.59	1332	1764	2344
.50	66.76	87.30	117.3	1335	1746	2346
.75	...	131.9	173.0	..	1759	2307
1.00	132.7	175.1	232.9	1327	1751	2329

The solubility has therefore increased between 25 and 50° to an extent corresponding to a negative heat of solubilization amounting to −3830, 3460 and 3830 calories per mole of soap for laurate, for mixture of laurate with myristate, and for myristate, respectively. These are similar to the values calculated from previous work.[3] They have the same order of magnitude as heats of solution or as heats of sorption of the van der Waals type.

The increase in temperature also has a marked effect on the concentration of soap at which the concentration necessary for full colloidality is higher at 50 than at 25°.

Solubilization and the Nature of Micelles.—Solubilization has been shown to be a property of the micelles in solutions of colloidal electrolytes. Conversely, solubilization can throw light upon the nature of these micelles.

The first micelles proposed were the spherical micelles of Reychler, McBain, and later Adam and Hartley. The radius of the spherical micelle is limited by the length of the hydrocarbon chain which is expelled from contact with the water as far as possible. Nevertheless, as Ward[6] points out, seven-tenths of the surface of a spherical micelle containing 50 soap ions of 12 carbon atoms is still hydrocarbon, even if it is assumed possible so to pack the short, thick rods, each length 15 Å., cross section 20–25 sq. Å., without interspaces.

It is an obvious suggestion that the solubilized dye merely dissolves in the hydrocarbon interior of the micelle. This accords well with the positive temperature coefficient of solubilization, and it has been adopted by Hartley in spite of some large numerical discrepancies between the amounts of dyes solubilized and their solubilities in a similar weight of hydrocarbon.

(6) A. F. H. Ward, *Proc. Roy. Soc.* (London), **A176**, 420 (1940).

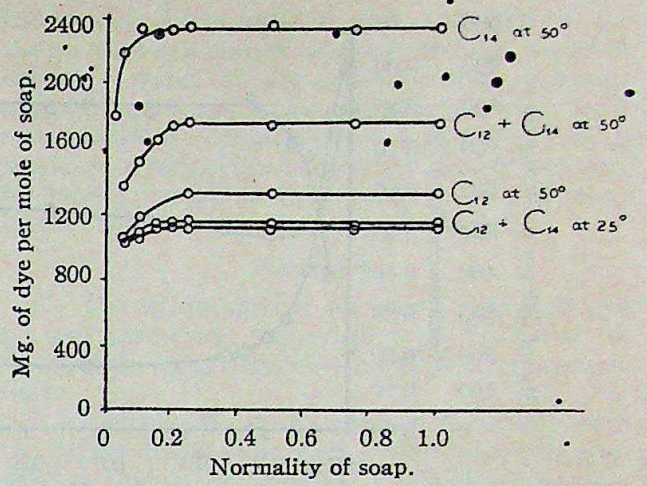

Fig. 2.—The solubility of orange OT in pure potassium soap solutions at 50° and in an equimolar mixture of potassium laurate and myristate at 25°.

The main result of the present communication is to show that the solubilization of the same dye by a homologous series of soaps changes with molecular weight in a manner which does not support the hypothesis that solubilization is solution in the hydrocarbon part of the soap. The results are expressed in milligrams of dye solubilized per mole of soap, because this allows of direct comparison with the number of CH_2 groups per molecule of soap.

The results show that for soaps containing 8, 10, 12 and 14 carbon atoms, respectively, the solubilizations are in the proportions 1:2.34:6.77:12.04.

Thus, for increases of 25, 20 and 16.7% in length of carbon chain, the increases in dye solubilized are 143.5, 190 and 79.5%, respectively. For an increase of 50% in carbon atoms from caprylate to laurate, the solubilization has increased 6.77-fold. The increments of these numbers are, in the same units, 1.34, 4.43 and 5.27 for each added pair of CH_2 groups, instead of being constant. It should be recalled that these numbers were strictly comparable because they refer to concentrations sufficiently high to ensure full colloidality in each case; likewise the numbers were constant for each soap as soon as full colloidality was reached. They are solubilization per molecule in the fully formed micelles.

The only form of micelle for which there is direct evidence is the lamellar micelle, first proposed by McBain. Several investigators[7] have

(7) P. Krishnamurti, *Indian J. Phys.*, **3**, 307 (1929); K. Hess, H. Kiessig and W. Philippoff, *Naturwissenschaften*, **26**, 184 (1938); K. Hess, W. Philippoff and H. Kiessig, *Kolloid-Z.*, **88**, 40 (1939b); H. Kiessig, *ibid.*, **98**, 213 (1942); H. Kiessig and W. Philippoff, *Naturwissenschaften*, **27**, 593 (1939); W. Philippoff and K. Hess, *Ber.*, **70**, 1808 (1937); J. Stauff, *Naturwissenschaften*, **27**, 213 (1939a); J. Stauff, *Kolloid-Z.*, **89**, 224 (1939b).

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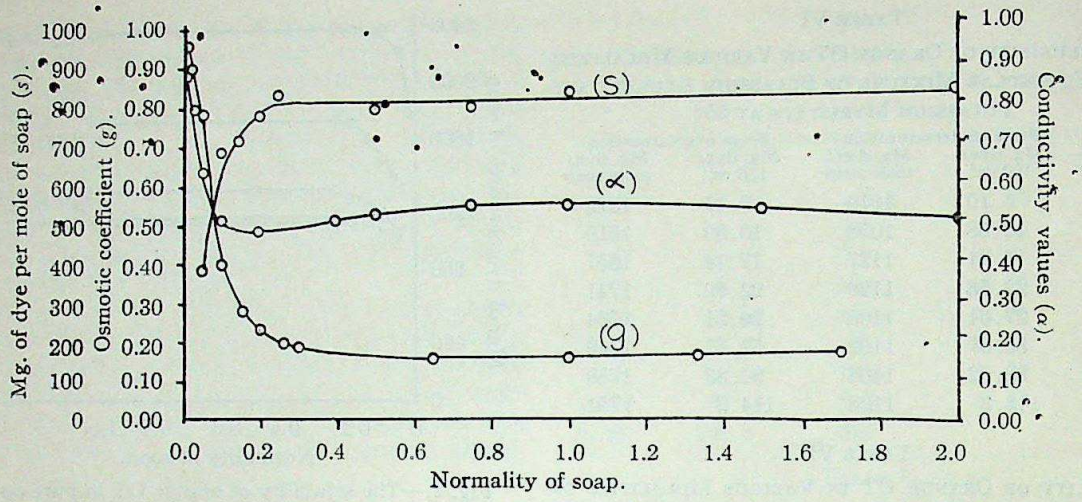

Fig. 3.—Comparison of the solubilization curve (s), the osmotic coefficient curve (g), and the conductivity curve (α) for potassium laurate.

found that the micelles in soaps and synthetic detergent solutions give an X-ray diffraction pattern corresponding to lamellar micelles in which molecules are packed side by side and layer to layer. According to Hess and his collaborators, when benzene is solubilized by the soap solution, spaces between the lamellar planes increase correspondingly. This mechanism, perhaps supplemented by sorption on the exterior of the micelles, would best accord with the present data.

It is of interest to compare the curve of solubilization by the typical soap, potassium laurate, with the corresponding curves for its osmotic coefficient, g, and conductivity ratio, α. This is done in Fig. 3. It is seen that solubilization attains its constant value at 0.25 m, while the osmotic coefficient is still definitely falling; whereas the conductivity has already reached its minimum value at 0.2 m and is on its way to the much higher value at 0.75 m. The changes in the micelles indicated by conductivity and osmotic activity are not reflected by any further change in solubilization. Most authors now agree that there are many sizes of micelles in different concentrations of the same colloidal electrolyte, ranging from "small micelles" or "ionic micelles" that raise the conductivity to larger lamellar micelles that greatly lower it.

A comparison of the relevant data for lauryl sulfonic acid is given in reference 2.

Effect of Added Salts on Solubilization.—McBain and Merrill[3,4] advanced the plausible hypothesis that addition of a salt to a colloidal electrolyte having a common ion would favor formation of micelles in the dilute region where they were not already formed and tend to salt out dye in higher concentrations where the micelles were already completely formed. This they found to be true for solutions of sodium desoxycholate.

Table VIII gives the data for the solubilization of two potassium soaps as affected by the presence of molal potassium chloride in each case, and the results are plotted in Fig. 4. Solutions of 1 m myristate and 1 m and 0.5 m laurate could not be measured, since the dye particles would not settle in such viscous or jelly-like systems.

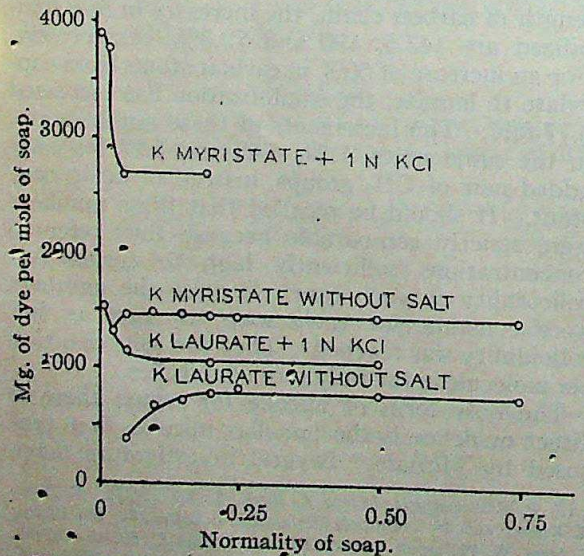

Fig. 4.—The solubility of orange OT at 25° in solutions of potassium laurate and potassium myristate with and without the presence of 1 m potassium chloride.

TABLE VIII

SOLUBILITY OF ORANGE OT IN VARIOUS MOLALITIES OF POTASSIUM LAURATE AND POTASSIUM MYRISTATE AT 25° IN THE PRESENCE OF 1 m POTASSIUM CHLORIDE

	Laurate		Myristate	
m	Mg. dye/ 100 cc. soln.	Mg. dye/ mole soap	Mg. dye/ 100 cc. soln.	Mg. dye/ mole soap
0.010	1.53	1530	3.895	3895
.025	2.70	1080	9.44	3776
.050	5.66	1132	13.39	2678
.200	20.72	1036	54.01	2700
.500	53.66	1073		

It is seen at once that the potassium chloride does greatly enhance the solubilization in dilute

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solutions, where but little micelle was previously present. Indeed, the micelle so formed appears to have a greatly increased solubilizing power, not only over the ordinary micelle of the same soap, but even over the same micelle in higher concentrations in the presence of the potassium chloride. Furthermore, even in the concentrated solutions, the potassium chloride has increased the solubilization. This is the opposite of the expected salting out effect. Neither can it be reconciled with the hypothesis of solution in the hydrocarbon, which must be unaffected since it is in equilibrium in all cases with solid crystals of dye. We have no adequate explanation either for the improved solubilizing power in concentrated solutions or for its still greater enhancement in dilute solutions. However, a similar effect in dilute solutions was indicated in Hartley's data for cetylpyridinium chloride with sufficient addition of sodium chloride (see reference 2, page 129). Likewise, Merrill found similar effects with pure *n*-(lauryl colamino formyl-methyl)-pyridinium chloride, commercially known as Catol 607, to which potassium chloride was added.

On the other hand, Dr. R. B. Dean in unpublished demonstrations in this Laboratory has shown that potassium chloride reduces the solubilizing power of 0.2 *m* potassium laurate for capryl alcohol. Addition of this chloride to a clear saturated solution of capryl alcohol in 0.2 *m* laurate produces a very evident turbidity, which is cleared by heating or by further addition of potassium laurate solution free from capryl alcohol.

Summary

1. The solubilization of water insoluble dye by four potassium soaps has been measured for equilibrium conditions over a range of concentrations.

2. The solubilization increases so rapidly with the higher soaps as to cast doubt upon the suggestion that it is solution in the hydrocarbon fraction of the molecule, but rather to favor its incorporation between the layers of lamellar micelles.

3. Potassium chloride not only greatly increases the solubilizing power of fully formed micelles, but it produces in dilute solution micelles of still higher solubilizing power.

STANFORD UNIV., CALIF. RECEIVED SEPTEMBER 2, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE STATE COLLEGE OF WASHINGTON]

The Ionization of Strong Electrolytes. II. Ionization, Raman Spectrum and Vibrations of Perchloric Acid

BY O. REDLICH, E. K. HOLT AND J. BIGELEISEN[1]

As discussed in the first paper of this series,[2] the Raman spectrum furnishes a fairly general and unambiguous criterion of the existence of molecules. This criterion, in addition, is cogent if one retains the historical concept of the molecule which characterizes the molecule as a mechanical unit without referring to the nature of the intramolecular forces. The principle of determining the degree of ionization by means of Raman spectra, its history, and some experimental details have also been discussed previously. In the present paper, a refinement of the experimental method and measurements on perchloric acid are reported.

In a check of the Raman frequencies of anhydrous perchloric acid, a previously missing line was discovered by resolution of a doublet. Since this line completes the spectrum of the simplified model, our results for the frequencies of perchloric acid and the perchlorate ion, and an assignment of the frequencies to the vibration forms are included.

The Experimental Method

The spectrograph and the general equipment have been described previously.[2,3] Cells of the smaller type (18 ml.) were used. The front face of the cells was ground and polished. The perchlorate line 931 cm.$^{-1}$, excited by the blue mercury line was used. Because of the instability of the acid, the violet and ultraviolet light was filtered out by a sodium nitrite solution. Exposure times ranged from three minutes with Eastman Kodak Co. plates 103a-O and a slit width of 0.10 mm. to twenty-four minutes with plates II-O and 0.25 mm.

Like the nitrate line, the perchlorate line is fairly sharp and narrow in solutions of sodium perchlorate and in the practically completely ionized acid solutions of moderate concentrations, but considerably broader in concentrated solutions of the acid. Several attempts were made to diminish the error involved in the photographic comparison of the intensity of lines which appreciably differ in width.

For convenience, the usual way of comparing the areas under the microphotometric curves will be called the first method. This method can be considered to be based on two assumptions: (a) that under appropriate experimental conditions, the microphotometric curves of two lines are equal only if the total intensities striking the plate are equal, and (b) that a microphotometric curve is sufficiently characterized by its area.

(1) Present address: Department of Chemistry, Columbia University, New York, N. Y.

(2) O. Redlich and J. Bigeleisen, THIS JOURNAL, 65, 1883 (1943).

(3) O. Redlich and L. E. Nielsen, *ibid.*, 65, 654 (1943).

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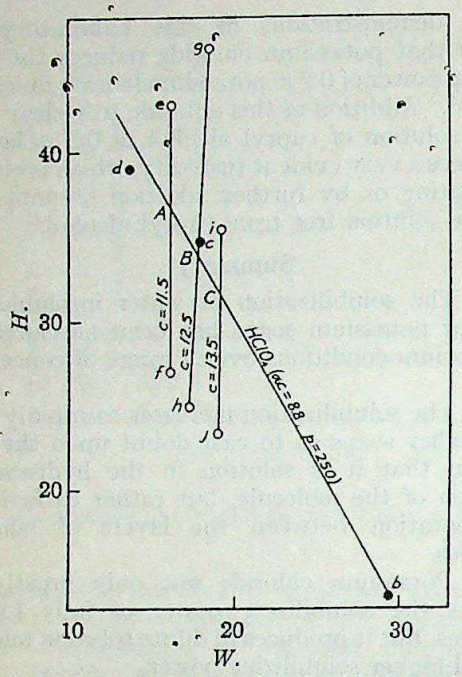

Fig. 1.—Second method: diagram of heights H and widths W of the microphotometric curves.

The first assumption can hardly be dispensed with in any photographic method. The second can be replaced by a less far reaching one: that a microphotometric curve is sufficiently characterized by its height H and width W, measured as usual at the level $H/2$. This assumption is supported by our experience that the area under the curves is practically proportional to the product HW.

The resulting "second method" consists in a comparison of microphotometric curves by interpolation with respect to the two independent variables H and W.

The practical procedure is conveniently described in an example (Fig. 1). The intensity of the light striking the plate is proportional to $I = \alpha cfw$, where αc is the concentration of the perchlorate ion, f the value of the stepfilter before the spectrograph slit, and w the width of this slit. Diffraction at the slit[4] is entirely negligible under the prevailing conditions. The calibration was carried out by means of a perchloric acid solution containing 8.9 moles per liter, corresponding to $\alpha c = 8.8$ according to the smooth curve of Fig. 2 (usually sodium perchlorate solutions were used for calibration). The points b, c and d were taken with different slit widths ($w = 0.250$, 0.323 and 0.595 mm.) but the product $p = fw$ was the same. The points e to j were all taken with $w = 0.250$, but p was 250 for e, g and i, and 194 for f, h, and j.

According to the basic assumptions of the second method, the intensity $I = \alpha cp$ at the crossing point A can be expressed in terms of both the calibrating solution ($\alpha c = 8.8$; $p = 250$) and the "unknown" solution (αc to be determined; $p = p_A$). Thus we have for the "unknown" solution $\alpha c = 8.8 \cdot 250/p_A$ where p_A is to be found by interpolation from the p-values of the points e and f.

The interpolation is to be carried out either linearly with respect to the distances in the diagram or better according to $\log(HW) = k_1 + k_2 \log p$. The values of H and W are read from the diagram and the constants k_1 and k_2 are eliminated by means of the known values of p for the points e and f.

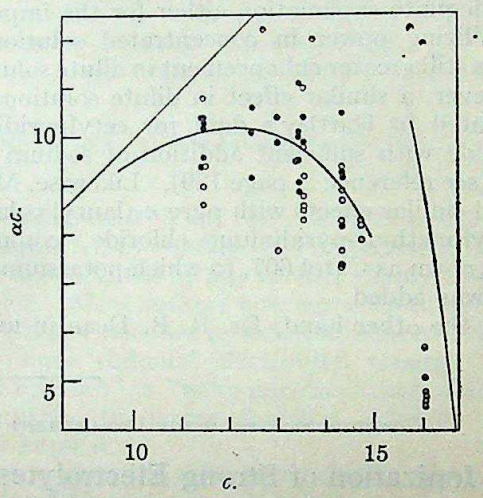

Fig. 2.—Concentration αc of the perchlorate ion in solutions of perchloric acid of the concentration c: ◒, first method, 30°; ○, 53°; ◓, second method, 30°; ●, 53°.

As to be seen from Fig. 2, the results of the second method scatter somewhat less than those of the first. Some additional gain in accuracy would be attained if the lines in a diagram like Fig. 1 were defined by more than two or three points. Practically, however, the number of exposures to be taken in one series and on one plate is limited, even if exposures can be taken as short as with our equipment.

Considerable progress might be achieved by a photoelectric method with the aid of the new photomultiplier tube.[5] The intrinsic difficulties of the photographic method arise from the logarithmic response of the plate. The intensity distribution within the line is necessarily distorted by the logarithmic response of the plate, and again by the influence of the finite width of the microphotometer slit. In addition, the linear response of the microphotometer with respect to the opacity restricts the usable range of the plate to a small interval in which, moreover, the plate is not very efficient. The photoelectric tube with its immediate linear response and large range is free from these disadvantages.

Substances

After a number of unsatisfactory attempts, the following

(4) J. Milazzo and G. B. Tommasi, *Spectrochim. Acta*, 1, 229 (1939).

(5) R. B. Janes and A. M. Glover, *R. C. A. Review*, 6, 43 (1941); D. H. Rank, *et al.*, *J. Opt. Soc. Am.*, 32, 390 (1942), 33, 31 (1943)).

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TABLE I

WAVE NUMBERS AND VIBRATIONS OF $(HO)ClO_3$ AND ClO_4^-

Interpretation[a]	O(s)	O(b)	OH(s)	O(s)	O(b)	OH(b)
Symmetry type	A_1	E	A_1	E	A_1	E
$(HO)ClO_3$	(12) 1032	(5) 585	(7) 738	(2b) 1312—1182	(7) 572	(3) 425
ClO_4^- in $NaClO_4$ soln.	(20) 940	(7) 631		(6b) 1167—1053		(7) 464
ClO_4^- in $HClO_4$ soln.	(20) 931	(8) 631		(3b) 1174—974		(8) 462
Symmetry type	A	E		F		F

[a] (s) and (b) denote stretching and bending vibrations, respectively.

reliable distillation conditions were established for the preparation of the anhydrous acid.[6] A mixture of 640 ml. chilled sulfuric acid and 160 ml. of chilled perchloric acid (70%) is sealed in a distilling flask and distilled at about 58° in the vacuum of an oil pump. In a period of sixteen hours, approximately 30 ml. of colorless anhydrous acid is collected in a receiver cooled by means of dry-ice. Solutions in the range between 70 and 100% can be prepared only by mixing since the boiling points are so high that the acid decomposes.

Acid of 70% was purified by distillation. Distillates were analyzed by weight titration.

Sodium perchlorate was recrystallized after the solution had been boiled with charcoal. The solutions were analyzed by evaporating in a platinum dish and drying at 150°.

The concentrations were calculated by means of the densities given in the "International Critical Tables," the values of Kohner[7] and two values which we determined with a pycnometer. The density of a solution containing 5.35 moles of sodium perchlorate per kilogram of solution was found to be 1.646 g. per ml. at 25.0°, and 1.618 at 53°.

The concentration range which had to be covered, includes the interval in which solid monohydrate appears at room temperature. Most measurements therefore were carried out at 53 ± 2°. The temperature was maintained by means of an electric hairdryer, the heater being controlled by a resistor.

Results

The results are given in Fig. 2. The straight line in the left part of the diagram indicates the limit of complete ionization. Even the commercial acid (60% or 9 moles per liter) is almost completely ionized.

The slightly curved line in the right part of the diagram indicates the ionization which would be obtained if each water molecule produced a perchlorate ion according to the equation $HClO_4 + H_2O = H_3O^+ + ClO_4^-$. The data of Fig. 2 indicate that a "complete ionization" of this kind might occur in the limit of high acid concentrations. In the case of nitric acid, this possibility was definitely excluded by the experimental data.

Considering the extreme value of the heat of dilution, one has to expect a considerable variation of the ionization with the temperature. Two exposures of moderately concentrated solutions at 30° confirmed this expectation. Similar results on nitric and iodic acids are mentioned in a recent note of Rao.[8]

The concentration range is limited by the decomposition of the acid under mercury light. For the concentration of 16.1 moles per liter, data could be obtained only at the lower temperature.

The calculation of the ionization constant according to the method used in the case of nitric acid has to be postponed, because the activity coefficients are known only in the range of practically complete ionization.

Frequencies and Vibrations

Owing to the rapid decomposition under mercury light, even if filtered, a good spectrum of anhydrous perchloric acid is difficult to secure. After several unsuccessful attempts, we obtained a strong and remarkably clear spectrum in forty minutes on an Eastman plate 103a-O with a slit width of 0.06 mm. One spectrum each of an acid solution (11.6 moles per liter) and of sodium perchlorate (9.06 moles per liter) were measured.

The results, indicated in Table I, agree fairly well with those of previous authors. There is only one significant difference: we were able to resolve a line in the spectrum of the anhydrous acid[9] into a doublet, namely, the sharp line 572 and the weaker and broader line[10] 585 $cm.^{-1}$.

This result affords a basis for revising and completing Fonteyne's interpretation of the perchloric acid spectrum. As pointed out by Fonteyne, the perchlorate ion has the tetrahedral symmetry T_d, and the acid has the trigonal symmetry C_{3v} provided the hydroxyl group is considered as a mechanical unit. This simplification implies that the three hydrogen frequencies are not taken into account.

The symmetry types according to Placzek and the interpretation of the vibrations are given in Table I. A_1 and A denote the totally symmetric types, E double, and F triple frequencies. In the transition from the acid to the ion, one hydroxyl stretching and two oxygen stretching vibrations become identical and coalesce into a triple vibration. The same holds true for bending vibrations. Thus the relations between the vibrations of the acid and the ion are unambiguously determined.

According to Fonteyne, the lines 1032 and 738 of the acid are polarized; they belong, therefore, to type A_1. The third line of this type undoubtedly is the stronger and sharper line of the doublet, namely, 572.

(6) We are indebted to Mr. L. E. Nielsen for extensive preparatory work.

(7) H. Kohner, *Z. physik. Chem.*, B1, 427 (1928).

(8) C. S. Rao, *Current Sci.*, 11, 428 (1942).

(9) (a) R. Fonteyne, *Nature*, 138, 886 (1936); (b) *Natuurwet. Tijdschr.*, 20, 112 (1938); (c) A. Simon and H. Reuther, *Naturwissenschaften*, 25, 477 (1937); (d) A. Simon, H. Reuther and G. Kratzsch, *Z. anorg. allgem. Chem.*, 239, 329 (1938).

(10) Actually the two lines are partially superimposed. Fonteyne (ref. 10b) in his Fig. 1 also indicates an asymmetric structure similar to our observation.

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The assignment of line 931 of the ion is based on its intensity and polarization. This frequency results from a stretching of four oxygen bonds which can be interpreted as the result of resonance between one single and three double bonds. The corresponding symmetric oxygen frequency of the acid must be higher, the hydroxyl frequency lower; in addition, the ratio of these two frequencies resulting from double and single bonds, respectively, should be approximately $\sqrt{2}:1$. The frequencies 1032 and 738 satisfy these conditions. The same argument has been used before by Chédin[11] in the case of nitric acid.

The remaining frequency 572 of type A_1 results from a bending vibration of the oxygen atoms.

Oxygen frequencies in the range around 1200 necessarily correspond to stretching vibrations. It happens frequently that antisymmetric or degenerate stretching frequencies are higher than the symmetric ones.

Thus all stretching vibrations have been assigned and none is left for another frequency of the acid near 1200, as assumed by Fonteyne on account of a doublet found in this region in the spectrum of chlorine heptoxide.[12] This doublet, one vibration symmetric, the other antisymmetric with respect to the twofold axis of the simplified chlorine heptoxide molecule, is to be expected in the spectrum of the oxide, but not in that of the acid.

(11) J. Chédin, *J. phys. radium*, **10**, 445 (1939).

(12) R. Fonteyne, *Natuurwet. Tijdschr.*, **20**, 275 (1938).

The assignment of the degenerate bending vibrations 585 and 425 is fairly safe. The hydroxyl group produces the weaker restoring force and therefore is to be correlated to the lower frequency. The two bending vibrations 572 (A_1) and 425 (E) of the acid condense to the frequency 462 (F) of the ion, while 585 (E) corresponds to 631 (E).

A very weak and uncertain line 277 in the spectrum of the anhydrous acid, 297 in the acid solution, could not be satisfactorily interpreted.[13]

The assignment presented here is consistent with Fonteyne's results on deuterium perchlorate.[14]

Summary

1. A refined photographic method of comparing the intensities of spectral lines of unequal width has been developed.

2. The degrees of ionization of perchloric acid have been determined. As to be expected, perchloric acid is ionized to a much greater extent than nitric acid. The ionization constant could not be calculated as the activity coefficients are not known in the range of high concentrations.

3. The Raman spectra of anhydrous perchloric acid and concentrated solutions of the acid and of sodium perchlorate have been measured. Fonteyne's interpretation of the vibration spectrum of the acid has been revised and completed.

(13) Simon, *et al.* (ref. 9d), found 284 in the anhydrous acid. The line might represent the restricted internal rotation.

(14) R. Fonteyne, *Natuurwet. Tijdschr.*, **21**, 6 (1939).

PULLMAN, WASHINGTON RECEIVED AUGUST 4, 1943

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 936]

The Heat Capacity, Heats of Transition, Fusion and Vaporization, Vapor Pressure and Entropy of 1,1,1-Trifluoroethane

BY HORACE RUSSELL, JR., D. R. V. GOLDING AND DON M. YOST

Part of the low temperature calorimetric research program of this Laboratory has been the careful determination of the entropy of simple compounds in which hindered rotation about single bonds would be expected and for which straightforward and reliable statistical mechanical calculations can be made. Of the compounds available, ethane and similar molecules with two symmetrical groups on a common axis seem best suited for study both because of their convenient boiling points and because their configurations and normal frequencies can be readily determined. The existence of a barrier of about 3000 cal./mole hindering internal rotation in ethane was established by Kemp and Pitzer and Kistiakowsky, Lacher and Stitt.[1] Work by Rubin, Levedahl and Yost[2] indicates a barrier of about 2700 cal./mole for 1,1,1-trichloroethane, CH_3CCl_3. From the results reported in this paper the barrier in 1,1,1-trifluoroethane is about 3400 cal./mole. The fact that the values for these three molecules are the same within experimental error points to the interesting and significant possibility that the barrier is a function of the type bonds formed by the carbon atom but is independent, to a first approximation at least, of the nature of the attached atoms.

Purification of CH_3CF_3 or Freon "F-143."—The material used for the measurements was part of a redistilled sample furnished through the courtesy of Dr. A. F. Benning of the Jackson Laboratory of the du Pont Co. The material was carefully dried with phosphorus pentoxide, pumped to remove a small amount of dissolved air, and then fractionally distilled at a reflux ratio of about 40:1 through a 150-cm. vacuum jacketed column packed with glass helices.

(1) J. D. Kemp and K. S. Pitzer, THIS JOURNAL, **59**, 276 (1937); G. B. Kistiakowsky, J. R. Lacher and F. Stitt, *J. Chem. Phys.*, **6**, 407 (1938).

(2) T. R. Rubin, B. H. Levedahl and D. M. Yost, to be published.

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From the 316-g. sample a 60-g. first fraction was taken and a 94-g. main fraction, leaving a 152-g. last fraction as the most probable impurities are higher boiling. There was no detectable drift in the pressure of 695 ± 2 mm. at 224.00°K. during the distillation of most of the first fraction and all of the main fraction. The presence of a transition only five and a half degrees below the melting point made it impossible to determine the solid-insoluble liquid-soluble impurity by Raoult's law in a completely satisfactory way. However, several attempts indicated 0.02–0.05 mole % impurity and we believe that this is approximately correct. The final sample was weighed in a small steel bomb from which it was transferred into the calorimeter. The weight of the sample checked to 0.01% on its removal from the calorimeter.

The Heat Capacity and Density.—All thermal measurements except that of the heat of vaporization were made in a new adiabatic calorimeter (gold plated, copper calorimeter II). The construction of this calorimeter is similar to one already described[3] except that greater pains were taken to prevent condensation in the filling tube. This tube is wound with No. 30 constantan wire down to the thermal anchor to the ring and the winding is covered with 0.00025 in. Al foil. A radiation shield soldered to the ring prevents the coil in the filling tube from radiating heat to the hydrogen tank. Thermocouple junctions at several points allow close control of the tube temperature. A further change was the installation of condenser plates within the calorimeter with which it is planned to make dielectric constant measurements in the future. A strain-free platinum resistance thermometer of laboratory designation[3] CT-7 was used for temperature measurements. The defined calorie of 4.1833 international joules is used throughout; the ice point is taken as 273.16°K.

The results of the heat capacity measurements are presented in Table I. There were 1.1183 moles in the calorimeter. Values at even temperatures read from a smooth curve are given in Table II; the points between the transition at 156.35° and the melting point are purely arbitrary and are given because they were assumed to arrive at our heat of fusion. The error in the heat capacities may be as high as 2% at 15°K. but decreases rapidly and above about 30°K. (except for the transition region) is about ±0.1%. The temperature interval used may be estimated from the spacing of the points in a single series as the final temperature of one point was the beginning temperature of the next. Corrections for vaporization were made using the observed vapor pressure and density. The maximum correction was 0.11%.

The density of the liquid under its own vapor pressure was determined by observing the volume of a weighed amount of CH_3CF_3 in a calibrated Pyrex bulb immersed in a stirred alcohol-bath. The four observed points are reproduced to better than 0.1% by the equation

$$d = 1.7374 - 0.00254\ T \quad (197°K. < T < 217°K.,\ d \text{ in g./ml.})$$

The absolute accuracy is estimated to be ±0.5%.

TABLE I

THE MOLAL HEAT CAPACITY OF 1,1,1-TRIFLUOROETHANE
0°C. = 273.16°K., molecular weight = 84.044

Series	T, °K.	C_p, cal./deg./mole	Series	T, °K.	C_p, cal./deg./mole
4	12.325	1.543	2	90.895	13.85
4	13.213	1.784	6	91.641	13.93
5	13.281	1.808	2	98.464	14.51
4	14.581	2.253	6	99.542	14.60
5	14.625	2.268	2	106.155	15.24
4	16.035	2.732	2	113.989	16.01
5	16.061	2.741	2	121.957	16.83
5	17.729	3.304	2	129.895	17.79
4	17.938	3.377	2	137.854	18.94
5	19.793	3.988	1	141.705	19.59
4	20.195	4.113	2	145.968	20.47
5	22.369	4.787	1	146.685	(20.57)[a]
4	22.707	4.892	3	151.381	21.87
5	25.084	5.584	1	152.137	(22.27)[a]
4	25.432	5.682	3	154.090	22.95
5	27.869	6.311	3	155.782	61.56
4	28.067	6.356	3	156.270	286.97
4	30.806	6.992	3	156.766	34.34
5	30.942	7.023	1	157.540	41.32
4	34.078	7.674	3	158.023	27.71
5	34.480	7.751	3	159.713	34.61
4	37.848	8.354	1	160.846	116.21
5	38.730	8.476		161.82	M. p.
4	41.891	8.972	7	165.407	24.31
4	46.183	9.611	3	165.808	24.33
4	50.726	10.17	7	170.508	24.43
4	55.812	10.71	3	172.001	24.48
6	57.053	10.84	7	177.585	24.63
4	61.044	11.22	3	179.210	24.68
6	63.203	11.42	3	187.032	24.91
4	66.579	11.73	3	195.522	25.27
6	69.698	12.01	3	203.689	25.51
6	76.627	12.63	3	212.446	25.86
6	83.910	13.26	3	220.743	26.25

[a] Intermediate temperature not an equilibrium value.

TABLE II

THE MOLAL HEAT CAPACITY OF 1,1,1-TRIFLUOROETHANE
0°C. = 273.16°K., molecular weight = 84.044

T, °K.	C_p, cal./deg./mole	T, °K.	C_p, cal./deg./mole
15	2.434	140	19.28
20	4.052	150	21.43
25	5.556	156.35	24.56[a]
30	6.807	156.35	Transition
35	7.846	156.35	(22.62)[b]
40	8.693	160	(23.26)[b]
45	9.454	161.82	(23.57)[b]
50	10.09	161.82	M. p.
55	10.63	165	24.31
60	11.12	170	24.43
70	12.04	180	24.70
80	12.94	190	25.01
90	13.77	200	25.37
100	14.66	210	25.76
110	15.61	220	26.21
120	16.62	225.855	B. p.
130	17.80		

[a] Extrapolated value. [b] Arbitrary values for purposes of calculation.

The Melting Point and the Heats of Transition and Fusion.—The results of the melting point determination are given in Table III. The only previously reported melting point is −107°.[4]

The heat capacity curve of solid CH_3CF_3 begins to bend upward at about 130°K. The heat capacity rises steadily but gradually until about 155.8°K. where it abruptly rises to very high values. At 158°K. the heat capacity has decreased to a relatively low value but the melting

(3) D. M. Yost, C. S. Garner, D. W. Osborne, T. R. Rubin and H. Russell, THIS JOURNAL, 63, 3488 (1941).

(4) F. Swarts, *Compt. rend.*, 197, 1261 (1933).

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TABLE III

THE MELTING POINT OF 1,1,1-TRIFLUOROETHANE

0°C. = 273.16°K.

Approx. % melted	Time since energy supplied	$T_{obs.}$, °K.
4	1 hr. 49 min.	161.614
27	1 hr. 26 min.	161.772
54	59 min.	161.797
81	58 min.	161.800

M. P. this sample = 161.80 ± 0.02°K.
M. P. pure compound = 161.82 ± 0.04°K. (−111.34°C.)

point of 161.82°K. is so close that reliable values cannot be obtained in this region. The observed values are shown in Table I. It is evident that a transition occurs with a relatively small latent heat; the maximum of the heat capacity curve lies at 156.35 ± 0.1°K. and may be taken as the transition point. There seems to be little hysteresis in the transition as no supercooling was observed and the heat capacity measurements were quite reproducible up to 155°K. As some premelting may have occurred any value for the heat of transition is somewhat arbitrary. That given was obtained by drawing a curve through the observed heat capacity up to 159.7°K. ignoring the high values at 155.8–156.8°K. The heat added in excess of that included under the curve is taken as the heat of transition and is shown in Table IV.

TABLE IV

THE HEAT OF TRANSITION IN 1,1,1-TRIFLUOROETHANE

Temp. interval, °K.	Total heat added to compound, cal./mole	$\int C_p dT$, cal./mole	Transition below starting temp., cal./mole	$\Delta H_{Trans.}$[a] cal./mole
155.352–157.205	115.88	45.49	0.21	70.60
155.486–157.379	117.43	46.79	0.28	70.92

[a] The absolute value depends on the interpretation of the heat capacity curve.

The two values do not agree well and this is probably because the transition is not quite complete at the upper temperature. The higher value is then more nearly correct and is taken as the heat of transition; from the method of calculation it represents a lower limit. The exact value is of little importance for the entropy calculation as the over-all energy input in this region is very precisely known.

The uncertainty in the heat of transition and the fact that the heat capacity of the high temperature form of the solid is not known prevents calculation of a unique value for the heat of fusion. The method of evaluation was as follows: a temperature interval starting below the transition and extending into the liquid range was selected; the heat of transition, 70.92 cal./mole, was subtracted from the total heat added; an arbitrary straight line (values in Table II) was drawn from 156.35 to 161.82°K. to represent the heat capacity of the high temperature form of the solid; and finally the heat represented by the area under the heat capacity curve and that absorbed by the calorimeter were subtracted from the total heat. Table V gives the value of the heat of fusion obtained in this way.

TABLE V

THE HEAT OF FUSION OF 1,1,1-TRIFLUOROETHANE

Temp. interval, °K.	Total heat added to compound, cal./mole	$\int C_p dT$, including transition, cal./mole	ΔH_{Fusion} at 161.82°K., cal./mole
155.002–166.876	1832.2	352.2	1480.0
150.045–164.953	1896.4	416.4	1480.1
155.486–163.866	1747.5	267.5	1480.0
		Av.[a]	1480 ± 75

[a] The indicated uncertainty is due to the difficulties of interpreting the heat capacity curve rather than to experimental error.

The total elapsed time in the runs shown varied from one hour and forty-five minutes to eight hours and twenty-three minutes; the measurements were made over a period of two weeks. The melting points in Table IV when combined with the heat of fusion given show a 0.02 mole % impurity. Our observations seem to be best correlated by this value but it is pointed out that by assuming a different amount of impurity and a different heat capacity curve for the high temperature solid the value for the heat of fusion may be changed as much as one hundred calories. The effect on the entropy would be less than 0.02 cal./deg./mole, however.

The Vapor Pressure and Heat of Vaporization.—A non-adiabatic calorimeter previously described[3] was used for these measurements. The vapor pressure was observed with a 13.5-mm. diameter mercury manometer read against a Gaertner steel meter bar suspended inside the manometer case. The results, corrected for capillary depression,[5] temperature of the mercury, and to g = 980.665, are given in Table VI. The error in the measurements is believed to be not greater than ±0.1 mm.

TABLE VI

THE VAPOR PRESSURE OF 1,1,1-TRIFLUOROETHANE

0°C. = 273.16°K.

T, °K.	$p_{obs.}$, int. mm. of Hg	$p_{calcd.}$,[a] mm.	$p_{calcd.} - p_{obs.}$, mm.
173.614	26.17	26.17	0.00
185.857	70.62	70.58	+ .04
195.430	138.41	138.42	− .01
202.213	213.14	213.16	− .02
208.839	314.91	314.86	+ .05
214.215	423.26	423.27	− .01
218.845	538.79	538.83	− .04
222.542	648.04	648.00	+ .04
225.790	757.62	757.67	− .05

[a] $\log_{10} p_{mm.} = 48.37340 - (2015.675/T) - 16.81950 \log_{10} T + 0.0133816\ T$.

The normal boiling point calculated from the equation is 225.855°K. (−47.305°C.). The only previously reported value found is −46.8°C.[6]

(5) W. Cawood and H. S. Patterson, *Trans. Faraday Soc.*, **29**, 514 (1933).

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The heat of vaporization measurements were made by collecting the vaporized gas in a thick-walled glass trap cooled in liquid air. A constant pressure was maintained by means of a 20-liter buffer of dry nitrogen separated from the calorimeter system by a mercury bubbler. The trap containing the condensed gas was sealed off and weighed at room temperature under pressure. In this way the same accuracy was achieved as on substances boiling at room temperature or above. Two measurements of the heat of vaporization of 1,1,1-trifluoroethane at 224.40°K. and 0.9339 atm. gave values of 4582 and 4583 cal./mole. About one-tenth mole was vaporized in each measurement and the heat exchange correction amounted to less than one per cent. of the heat added. The absolute accuracy is estimated as ±5 cal./mole. Calculated from the modified Berthelot equation with $P_c = 42$ atm.[6] and $T_c = 344.6$°K.,[4] the heat of vaporization is 4625 cal./mole. Correction for gas imperfection = −180 cal.

The Entropy from Calorimetric Data.—The only uncertainty in the calculation of the entropy arises in the transition–fusion region. The method used was indicated in discussing the heats of transition and fusion; it seems a direct and reasonable one. Other methods could be used involving the assumption of a different heat capacity curve for the high temperature solid form and possibly more premelting but the difference in entropy between the two methods would almost surely be less than 0.03 cal./deg./mole. The extrapolation from 12 to 0°K. was made by using a Debye function plus an Einstein function, each for three degrees of freedom. The combined functions fit the observed values to at least 25°K. within a few tenths of a per cent. The entropy calculation is summarized in Table VII.

TABLE VII

THE ENTROPY OF 1,1,1-TRIFLUOROETHANE

0°C. = 273.16°K., molecular weight = 84.044

	ΔS, cal./deg./mole
0–12.182°K. Debye function $\Theta_D = 77.3$	0.548
Einstein function $\Theta_E = 103.1$	.012
12.182–156.35°K. graphical	24.222
Transition (70.92/156.35)	.454
156.35–161.82°K. graphical	.794
Fusion (1480.0/161.82)	9.146
161.82–224.40°, graphical	8.215
Vaporization (4583/224.40)	20.423
Entropy of real gas at 224.40°K. (0.9330 atm.)	63.814
Correction for gas imperfection[a]	.135
Entropy of ideal gas at 224.40°K. (0.9330 atm.)	63.95 ± 0.10
Entropy of real liquid at b. p. of (225.855° K.)	43.56 ± 0.05
Entropy of ideal gas at 298.16°K. (1 atm.)	66.87 ± 0.15

[a] $S_{ideal} - S_{real} = \frac{27RT_c^3P}{32T^3P_c}$, $T_c = 344.6$°K.,[4] $P_c = 42$ atm.[6]

(6) Estimated by the method of H. P. Meissner and E. M. Redding, *Ind. Eng. Chem.*, **34**, 521 (1942).

The Entropy from Molecular Data.—Standard statistical mechanical formulas were used for the entropy calculations. The physical constants given by Birge[7] were used in conjunction with the defined calorie. The moments of inertia were calculated from the results of an unpublished electron diffraction investigation by Mr. William Shand and Dr. R. A. Spurr at this Institute. The C–F bond distance is 1.37 ± 0.02 Å., the C–C distance 1.52 ± 0.02 Å. the C–C–F angle 112°10′ ± 2°, and the F–C–F angle 107° 32′ ± 2°. A tetrahedral methyl group with a C–H distance of 1.09 Å. was assumed. The principle moments of inertia are $I_x = 150.4 \times 10^{-40}$ g. cm.^{2}, $I_y = I_z = 166.7 \times 10^{-40}$ g. cm.^{2} The entropy due to the internal rotation was evaluated from the table of Pitzer and Gwinn[8]; the reduced moment of the methyl group is 5.125×10^{-40} g. cm.^{2} The normal vibrations were assigned from the Raman lines given by Hatcher and Yost.[9] The original notebooks and plates were examined and two slight changes made. There was a typographical error in the lowest frequency published which should be 368 cm.$^{-1}$ instead of 358 cm.$^{-1}$ The line 2792 cm.$^{-1}$ was assumed to be scattered from the 4047 Å. Hg line; it seems equally reasonable to assign it to the 4358 Å. Hg line with a value of 1025 cm.$^{-1}$ and this aids considerably in the analysis. The 1025 cm.$^{-1}$ frequency scattered from the 4047 Å. Hg line would overlap another line. By comparison with ethane and 1,1,1-trichloroethane a reliable assignment of the observed frequencies to normal modes can be made. The frequencies and their degeneracies are: 368 (2), 541 (2), 603 (1), 829 (1), 968 (1), 1025 (2), 1279 (2), 1450 (1), 1450 (2),

TABLE VIII

THE ENTROPY OF 1,1,1-TRIFLUOROETHANE FROM MOLECULAR DATA

Ideal Gas at 224.40°K. and 0.9330 atm.

	Entropy, cal./deg./mole
Translational	37.925
Rotational (excluding the internal rotation)	22.261
Vibrational	2.297
Entropy from molecular data excluding the entropy of internal rotation	62.48 ± 0.10
Calorimetric entropy	63.95 ± 0.10
Entropy contributed by internal rotation (experimental)	1.47 ± 0.14
Entropy of free rotation	3.28
Entropy of rotation with barrier of:	
3040 cal./mole	1.61
3450 cal./mole	1.47
3950 cal./mole	1.33

(7) R. T. Birge, *Rev. Mod. Phys.*, **13**, 235 (1941).

(8) K. S. Pitzer and W. D. Gwinn, *J. Chem. Phys.*, **10**, 428 (1942).

(9) J. B. Hatcher and D. M. Yost, *ibid.*, **5**, 992 (1937).

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2975 (1), 3040 (2) cm.$^{-1}$. A summary of the entropy calculation is given in Table VIII. The best value for the barrier to internal rotation is seen to be 3450 cal./mole.

This work adds to the evidence from thermodynamic measurements and other sources[10] that rotation about single carbon–carbon bonds is restricted considerably. Although the method used in this work is the most accurate now available for the determination of the magnitude of the barrier, the possible experimental error is always rather high, being probably in no case less than ±200–300 cal./mole. This is because the quantity of interest, *i. e.*, the contribution of the internal rotation to the entropy, is the small difference between two essentially experimental quantities each burdened with its own errors. It should also be remembered that the height of the barriers is of significance only in connection with the potential function assumed for the rotation. The tables used[8] assume a potential $\varphi = (V/2)(1 - \cos 3X)$; this is used largely because of the mathematical simplification introduced and its correctness has no conclusive support, either theoretical or experimental. Other assumptions as to the potential would give different barrier heights. For example Charlesby[11] has shown that for ethane the assumption of a rectangular barrier 1700 cal./mole high and 1.35 radians wide also gives a fit with available data. The cosine potential is more reasonable, however, and is quite satisfactory for comparing different molecules.

We believe that the values for ethane, 1,1,1-trichloroethane, and 1,1,1-trifluoroethane of 2700–3000, 2700, and 3450 cal./mole, respectively, do not differ enough to allow any reliable ordering as to magnitude, although the higher value of 1,1,1-trifluoroethane is probably significant. However, the important fact that the values are so nearly the same, should stimulate work on a fundamental theory of hindered rotation. Until such a theory is developed, a serious gap exists in our knowledge of simple molecular structures.

We wish to thank Mr. William Shand and Dr. R. A. Spurr for the use of their unpublished electron diffraction data for 1,1,1-trifluoroethane and Professor Alexander Goetz for supplying us with liquid hydrogen.

Summary

1. The heat capacity, heats of transition, fusion and vaporization, and vapor pressure of 1,1,1-trifluoroethane have been measured in the temperature range 13–226°K. From these data the calorimetric entropy has been calculated.

2. The Raman spectrum data have been reconsidered and slightly revised. From this and other molecular data, the entropy of the compound has been calculated statistically. Comparison of the calculated and observed entropies indicates a barrier of 3450 ± 400 cal./mole hindering the internal rotation of the molecules.

PASADENA, CALIFORNIA RECEIVED JULY 21, 1943

(10) For an excellent review see G. Glockler, *Rev. Mod. Phys.*, **15**, 145 (1943).

(11) A. Charlesby, *Proc. Phys. Soc.* (London), **54**, 471 (1942).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, THE UPJOHN COMPANY]

Concerning Racemic α-Hydroxy-β,β-dimethyl-γ-butyrolactone (Pantolactone)[1a]

BY JARED H. FORD

Glaser[1b] reported that he obtained pantolactone by vacuum distillation in the form of a transparent crystalline mass, m. p. 55°, that appeared under the microscope as clumps of prismatic needles. Stiller and co-workers[2] obtained a glassy product on vacuum distillation which on recrystallization from ether–petroleum ether gave clusters of fine colorless needles, m. p. 56–58°. Reichstein and Grüssner[3] and Carter and Ney[4] also obtained glassy products, but they reported melting points of 75–78° and 75–80°, respectively.

In the present investigation racemic pantolactone was obtained by vacuum distillation as a colorless transparent solid which became translucent at 80° and which melted at 89.8–91.0°. The melting point was not changed by recrystallization from a benzene–cyclohexane mixture. The melting point of 89.8–91.0° is practically the same as that reported for optically active pantolactone.[4a] On comparison, (−)-pantolactone ($[\alpha]^{25}D$ −49.2° in water; C = 2%) was found to melt at 89.9–91.1°, and a mixture of approximately equal parts of racemic and (−)-forms was found to melt at 89.8–91.0°. Thus it appears that the *d* and *l* forms of this compound form a racemic solid solution which, when partly melted, has the same composition in the liquid and solid phases.[5] The 56° melting form reported by previous investigators[1,2] is probably a racemic compound.

(1a) This name has been suggested by Barnett and Robinson [*Biochem. J.*, **36**, 357 (1942)] for α-hydroxy-β,β-dimethyl-γ-butyrolactone, the lactone half of pantothenic acid.

(1b) Glaser, *Monatsh.*, **25**, 46 (1904).

(2) Stiller, Harris, Finkelstein, Keresztesy and Folkers, THIS JOURNAL, **62**, 1785 (1940).

(3) Reichstein and Grüssner, *Helv. Chim. Acta*, **23**, 650 (1940).

(4) Carter and Ney, THIS JOURNAL, **63**, 312 (1941).

(4a) Stiller and co-workers[2] have reported a melting point of 90–91° for synthetic (−)-pantolactone and 91–92° for the (−)-pantolactone that they isolated from natural pantothenic acid.

(5) Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, Vol. I, p. 182.

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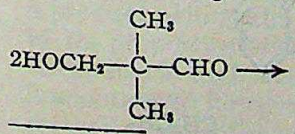
540.5 J82JA V.66 4854

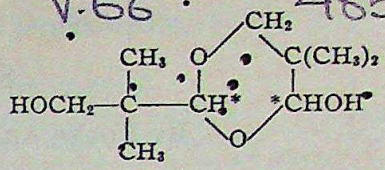
The racemic pantolactone, m. p. 89.8–91.0°, described in this communication, was prepared from α,α-dimethyl-β-hydroxypropionaldehyde[6] that had been recrystallized once from ethyl acetate and once from 95% ethanol. The cyanohydrin reaction was carried out with calcium chloride and sodium cyanide[3,4], and the resulting cyanohydrin was hydrolyzed with hydrochloric acid.[1,2] When the synthesis was carried out with crude α,α-dimethyl-β-hydroxypropionaldehyde as reported by Carter and Ney,[4] the melting point of the resulting pantolactone was in good agreement with the value reported by these investigators (75–80°) and by Reichstein and Grüssner[3] (75–78°). Fractional distillation of the impure material, using a 2-ft. column packed with Raschig rings, gave a product melting at 85–88°.

In order to obtain pure racemic pantolactone it is essential that the intermediate aldol, α,α-dimethyl-β-hydroxypropionaldehyde, be free from certain impurities, but the melting point was found to be a poor criterion of its purity. It usually melts over a range of 2 to 5 degrees. Melting points from 79–82° to 100–103° have been obtained on samples that were recrystallized several times from alcohol. Furthermore, some samples of crude aldol were found to have melting points within this range. The recrystallized samples differ from the crude ones in that they are substantially odorless and give clear solutions when dissolved in 10 parts of hot water.

Since three recrystallized samples having melting points of 79–82°, 82–84° and 100–103°, respectively, were found to give high yields of pure racemic pantolactone, it is believed that they were substantially pure. Melting points of 89–90°[6] and 96–97°[2] have been previously reported for this compound.

Wessely[6] has determined the molecular weight of crystalline α,α-dimethyl-β-hydroxypropionaldehyde and found it to be dimeric. By analogy with the structure proposed by Späth and Schmid[7] for the dimer of aldol it appears likely that the dimer of α,α-dimethyl-β-hydroxypropionaldehyde has the following structure





Since this structure contains two different asymmetric carbon atoms, the compound should exist in two racemic modifications. This affords a logical explanation of the fact that samples having different melting points may give equally good yields of pantolactone. The above structure requires only the splitting of hemiacetal linkages to convert the dimeric into the monomeric form.

The author wishes to thank Messrs. Harold Emerson and William Struck of these Laboratories who carried out the analyses.

Experimental

α,α-Dimethyl-β-hydroxypropionaldehyde.—The proportions of reactants were the same as those described by Wessely,[6] but the temperature was held at approximately 25° by means of an ice-bath. A mechanical stirrer was used. After being recrystallized once from ethyl acetate and once from 95% ethanol, the product melted at 78–81°. The yield of crude aldol was 80%. Each recrystallization caused a loss of about 50% in the yield.

Pantolactone.—To a mechanically stirred mixture of 128.8 g. of α,α-dimethyl-β-hydroxypropionaldehyde (passed through a 12-mesh sieve), 400 g. of chopped ice, and 400 g. of water was added a solution of 111.0 g. of calcium chloride dihydrate (Mallinckrodt) in 100 ml. of water. A solution of 71.0 g. of sodium cyanide in 125 ml. of water was then added rapidly, and the stirring was continued for one hour. Concentrated hydrochloric acid (500 ml.) was then added, and the resulting clear solution was heated for eighteen hours on the steam-bath. The lactone was separated from the aqueous solution by continuous extraction with chloroform. The chloroform was removed, and the residue was vacuum distilled, using an ordinary Claisen flask. The lactone boiled at 117–121° (10 mm.) and was a sticky, wax-like semi-transparent solid, melting at 89.6–91.0°. The yield was 155.5 g. (95%). On redistillation a middle fraction (b. p. 120–121° (11 mm.)) was obtained which melted at 89.8–91.0°.[8]

Anal. Calcd. for $C_6H_{10}O_3$: C, 55.35; H, 7.75; sap. eq., 130.1. Found: C, 55.39; H, 8.05; sap. eq., 130.4, 130.4.

The saponification equivalent was determined by dissolving the sample in an excess of normal alkali, warming to 80° for fifteen minutes, cooling to 0° and titrating with normal acid at 0 to 5°.

Summary

1. Racemic pantolactone has been obtained as a solid solution which has the same melting point as the optically active forms.

KALAMAZOO, MICHIGAN RECEIVED AUGUST 28, 1943

(6) Wessely, *Monatsh.*, **21**, 216 (1900).
(7) Späth and Schmid, *Ber.*, **74B**, 859 (1941).
(8) All melting points were corrected. Those on the lactone were taken in sealed tubes as the compound is very hygroscopic.

48545

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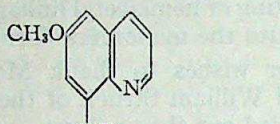
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

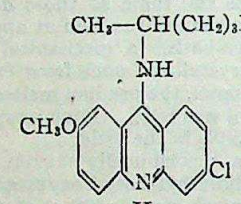
Substituted Aminobenzofuroquinolines

BY ROGER ADAMS, J. H. CLARK,[1] NATHAN KORNBLUM AND HANS WOLFF

The intensive search in many laboratories to find an anti-malarial with more favorable properties than plasmochin (I) or atabrine (II) has led us to a study of certain aminobenzofuroquinolines. These compounds resemble plasmochin in their basic structure.

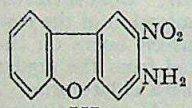


I



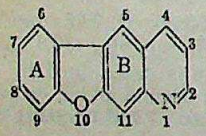
II

The failure of Kirkpatrick and Parker[2] to isolate a nitroquinoline from a Skraup reaction involving 2-nitro-3-aminodibenzofuran (III) made

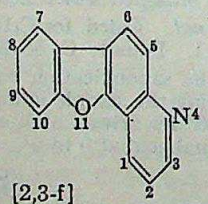


III

it appear advisable to prepare the desired nitrobenzofuroquinolines by nitration of the previously described[2,3] benzofuroquinolines, IV and V.



[3,2-g]
IV

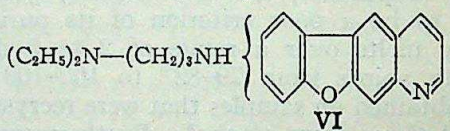


[2,3-f]
V

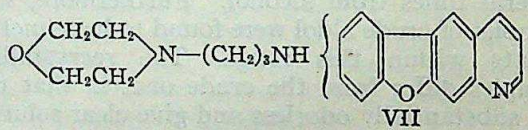
These latter compounds were synthesized following the method of Mosettig and Robinson,[3] and the isomers were isolated taking advantage of the contrasting solubility relationships of the free bases and their sulfates.

The pure quinolines were nitrated by treating the crystalline material with a large excess of fuming nitric acid followed by immediate dilution of the reaction mixture with water. A single isomer was isolated readily from the compound IV but some difficulty was encountered with compound V. In this latter case a mixture resulted from which two pure isomeric mononitrobenzofuroquinolines were finally isolated. It has not been possible, as yet, to determine the position at which nitration occurred in any of the three cases.

Owing to the tediousness of separation of the isomeric mononitro compounds from V, only the derivative of IV was studied from the standpoint of obtaining a substance with antimalarial activity. The corresponding amine was condensed with 3-chloro-N,N-diethylpropylamine hydrochloride to give compound VI and with N-(3-chloropropyl)-morpholine hydrochloride to give compound VII. Neither of these substances showed antimalarial activity.

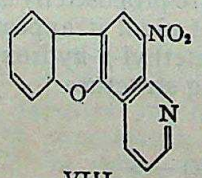


VI

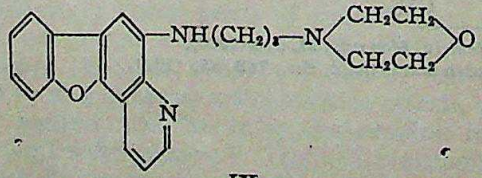


VII

Further efforts were turned toward the synthesis of compounds of unquestionable structure in which the side chain would be attached to the quinoline portion of the benzofuroquinoline nucleus. Contrary to the experience of Kirkpatrick and Parker, it was found possible to prepare 5-nitrobenzofuro[2,3-f]quinoline (VIII) from 2-nitro-3-aminodibenzofuran (III). This compound was reduced and the morpholinylpropyl group introduced to give compound IX. This also showed no antimalarial properties.



VIII



IX

An isomer of the amine from which this derivative IX was obtained is shown in XIII. This resembles much more closely the base from which the plasmochin molecule is derived. Its synthesis was accomplished from the 3-benzenesulfon-

(1) An abstract of a thesis submitted in partial fulfillment for the degree of Doctor of Philosophy in Chemistry.
(2) Kirkpatrick and Parker, THIS JOURNAL, 57, 1123 (1935).
(3) Mosettig and Robinson, *ibid.*, 57, 903 (1935).

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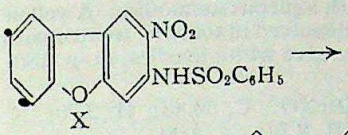
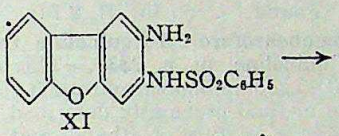
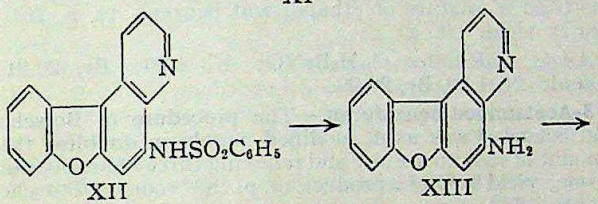
amido-2-nitrodibenzofuran (X) which was prepared by the action of benzenesulfonyl chloride on compound III. In this case the dibenzenesulfonamido derivative was formed very easily and, therefore, it was preferable to prepare compound X by nitration of 3-benzenesulfonamidodibenzofuran. Upon reduction the corresponding amine



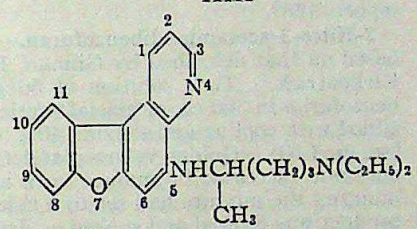
X



XI



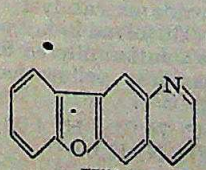
XII XIII



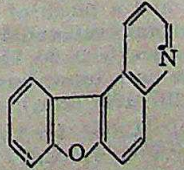
[3,2-f]
XIV

(XI) resulted; by means of a Skraup synthesis this yielded the benzofuroquinoline derivative (XII). Hydrolysis gave the aminobenzofuroquinoline (XIII). Alkylation of compound XIII proved to be unusually difficult and an absolutely pure product (XIV) was not isolated.

From a Skraup synthesis on 2-aminodibenzofuran, Kirkpatrick and Parker[2] have obtained two isomeric benzofuroquinolines, presumably having the structures of XV and XVI. These two products, to which individual structures were not assigned, melted at 185–186° and 160.5–161.5°. It was anticipated that replacement of the amino group in compound XIII by hydrogen would give a product having the structure XVI and identical in its properties with one of those obtained by Kirkpatrick and Parker. The benzofuroquinoline obtained, however, melted at 82–83.5°. The method used in the preparation of this compound would seem to leave no doubt as to its structure; no explanation for this discrepancy presents itself.



XV



XVI

By diazotization and treatment with sodium bromide, the two aminobenzofuro[2,3-f]quinolines were converted to the corresponding bromo derivatives.

Experimental

Benzofuro[3,2-g]quinoline (linear compound) (IV) and Benzofuro[2,3-f]quinoline (angular compound) (V).—The procedure of Mosettig and Robinson[3] was used with slight variations. It was found advantageous to use crude 3-aminodibenzofuran sulfate in the quinoline synthesis since the amine is isolated more readily in this form.[4]

The crude reaction product was distilled without any attempt at fractionation, b. p. around 200° (1 mm.); yield, 74%. The two isomers, linear and angular, were separated by the following procedure. Crystallization of 59 g. of the distilled material from 300 cc. of 95% ethanol gave 13 g. of crude linear polymer, m. p. 160–167°. The mother liquor was diluted to 600 cc. with 95% ethanol, and 15 cc. of concentrated sulfuric acid in 50 cc. of ethanol was added. At the end of fifteen minutes a heavy precipitate had formed. This was collected on a filter, washed with hot ethanol to remove the more soluble linear isomer and dissolved in water. The base, freed with concentrated aqueous ammonia, separated as an oil but solidified on standing. It was collected on a filter, dissolved in boiling petroleum ether (b. p. 60–110°), filtered hot and allowed to crystallize. In this way 10 g. of crude angular isomer was obtained, m. p. 100–106°.

The mother liquor from the sulfate of the angular isomer was evaporated to a thick sirup, treated with aqueous ammonia to free the base, diluted with water to a volume of 600 cc. and digested on a hot plate for thirty minutes. The solid was collected on a filter and recrystallized from ethanol to obtain more of the linear isomer. Repetition of this whole procedure four times gave 24.4 g. of angular isomer, m. p. 100–106°, and 24 g. of linear isomer, m. p. 160–166°. Residual material melting below 95° was discarded.

Two further crystallizations of the linear isomer from ethanol gave 21 g. (26%) of material, m. p. 168–169° (cor.), a value in agreement with that previously reported.[2,3]

Three crystallizations of the sulfate of the angular isomer from ethanol were necessary to give 19.5 g. (24%) of free base, m. p. 106–106.5° (cor.) which agrees with the value reported by Mosettig and Robinson.[3]

Nitrobenzofuro[3,2-g]quinoline.—To 9.6 g. of benzofuro[3,2-g]quinoline (IV) was added 30 cc. of fuming nitric acid (sp. gr. 1.50). A vigorous reaction with evolution of oxides of nitrogen ensued and the solid dissolved within thirty seconds. The reaction mixture was diluted immediately with 400 cc. of water and the product, a solid pasty mass, filtered and digested on a steam-bath with excess aqueous ammonia. The precipitate was filtered, sucked as dry as possible, suspended in 800 cc. of xylene, boiled until all the water was removed and filtered hot through a fluted filter. Upon cooling, a cream-colored crystalline product separated which was essentially pure, m. p. 267–268° (cor.); yield, 9.6 g. (84%).

Anal. Calcd. for $C_{15}H_8N_2O_3$: N, 10.60. Found: N, 10.68.

Aminobenzofuro[3,2-g]quinoline.—A suspension of 5 g. of nitrobenzofuro[3,2-g]quinoline in 150 cc. of 95% ethanol was reduced with 3 g. of Raney nickel and hydrogen at 2-3 atmospheres pressure. At the end of about sixteen hours the reduction was complete. The reaction mixture was heated to boiling, filtered from catalyst and then cooled. Recrystallization from ethanol gave yellow needles, m. p. 236.5–237° (cor.); yield, 3.9 g. (88%).

Anal. Calcd. for $C_{15}H_{10}N_2O$: N, 11.96. Found: N, 12.19.

(3-Diethylaminopropylamino)-benzofuro[3,2-g]quinoline (VI).—A mixture of 16 g. of aminobenzofuro[3,2-g]quinoline and 30 g. of 3-chloro-N,N-diethylpropylamine hydrochloride in 75 cc. of pure *n*-butanol was heated in an oil-bath at 140° with stirring for sixty hours. After evaporation of the ethanol an excess of 10% aqueous sodium

(4) Borsche and Bothe, *Ber.*, 41, 1940 (1908).

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hydroxide was added to liberate the base. It was extracted with benzene. The product, a viscous yellow oil, was obtained by high vacuum (0.02 mm.) distillation; bath temperature, 250–260°; yield 11.5 g. (48%).

Anal. Calcd. for $C_{22}H_{25}N_3O$: C, 76.05; H, 7.25; N, 12.09. Found: C, 76.16; H, 7.26; N, 11.87.

The product could not be crystallized and no crystalline salts were found. A large excess of 3-chloro-N,N-diethylpropylamine hydrochloride is necessary if a pure product is to be obtained.

[3-(4-Morpholinyl)-propylamino]-benzofuro[3,2-g]quinoline (VII).—A mixture of 15 g. of aminobenzofuro[3,2-g]-quinoline, 20 g. of N-(3-chloropropyl)-morpholine hydrochloride and 100 cc. of pure *n*-butanol was heated in an oil-bath at 140–150° with stirring for fifteen hours. The butanol was distilled and the residual gummy solid washed with three 50-cc. portions of absolute ethanol-ethyl acetate mixture (1:2). The solid was recrystallized once from glacial acetic acid to give a pale pink powder which appeared to be a mixture of the hydrochlorides of the base. Upon dissolving in water and treating with excess of aqueous ammonia, a yellow solid separated. It was purified by recrystallization from petroleum ether (b. p. 60–110°); yellow needles, m. p. 120° (cor.); yield, 7.5 g. (32%).

Anal. Calcd. for $C_{22}H_{23}N_3O_2$: C, 73.10; H, 6.42; N, 11.63. Found: C, 72.96; H, 6.24; N, 11.81.

Nitration of Benzofuro[2,3-f]quinoline.—The same procedure was used as in the nitration of the isomer. The crude reaction product from 9 g. of starting material was treated with aqueous ammonia, filtered, sucked dry, treated with 400 cc. of xylene, boiled until all the water was removed, treated with Norite and filtered hot. Evaporation of the solvent gave 9.5 g. of yellow solid. This material was suspended in about 200 cc. of ethanol, the mixture boiled for ten minutes and filtered hot through a preheated fluted filter. The ethanol-insoluble material remaining on the filter amounted to 6 g. and the ethanol-soluble 3.5 g. No pure compounds could be obtained from the soluble portion.

The ethanol-insoluble product was recrystallized six to eight times from glacial acetic acid. Cream-colored needles were obtained thus, m. p. 297–298° (cor.).

Anal. Calcd. for $C_{15}H_8N_2O_3$: C, 68.18; H, 3.05; N, 10.60. Found: C, 68.07; H, 3.28; N, 10.66.

The residues from the glacial acetic acid filtrate after removal of the solvent were extracted thoroughly four times with cold 5% aqueous hydrochloric acid to remove any isomer, m. p. 297–298°, which was present. They were then treated with aqueous ammonia and recrystallized from toluene; yellow needles, m. p. 282° (cor.).

Anal. Calcd. for $C_{15}H_8N_2O_3$: C, 68.18; H, 3.05; N, 10.60. Found: C, 68.13; H, 3.02; N, 10.48.

Aminobenzofuro[2,3-f]quinolines.—A suspension of 15 g. of pure nitrobenzofuro[2,3-f]quinoline, m. p. 297–298°, in 150 cc. of ethanol, was reduced with hydrogen at 3 atmospheres pressure using 3 g. of Raney nickel catalyst. The product was crystallized from toluene; yellow needles, m. p. 200° (cor.); yield, 10 g. (75%).

Anal. Calcd. for $C_{15}H_{10}N_2O$: C, 76.91; H, 4.30; N, 11.96. Found: C, 77.25; H, 4.54; N, 12.16.

Reduction of the nitro isomer, m. p. 282°, gave the corresponding amine. It was purified from benzene; yellow platelets, m. p. 233° (cor.).

Anal. Calcd. for $C_{15}H_{10}N_2O$: N, 11.96. Found: N, 12.15.

Bromobenzofuro[2,3-f]quinoline from Aminobenzofuro[2,3-f]quinoline, m. p. 200°.—To a boiling suspension of cuprous bromide prepared from 6.3 g. of copper sulfate, 20 g. of copper turnings, and 15.4 g. of sodium bromide according to the method given in "Organic Syntheses,"[5] was added the diazonium bromide prepared from 2 g. of aminobenzofuro[2,3-f]quinoline, m. p. 200°, 15 cc. of 42% hydrobromic acid, 35 cc. of water, and 0.65 g. of sodium nitrite. The mixture was refluxed for thirty minutes, cooled, and 100 cc. of benzene added, followed by an excess of aqueous ammonia. The aqueous layer was removed and the benzene solution washed three times with water. The washings were discarded.

The benzene layer was then extracted four times with an excess of dilute hydrochloric acid. The aqueous layer contained a pink solid in suspension. This aqueous suspension was removed and heated to drive off traces of benzene and then made alkaline with aqueous ammonia. A yellow solid separated which was dissolved in toluene, treated with Norite and concentrated to give white needles, m. p. 180–182° (cor.); yield, 1.28 g.

Anal. Calcd. for $C_{15}H_8BrNO$: C, 60.43; H, 2.70; N, 4.70. Found: C, 60.45; H, 2.74; N, 5.00.

Bromobenzofuro[2,3-f]quinoline from Aminobenzofuro[2,3-f]quinoline, m. p. 233°.—This compound, prepared from 0.45 g. of aminobenzofuro[2,3-f]quinoline, m. p. 233°, by the method previously described, formed white platelets from a mixture of ethanol and benzene, m. p. 204° (cor.); yield, 0.05 g.

Anal. Calcd. for $C_{15}H_8BrNO$: N, 4.70; Br, 26.81. Found: N, 4.52, Br, 26.20.

3-Acetaminodibenzofuran.—The procedure of Borsche and Schacke[6] was used, modified merely in doubling the amount of sodium acetate and refluxing three hours instead of one; yield 92% of a product, m. p. 183° (cor.). Borsche reports 178°.

2-Nitro-3-acetaminodibenzofuran.—The procedure was based on that described by Gilman, Brown, Bywater and Kirkpatrick.[7] To a solution of 56 g. of 3-acetaminodibenzofuran in 300 cc. of glacial acetic acid was gradually added with cooling and stirring 40 g. of fuming nitric acid (sp. gr. 1.50). Golden yellow platelets appeared almost at once and increased in amount until at the end of twenty minutes, the mixture had set to a thick pasty mass. The product was filtered and sucked as dry as possible; yellow platelets from glacial acetic acid, m. p. 205° (cor.); yield 49 g. (73%). Gilman, *et al.*, report 196°.

Dilution of the filtrate from the reaction mixture caused the precipitation of a dirty yellow solid. It was composed of a little impure starting material and a compound which crystallized from boiling xylene in the form of silky yellow needles, m. p. 261–262° (cor.). This compound was not investigated further.

2-Nitro-3-aminodibenzofuran.—The method of Borsche and Schacke[7] was employed. The product was purified from xylene; orange needles, m. p. 232–233° (cor.); yield, 86%. Borsche reports m. p. 222°.

5-Nitrobenzofuro[2,3-f]quinoline (VIII).—To a mixture of 32 g. of 2-nitro-3-aminodibenzofuran and 21 g. of arsenic acid ($H_3AsO_4 \cdot {}^1/_2H_2O$) was added 32 g. of dry glycerol followed by 41 g. of concentrated sulfuric acid in small portions. The mixture was heated in an oil-bath at 130–140° for five hours and then poured over cracked ice. The product, a black tar, was extracted three times with 600-cc. portions of 10% sulfuric acid, then with boiling xylene. From the xylene solution were obtained yellow crystals which were pure after one recrystallization from the same solvent, m. p. 206–207° (cor.); yield, 9 g. (24%).

Anal. Calcd. for $C_{15}H_8N_2O_3$: C, 68.18; H, 3.05; N, 10.60. Found: C, 68.10; H, 3.09; N, 10.55.

5-Aminobenzofuro[2,3-f]quinoline.—The product was formed by reducing 5.7 g. of the nitro compound in ethanol at 50° and 3 atmospheres pressure, with Raney nickel and a pinch of platinum oxide as catalyst. The solvent was evaporated, the residue dissolved in hot petroleum ether (b. p. 60–110°) and the solution filtered hot to remove dark brown insoluble impurities; yellow needles, m. p. 197–198° (cor.); yield, 4.4 g. (87%).

Anal. Calcd. for $C_{15}H_{10}N_2O$: C, 76.91; H, 4.30; N, 11.96. Found: C, 77.28; H, 4.30; N, 11.67.

(5) "Organic Syntheses," Coll. Vol. I, p. 131.

(6) Borsche and Schacke, *Ber.*, **56**, 2498 (1923).

(7) Gilman, Brown, Bywater and Kirkpatrick, THIS JOURNAL, **56**, 2473 (1934).

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5-[3-(4-Morpholinyl)-propylamino]-benzofuro[2,3-f] quinoline (IX).—A suspension of 13 g. of 5-aminobenzofuro[2,3-f]quinoline and 30 g. of N-(3-chloropropyl)-morpholine hydrochloride in 100 cc. of *n*-butanol was stirred at 145° for twenty-four hours. At this point 5 cc. of 3-(4-morpholinyl)-1-propanol was added to free any of the 5-aminobenzofuro[2,3-f]quinoline which may have been in the form of hydrochloride. The reaction mixture became much less viscous. Heating was continued for twenty-four hours more and a part of the butanol then removed on the steam cone under an air jet.

To the resulting brick red, pasty product was added a mixture of 60 cc. of methyl acetate and 30 cc. of methanol. Most of the product dissolved leaving in suspension fine, cream-colored needles which were found to be the hydrochloride of 5-aminobenzofuro[2,3-f]quinoline. The recovered material amounted to 2 g. The solvent was evaporated and a thick brown oil resulted. This was made alkaline with aqueous sodium hydroxide and extracted with benzene. The solvent was evaporated and the product distilled at a pressure of 0.03 mm. About 2 cc. of an oil distilling at 80–100° was not investigated further. It was probably a polymer of chloropropylmorpholine. An additional 0.5 g. of unchanged 5-aminobenzofuro[2,3-f]quinoline distilled at about 200°. It was necessary to stop the distillation and remove this solid from the sidearm of the distilling flask.

The desired product distilled as an orange-yellow, semi-solid resin, b. p. 238–240° (0.03 mm.) (bath temperature 265–275°).

Anal. Calcd. for $C_{22}H_{23}N_3O_2$: C, 73.10; H, 6.42. Found: C, 72.98; H, 6.75.

3-Benzenesulfonamidodibenzofuran.—A mixture consisting of 2 g. of 3-aminodibenzofuran, 25 cc. of 10% aqueous sodium hydroxide and 2.5 cc. of benzenesulfonyl chloride was shaken vigorously for five to ten minutes. The white solid was filtered and sucked as dry as possible.

The sodium salt thus obtained was added to 800 cc. of boiling water and filtered. The solution was then acidified with hydrochloric acid and digested on the steam-bath for one-half hour. The precipitate was dissolved in 95% ethanol, treated with Norite, concentrated and cooled. The white needles which separated were recrystallized from aqueous ethanol, m. p. 162–163° (cor.). The product is soluble in hot chloroform and hot glacial acetic acid.

Anal. Calcd. for $C_{18}H_{13}NO_3S$: C, 66.87; H, 4.02; N, 4.33. Found: C, 66.52; H, 4.14; N, 4.07.

2-Nitro-3-benzenesulfonamidodibenzofuran (X).—A. (Used for preparation.) A solution of 0.5 g. of 3-benzenesulfonamidodibenzofuran in 15 cc. of hot glacial acetic acid was cooled to 18° and while stirring and cooling, 0.17 cc. of nitric acid (sp. gr. 1.5) was added dropwise. The mixture was maintained at 18°. After a few minutes the nitro compound started to precipitate and was filtered with suction after ten minutes of standing. The yellow solid was sucked as dry as possible and then recrystallized from pyridine; yellow needles, m. p. 226–227° (cor.); yield, 0.26 g.

Anal. Calcd. for $C_{18}H_{12}N_2O_5S$: C, 58.69; H, 3.26. Found: C, 58.68; H, 3.19.

Hydrolysis of this compound was accomplished by refluxing for sixty hours 0.085 g. of 2-nitro-3-benzenesulfonamidodibenzofuran with 250 cc. of 25% hydrochloric acid. The mixture was filtered hot and the filtrate made alkaline. The precipitate was dried and recrystallized from xylene; orange needles, m. p. 232–233° (cor.). A mixed melting point with an authentic sample of 2-nitro-3-aminodibenzofuran showed no depression.

B.—A solution of 2.25 g. of 2-nitro-3-aminodibenzofuran in 100 cc. of pyridine was treated with 1.5 cc. of benzenesulfonyl chloride and immediately refluxed for seven and one-half hours. By addition of water a precipitate formed (1.85 g.). To remove any unchanged amine the crude material was dissolved in nitrobenzene and dry hydrogen chloride passed in. A small amount of precipitate was filtered and discarded. The nitrobenzene was distilled off and the residue purified from pyridine; orange crystals, m. p. 226–227° (cor.).

Anal. Calcd. for $C_{18}H_{12}N_2O_5S$: C, 58.69; H, 3.26. Found: C, 58.70; H, 3.29.

This product was identical with that obtained by nitrating 2-benzenesulfonamidodibenzofuran. It was always difficult to obtain it in a pure state by use of procedure B.

In several experiments the preparation B just described was not duplicated. Thus, in some cases, upon dilution of the reaction mixture, a yellow solid separated which was purified twice from xylene followed by two purifications from pyridine; yellow crystals, m. p. 263–265° (cor.) with decomposition and evolution of gas. It proved by analysis to be a disulfonamido derivative.

Anal. Calcd. for $C_{24}H_{16}N_2O_7S_2$: C, 56.69; H, 3.15; N, 5.51. Found: C, 56.83, 56.98; H, 3.21, 3.24; N, 5.52.

2-Amino-3-benzenesulfonamidodibenzofuran (XI).—To a suspension of 7.2 g. of 2-nitro-3-benzenesulfonamidodibenzofuran in 150 cc. of 95% ethanol, 0.05 g. of platinum oxide catalyst was added and the reduction carried out at 2–3 atmospheres pressure. The color of the material changed from deep yellow into a very light gray. The suspended amine and catalyst were refluxed with toluene. The resulting solution was filtered from the catalyst and the toluene cooled, giving asbestos-like needles; m. p. 227–228° (cor.); yield, 5.1 g.

Anal. Calcd. for $C_{18}H_{14}N_2O_3S$: C, 63.89; H, 4.18. Found: C, 63.94; H, 4.10.

5-Benzenesulfonamidobenzofuro[3,2-f]quinoline (XII).—To 60 g. of the 2-amino-3-benzenesulfonamidodibenzofuran, 68 g. of nitrobenzene and 73.1 g. of freshly distilled glycerol, 41.6 g. of concentrated sulfuric acid was added and the mixture was heated on a steam cone for one hour. Heating was continued in an oil-bath, the temperature of which was gradually raised to 145–150° and maintained at that temperature for five hours. The excess of nitrobenzene was separated by steam distillation and the remaining black residue was filtered, washed with water and dried. A black powdery material remained which was refluxed with 1 liter of xylene, filtered and the process repeated with the solid residue. On cooling, a slightly brown-colored material crystallized. The quinoline thus obtained was purified from xylene; brownish yellow crystals, m. p. 197–198° (cor.); yield 30 g. (45%).

Anal. Calcd. for $C_{21}H_{14}N_2O_3S$: C, 67.35; H, 3.77; N, 7.49. Found: C, 67.59; H, 3.73; N, 7.45.

5-Aminobenzofuro[3,2-f]quinoline (XIII).—To 7 g. of the sulfonamide, 17 cc. of sulfuric acid (prepared from 3 volumes of concentrated sulfuric acid and 1 volume of water) was added and the mixture was heated for twenty minutes in an oil-bath at 145° (bath temperature). Water was added after cooling and the red solution made alkaline and refluxed. After cooling, the amine was filtered, dried and purified by recrystallization from petroleum ether (b. p. 60–110°); yellow crystals, m. p. 139–140° (cor.); yield, 3.3 g. (78%).

Anal. Calcd. for $C_{15}H_{10}N_2O$: C, 76.91; H, 4.30; N, 11.96. Found: C, 77.18; H, 4.45; N, 11.44.

Concentrated hydrochloric acid with or without glacial acetic acid, sodium in liquid ammonia or sodium amide were all unsatisfactory reagents for hydrolysis.

5-[4-Diethylamino-1-methylbutylamino]benzofuro[3,2-f]quinoline (XIV).—A mixture of 4.7 g. of 5-aminobenzofuro[3,2-f]quinoline and 4.2 g. of 4-chloro-N,N-diethylamylamine hydrochloride was heated in an atmosphere of nitrogen to 180°. When the temperature reached about 100° the mixture liquefied and was thoroughly shaken. On raising the temperature a red paste was obtained which was heated for two hours at 180°. After cooling the material was transferred into a three-necked flask with 30 cc. of *n*-butanol. Another 10 g. of 4-chloro-N,N-diethylamylamine hydrochloride was added and 3 g. of anhydrous potassium carbonate and the mixture heated with mechanical stirring for thirty hours at 140–150°. At this point 2 cc. of 1-diethylamino-4-pentanol was added. Heating and stirring were continued for another thirty hours. The solvent was evaporated and the residue shaken with 10% aqueous sodium hydroxide and extracted with

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benzene. The benzene layer was washed with water several times. The residue obtained by evaporation of the benzene was boiled with 500 cc. of petroleum ether (b. p. 60–110°) and filtered. On cooling, the unreacted aminoquinoline was obtained as yellow crystals. More of this starting amine was obtained on concentrating the petroleum ether solution. The product was distilled at 0.01 mm. The excess 1-diethylamino-4-pentanol was much lower boiling than the desired alkylated amine which was distilled at a bath temperature of 230–250°. The distillate was dissolved in 80 cc. of petroleum ether and more of the unalkylated amine separated after cooling at 4° for twenty-four hours. The petroleum ether again was evaporated and the resulting viscous material distilled at 0.01 mm. The first few drops of the distillate were discarded because they contained most of the starting amine still present. Finally 1.8 g. of product was obtained as a red viscous oil which still contained a small amount of unalkylated amine.

Anal. Calcd. for $C_{24}H_{29}N_3O$: C, 76.67; H, 7.78. Found: C, 77.14; H, 7.63.

The presence of potassium iodide did not improve the yield of alkylated amine.

Deamination of 5-Aminobenzofuro[3,2-f]quinoline (XIII).—The amine (0.2 g.) was dissolved in 35 cc. of hot concentrated hydrochloric acid and the resulting solution cooled to 0°. The suspension thus obtained was diazotized rapidly with 0.088 g. of sodium nitrite in 5 cc. of water. After five minutes at 0–3°, the diazonium solution was filtered quickly and to the clear filtrate 35 cc. of ice-cold 50% aqueous hypophosphorous acid was added. The reaction mixture was allowed to stand in the refrigerator for twelve hours, followed by an additional twelve hours at room temperature. The solution was made alkaline with aqueous sodium hydroxide and the precipitate which formed was filtered, washed with a little water and dried.

After two "short path" distillations at a pressure of 2 mm. and a bath temperature of 100–120°, 0.090 g. of needles which melted at 81–82° was obtained. The product was recrystallized from petroleum ether (b. p. 35–60°); very pale yellow needles, m. p. 82–83.5° (cor.). The melt solidified and remelted at the same value. The product is insoluble in Claisen potash solution and gives a negative ferric chloride test and a negative Beilstein test for halogens.

Anal. Calcd. for $C_{15}H_9NO$: C, 82.17; H, 4.14; N, 6.39. Found: C, 82.13; H, 4.42; N, 6.41.

Summary

1. Benzofuro[3,2-g]quinoline was nitrated to a single mononitro derivative. By reduction the corresponding amino compound was synthesized and converted into 3-diethylaminopropylamino and 3-(4-morpholinyl)-propylamino derivatives. Neither showed antimalarial activity.

2. Benzofuro[2,3-f]quinoline yielded two difficultly separated mononitro derivatives. The corresponding amines and, through them, the corresponding bromo compounds were synthesized.

3. 5-Nitrobenzofuro[2,3-f]quinoline was synthesized from 2-nitro-3-aminodibenzofuran. It was then reduced, and the morpholinylpropyl derivative prepared. This latter compound had no antimalarial activity.

4. 3-Benzenesulfonamido-2-nitrodibenzofuran was reduced to the corresponding amine which, in turn, was converted by means of a Skraup synthesis to the benzenesulfonamidobenzofuroquinoline. This last compound was hydrolyzed to the aminobenzofuroquinoline and attempts made to substitute the amino group with appropriate alkyl radicals.

URBANA, ILLINOIS RECEIVED JULY 31, 1943

[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

Studies on Lignin and Related Compounds. LXXIV. Relation of Wood Ethanolysis Products to the Hibbert Series of Plant Respiratory Catalysts. Allylic and Dismutation Rearrangements of 3-Chloro-1-(3,4-dimethoxyphenyl)-2-propanone and 1-Bromo-1-(3,4-dimethoxyphenyl)-2-propanone

BY ARTHUR M. EASTHAM,[1] H. E. FISHER,[1] MARSHALL KULKA AND HAROLD HIBBERT

In previous communications[2,3] on the origin and function of lignin in the plant, a comparison was drawn between the Szent-Györgyi animal cell system of hydrogen-transporting respiratory catalysts[4] and a suggested analogous system composed of assumed lignin progenitors capable of functioning in a similar manner in the plant cell (Scheme 1).

SCHEME 1

Szent-Györgyi System (Animal)	Hibbert System (Plant)
A. $COOH—CH_2—CO—COOH$	A′. $R—CH_2—CO—CH_2OH$
B. $COOH—CH_2—CHOH—COOH$	B′. $R—CH_2—CHOH—CH_2OH$
C. $COOH—CH=CH—COOH$	C′. $R—CH=CH—CH_2OH$
D. $COOH—CH_2—CH_2—COOH$	D′. $R—CH_2—CH_2—CH_2OH$

(R = 4-hydroxy-3-methoxyphenyl)

The third member of the Hibbert system, coniferyl alcohol (C′) (corresponding to fumaric acid in the animal system), is known to be present in practically all plants in the early stages of growth.[5] The non-appearance of this and the other three members among the lignin fission products isolated in the ethanolysis of wood is assumed to be due to their very labile character, resulting in their ready conver-

(1) Holder of a National Research Council of Canada Studentship 1941–1942.

(2) Hibbert, *Paper Trade J.*, **113**, No. 4, 35 (1941).

(3) Hibbert, *Ann. Rev. Biochem.*, **11**, 183 (1942).

(4) Szent-Györgyi, *Ber.*, **72A**, 53 (1939).

(5) Czapek, "Biochemie der Pflanzen," Vol. III, G. Fischer, Jena, 1921, p. 464.

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sion, under the influence of the extraction medium, into stabilized end-products.

It was suggested[3] that possibly only the first and second members (A′ and B′) actually are present (probably as dimers) in native lignin, in view of the pronounced oxidizing character of the postmortal plant cell environment. Moreover, it was predicted that the first member of the series, namely, 3-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-2-propanone, should exist in equilibrium with its enol form, oxyconiferyl alcohol, and that the latter should readily undergo an allylic rearrangement to give a more stable benzoin type. There existed the further probability that this benzoin would form an equilibrium mixture with its ene-diol and dismutation isomers.

$$R{-}CH_2{-}CO{-}CH_2OH\ (A') \rightleftharpoons$$
$$R{-}CH{=}C(OH){-}CH_2OH \rightleftharpoons$$
$$R{-}CHOH{-}C(OH){=}CH_2 \rightleftharpoons$$
$$R{-}CHOH{-}CO{-}CH_3 \rightleftharpoons$$
$$R{-}C(OH){=}C(OH){-}CH_3 \rightleftharpoons R{-}CO{-}CHOH{-}CH_3$$

In preceding communications[6] the isolation of the isomeric benzoin dismutation forms as their ethyl ethers from the ethanolysis products of spruce wood is described, and in the present paper experimental proof is given of the above theoretical conceptions.

It is a well-known fact that aromatic and aliphatic substituted allyl halides, such as cinnamyl chloride[7] and crotyl chloride[8] readily undergo rearrangement when the halide is replaced by hydroxyl, ethoxyl or acetate groups. Thus, when cinnamyl chloride is treated with aqueous or alcoholic alkali, or potassium acetate in glacial acetic acid, equilibrium mixtures of cinnamyl and phenylvinylcarbinyl alcohols, -ethyl ethers and -acetates are formed. The treatment of either crotyl chloride or methylvinylcarbinyl chloride with potassium or silver acetate gives a mixture of crotyl- and methylvinylcarbinyl acetates, the extent of rearrangement being determined by the type of solvent used.[8]

This communication deals with (i) the synthesis of the four new products 1-bromo-, 1-hydroxy- and 1-acetoxy-1-(3,4-dimethoxyphenyl)-2-propanone (Series II), and 3-acetoxy-1-(3,4-dimethoxyphenyl)-2-propanone (Series I), and (ii) the rearrangements (see below) occurring when the halogen atoms in 1-bromo-1-(3,4-dimethoxyphenyl)-2-propanone (Series II, X = Br) and 3-chloro-1-(3,4-dimethoxyphenyl)-2-propanone (Series I, X = Cl) are replaced by hydroxyl, ethoxyl and acetate groups.

$$R'{-}CH_2{-}CO{-}CH_2X \underset{\text{rearr.}}{\overset{\text{allylic}}{\rightleftharpoons}}$$

SERIES I

$$R'{-}CHX{-}CO{-}CH_3 \underset{\text{rearr.}}{\overset{\text{dismutation}}{\rightleftharpoons}}$$

SERIES II

$$R'{-}CO{-}CHX{-}CH_3$$

SERIES III

(R′ = 3,4-dimethoxyphenyl- and X = —Br or —Cl, —OH, —O—CO—CH_3 or —OC_2H_5)

Synthesis of Members of the Series I, II and III.—In order to study the rearrangement reactions involved in the conversion of the halides of Series I, II and III to the corresponding alcohols, acetates and ethyl ethers, it was necessary to have available twelve pure reference compounds, namely: **Series II:** 1-bromo-1-R″; 1-hydroxy-1-R″; 1-acetoxy-1-R″; 1-ethoxy-1-R″.[9] **Series I:** 3-chloro-1-R″[10]; 3-hydroxy-1-R″; 3-acetoxy-1-R″; 3-ethoxy-1-R″.[9] **Series III:** 2-bromo-1-R‴[6c]; 2-hydroxy-1-R‴[6b,6c]; 2-acetoxy-1-R‴[6b,6c]; 2-ethoxy-1-R‴.[6b,6d]

(R″ = (3,4-dimethoxyphenyl)-2-propanone; R‴ = (3,4-dimethoxyphenyl)-1-propanone)

Synthesis of Members of Series II.—The derivatives of Series II (X = Br, —OH, —O—CO—CH_3 and —OC_2H_5) were synthesized from 1-(3,4-dimethoxyphenyl)-2-propanone by the following type reactions[11]

$$R'{-}CHO + NO_2{-}CH_2{-}CH_3 \longrightarrow$$
$$R'{-}CH{=}C(NO_2){-}CH_3 \longrightarrow$$
$$R'{-}CH_2{-}C(=NOH){-}CH_3 \longrightarrow$$
$$R'{-}CH_2{-}CO{-}CH_3 \xrightarrow{Br_2} R'{-}CHBr{-}CO{-}CH_3 \xrightarrow[aq.]{KOAc} R'{-}CHOH{-}CO{-}CH_3$$
$$\text{Also } R'{-}CH_2{-}CO{-}CH_3 \xrightarrow{Pb(OAc)_4} R'{-}CHOAc{-}CO{-}CH_3$$

(R′ = 3,4 dimethoxyphenyl-)

In an attempt to synthesize 3-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone (Series I) from the corresponding halide (Series I) rearrangement reactions resulted, no normal product being formed, the latter evidently undergoing rapid transformation into a mixture of members of Series II and III (Scheme 2)

Synthesis of Members of Series I.—3-Acetoxy-1-(3,4-dimethoxyphenyl)-2-propanone (Series I) was synthesized from homoveratric acid[12] by treatment of the acid chloride with diazomethane and interaction of the resulting diazomethyl ketone with acetic acid as applied by Wolfrom.[13]

$$R'{-}CH_2{-}COOH \xrightarrow{SOCl_2} R'{-}CH_2{-}COCl \xrightarrow{CHN_2}$$

(6) (a) E. West, MacInnes and Hibbert, THIS JOURNAL, **65**, 1187 (1943); (b) Cramer, Hunter and Hibbert, *ibid.*, **61**, 509 (1939); (c) Cramer and Hibbert, *ibid.*, **61**, 2204 (1939); (d) Hunter, Cramer and Hibbert, *ibid.*, **61**, 516 (1939).

(7) Meisenheimer and Link, *Ann.*, **479**, 211 (1930).

(8) Roberts, Young and Winstein, THIS JOURNAL, **64**, 2157 (1942).

(9) Kulka and Hibbert, *ibid.*, **65**, 1185 (1943).

(10) Haworth and Atkinson, *J. Chem. Soc.*, 797 (1938).

(11) Kulka and Hibbert, THIS JOURNAL, **65**, 1180 (1943).

(12) (a) Hahn, Stiehl and Schultz, *Ber.*, **72**, 1291 (1939); (b) Hahn and Schultz, *ibid.*, **72**, 1302 (1939).

(13) Wolfrom, Waisbrot and Brown, THIS JOURNAL, **64**, 2329 (1942).

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$$R'-CH_2-CO-CHN_2 \xrightarrow{HOAc} R'-CH_2-CO-CH_2-O-CO-CH_3$$

The method of Hahn, Stiehl and Schultz[12a] for the preparation of homoveratric acid was slightly modified, in that α-chlorohomoveratric amide was converted to homoveratric amide by use of hydriodic acid in glacial acetic acid instead of by catalytic hydrogenation.

Members of Series III.—These have been synthesized previously.[6b,d] The physical constants of the three series of reference compounds (I, II and III) are summarized in Table I. The fourth isomeric series ($R'-CO-CH_2-CH_2-X$)[14] is included for comparative purposes.

TABLE I

PHYSICAL CONSTANTS OF REFERENCE COMPOUNDS

M. p. °C., if solid or $n^{25}D$ if liquid

Compound	Bromide	Alcohol	Acetate	Ethyl ether
1-Substituted-1-R″	87–88	77–78	1.5260	1.5160
3-Substituted-1-R″	44–45	....	55–56	1.5215
2-Substituted-1-R‴	88–89	1.5590	65–66	81–82
3-Substituted-1-R‴	107–108	83–84	100–101	50–51

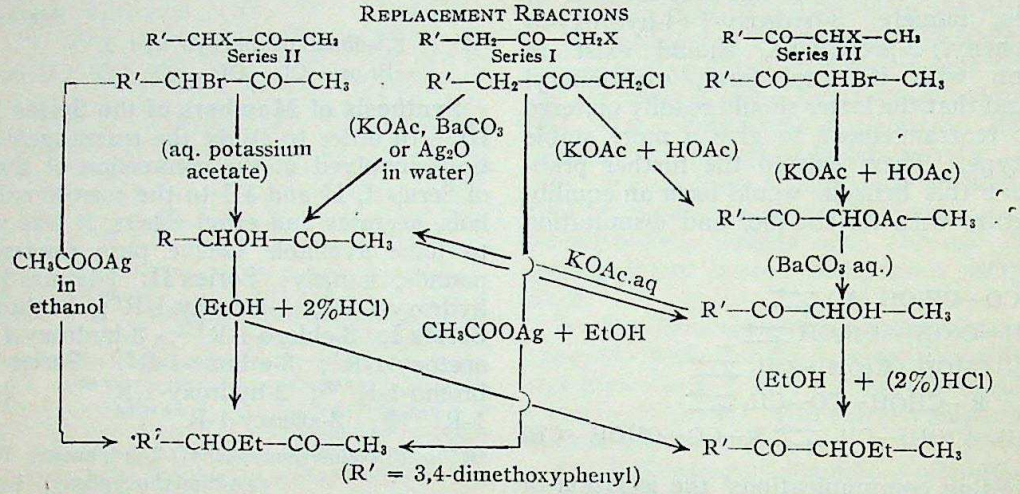
R″ = (3,4-dimethoxyphenyl)-2-propanone; R‴ = (3,4-dimethoxyphenyl)-1-propanone.

Since the three bromides of Series I, II and III were prepared by standard methods and also were found to be different from each other, it was assumed that the formulas assigned them according to the method of preparation were correct and that no rearrangements had taken place. The structures of the alcohols, acetates and ethyl ethers were arrived at in a similar manner. Further proof of structure in certain cases was obtained from absorption spectra studies.[15]

Replacement Reactions.—The attempted replacement of halogen in the halides, $R'-CHBr-CO-CH_3$ (Series II) and $R'-CH_2-CO-CH_2Cl$ (Series I), by hydroxyl, acetate or ethoxyl groups resulted in some cases in a complete, in other cases a partial, rearrangement whereby a mixture of the normal and abnormal products was obtained. These replacement reactions are summarized in Scheme 2.

SCHEME 2

REPLACEMENT REACTIONS



(R′ = 3,4-dimethoxyphenyl)

Treatment of the bromide (Series II) with silver acetate in ethanol gave the normal ethyl ether, namely, 1-ethoxy-1-(3,4-dimethoxyphenyl)-2-propanone in yield of 88%; no ethyl ethers of I or III could be detected. On the other hand, treatment of the 1-hydroxyketone (II) with 2% hydrogen chloride in ethanol yielded a mixture of the dismutation rearrangement products, namely, 2-ethoxy-1-(3,4-dimethoxyphenyl)-1-propanone (III) (60%) and the normal 1-ethyl ether (II) (30%). The replacement of bromine by the hydroxyl group on treatment of II (X = Br) with aqueous potassium acetate yielded the normal 1-hydroxyketone (II), some unchanged bromide and a small amount of the 2-hydroxyketone (III) formed as the result of a dismutation rearrangement.

Members of Series III showed, as far as could be ascertained, no tendency to rearrangement[6b,d] and also the 1-hydroxyketone (II) was found to be quite stable toward dilute acid. On the other hand, members of I proved to be very reactive and underwent rearrangements frequently. Thus treatment of the chloroketone (I) with aqueous potassium acetate, barium carbonate or silver oxide gave the 1-hydroxyketone (II) in 70% yield (as the result of an allylic rearrangement), and a small amount of the diketone, 1-(3,4-dimethoxyphenyl)-1,2-propanedione. Treatment of the chloroketone (I) with silver acetate in ethanol yielded the 1-ethyl ether (II) in approximately 60% yield together with a high alkoxyl-containing compound not further investigated. Refluxing the same chloroketone (I) with potassium acetate in glacial acetic acid also yielded a mixture of substances one of which was identified as the acetate (III).

(14) (a) K. A. West and Hibbert, THIS JOURNAL, 63, 3035 (1941); (b) Baker, Evans and Hibbert, unpublished results.

(15) Patterson and Hibbert, *ibid.*, 65, 1862 (1943).

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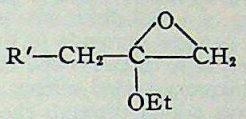
In other attempts to prepare the normal 3-ethyl ether of I, the 3-chloroketone (I) was treated with sodium ethylate and also with potassium hydroxide in ethanol solution. In both cases the reaction product was a carbonyl-free ethyl ether believed to have the structure[16]



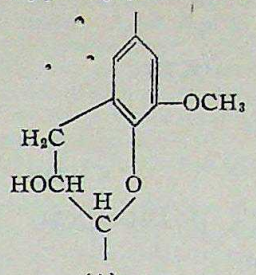
The remarkable ease with which members of Series I rearrange to give types II and III possesses marked significance for the structure of lignin. In the former type (I) there are no terminal methyl groups, in contrast to the presence of these in each of the latter (II and III). Moreover, members of Series III, when subjected to ethanolysis conditions, do not readily undergo rearrangement, while under similar treatment members of Series II are partially converted to type III.

It follows that if native lignin contains structures of the type Series I these might very well rearrange during ethanolysis to give products containing $-CH_3$ groups and belonging to Series II and III.

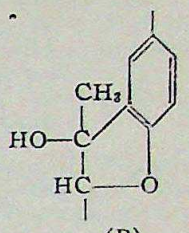
Previous work on the hydrogenation of lignin and of wood under high pressure[17] has demonstrated the presence in native lignin of large amounts of products containing terminal $-CH_2OH$ or $-CH_2-O-CH_2-$ groupings. In a following communication[18] it is shown by a chromic acid oxidation technique that native lignin contains no terminal methyl groups as postulated by Freudenberg, so that the present experimental evidence permits of the conclusion that the ethanolysis products from wood, R—CHOH—$COCH_3$[7]; R—CO—CHOH—CH_3 and R—CO—$COCH_3$ (R = 4-hydroxy-3-methoxyphenyl- or 4-hydroxy-3,5-dimethoxyphenyl-), represent stabilized end products derived from a more reactive lignin progenitor[3b], namely, the keto form of oxyconiferyl alcohol. The present experimental observation that hydrolysis with aqueous barium carbonate or potassium acetate of the chloroketone R—CH_2—CO—CH_2Cl (Series I) yields a small amount of the diketone, R—CO—$COCH_3$, in addition to the main product R—CHOH—$COCH_3$, is of marked significance in this connection.

The present experimental results bring into contrast the marked divergence of theoretical views on the structure of lignin advocated by Freudenberg and by Hibbert.

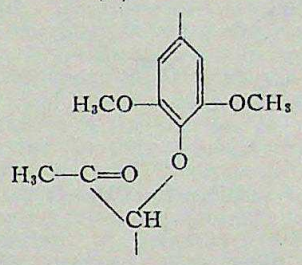
According to the former investigator[19] native spruce lignin consists of the polymeric forms of propylphenol units (A) and (B) essentially derived by condensation reactions from the two building stones R—CHOH—CHOH—CH_2OH and R—CHOH—CO—CH_3 (R = 4-hydroxy-3-methoxyphenyl).



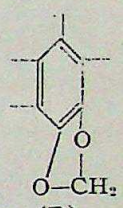
(A)



(B)



(C)



(D)

Freudenberg considers that five out of eight units in spruce lignin belong to types (A) and (B), two units contain methylenedioxy groups, type (D), and one is of the pyrogallol type (C).

Hibbert has pointed out repeatedly[20,21] the complete lack of experimental evidence supporting Freudenberg's claim of the presence of the piperonyl type (D) (based on the amount of formaldehyde formed on hydrolysis of an "extracted" lignin[18]) and has suggested "that the formaldehyde (1–4%) is formed from an aromatic side-chain, possibly one existing as part of a complex present in lignin condensation polymers and similar to cinnamyl alcohol."[21]

Freudenberg has now accepted this explanation[22] in his very recent abandonment of type (D) as part of the native lignin aggregate. His type (B) is characterized by the presence of terminal methyl groups while type (A) could give rise to a minor amount of free primary alcohol groups. No adequate experimental evidence is available indicating the presence in spruce lignin of his type (C)—syringyl component—in other than minute quantity. Up to the present Freudenberg has not been successful in isolating any propylphenol lignin units.

Hibbert regards native lignin as a mixture of polymers derived by condensation reactions from a different type of propylphenol building unit, oxyconiferyl alcohol ($\beta\gamma$-dioxyisoeugenol) the keto form of which is R—CH_2—CO—CH_2OH.

Polymer formation is assumed to occur by one or more of three mechanisms (E), (F), (G).

The syringyl lignin building unit R′—CH_2—$COCH_2OH$ (R′ = 4-hydroxy-3,5-dimethoxyphenyl) is assumed by Hibbert to be present in

(16) Aston and Greenburg, THIS JOURNAL, 62, 2590 (1940).
(17) Ref. 3b, pp. 186–187.
(18) MacGregor, Evans and Hibbert, THIS JOURNAL, 65, 41 (1944).
(19) Freudenberg, *Ann. Rev. Biochem.*, 8, 81–112 (1939).
(20) Hunter, Wright and Hibbert, *Ber.*, 71, 734 (1938).
(21) Hunter and Hibbert, THIS JOURNAL, 61, 2196 (1939).
(22) Freudenberg, *Ber.*, 76, 305 (1943).

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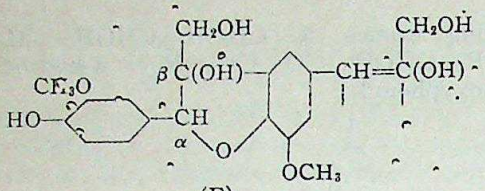
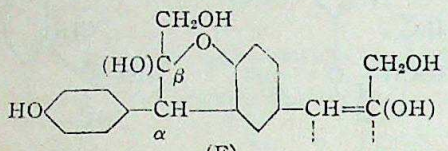
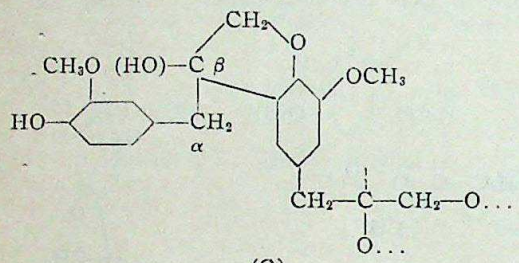


(E)



(F)



(G)

the native lignin of all angiosperms and is probably present as the initial monomeric building-stone since the blocking by methoxyl groups of both positions ortho to the phenol group would prevent polymerization proceeding in the manner indicated above.

(E) and (F) represent condensation polymers of dehydro-di-(dioxyisoeugenol), while (G) is related to the furan series. Available experimental evidence does not permit of a distinction between the three types but it is evident that they differ markedly in structure from those proposed by Freudenberg, and in particular are distinguished by the absence of methyl groups.

Removal of water from the positions (α) and (β) would yield an unsaturated type, capable of forming cross linkages, and such may form part of the native lignin aggregate.

These structural theories of Freudenberg and of Hibbert are still highly speculative in character. The source of the small quantity of monomolecular ethanolysis products obtained in the case of spruce, and of the much larger amount in the case of maple, is still unknown. That they are derived from oxyconiferyl and oxysyringyl alcohols now seems reasonably certain, but the actual form in which the latter are present in native lignin, whether as mono- or diglucosides, phenol ethers, ketals involving the carbonyl and phenol groups, or as readily reversible dimers of the truxillic acid type is, as yet, quite unknown. It would seem somewhat unlikely they are formed from polymers of the type depicted above.

Experimental

1-(3,4-Dimethoxyphenyl)-2-nitro-1-propene.—This was synthesized by the condensation of veratric aldehyde with nitroethane.[23]

(23) Kaufmann, *Ber.*, **52**, 1431 (1919).

1-(3,4-Dimethoxyphenyl)-2-propanone.—1-(3,4-Dimethoxyphenyl)-2-nitro-1-propene was reduced to the oxime by treatment with a mixture of iron dust, ferric chloride and hydrochloric acid and the oxime hydrolyzed to the ketone[11]; yield, 70%; b. p. 118° (0.2 mm.); $n^{25}D$, 1.5330. *Anal.* Calcd. for $C_{11}H_{14}O_3$: C, 68.0; H, 7.2; OCH_3, 32.0. Found: C, 67.8; H, 7.1; OCH_3, 32.0.

1-Bromo-1-(3,4-dimethoxyphenyl)-2-propanone (Series II).—To a solution of 1-(3,4-dimethoxyphenyl)-2-propanone (10.14 g.) and benzoyl peroxide (0.1 g.) in chloroform (100 cc.), contained in a three-necked flask fitted with a dropping funnel, mercury-sealed stirrer and drying tube, bromine (9.6 g.) was added through the dropping funnel over a period of ninety minutes. The temperature of the reaction mixture was kept below 10° by means of an ice-bath. At the conclusion of the addition, the reaction mixture was allowed to attain room temperature and then stirred for two hours. The chloroform solution was washed, successively, twice with cold water, twice with cold 1% bicarbonate solution and finally with water, then decolorized with charcoal and dried over sodium sulfate. Removal of the solvent under reduced pressure yielded a dark oily product, convertible to a white crystalline solid from a mixture of ether and petroleum ether (b. p. 30–50°), m. p. 87–88°; yield 8.5 g. (58%). *Anal.* Calcd. for $C_{11}H_{13}O_3Br$: C, 48.4; H, 4.8; OCH_3, 22.7; Br, 29.3. Found: C, 48.5; H, 4.9; OCH_3, 22.7; Br, 29.5.

Semicarbazone of 1-Bromo-1-(3,4-dimethoxyphenyl)-2-propanone.—Fine white crystals from water, m. p., 201.5–202.5°. *Anal.* Calcd. for $C_{12}H_{16}O_3N_3Br$: C, 43.6; H, 4.9; OCH_3, 18.8. Found: C, 43.8; H, 5.0; OCH_3, 18.7.

1-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone (Series II).—1-Bromo-1-(3,4-dimethoxyphenyl)-2-propanone (2.0 g.) was dissolved in 5% potassium acetate (200 cc.) and the solution heated on the steam-bath for four hours. The reaction mixture was extracted with chloroform, the extract dried over sodium sulfate and the solvent removed. The residual oil distilled at 135–145° bath temperature (0.1 mm.); yield of light-yellow distillate which soon solidified, 1.27 g.; recrystallized from a mixture of ether and petroleum ether as white plates, m. p. 76–77°; yield, 0.84 g. (55%). *Anal.* Calcd. for $C_{11}H_{14}O_4$: C, 62.8; H, 6.7; OCH_3, 29.6. Found: C, 63.0, H, 6.8; OCH_3, 29.5

Semicarbazone of 1-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone.—White crystals from water, m. p. 155–156°. *Anal.* Calcd. for $C_{12}H_{17}O_4N_3$: C, 53.9; H, 6.4; OCH_3, 23.2. Found: C, 53.8; H, 6.4; OCH_3, 23.0.

Action of Aqueous Potassium Acetate on 1-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone (Series II).—The hydroxyketone (0.5 g.) was heated twelve hours (100°) with 5% aqueous potassium acetate (50 cc.) in an atmosphere of carbon dioxide. The reaction mixture was extracted with chloroform and the solvent removed, leaving a yellow oil which distilled at 125–135° bath temperature (0.02 mm.). The distillate quickly solidified and was recrystallized from ether-petroleum ether (b. p. 30–50°). 1-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone (0.205 g.) (45%) was recovered, m. p. 76–77°. On evaporation of the mother liquors, a yellow oil (0.230 g., 50%) $n^{25}D$ 1.5610 was obtained. The semicarbazone of this oil when mixed with that of 2-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone showed no depression in melting point.

Synthesis of 1-Acetoxy-1-(3,4-dimethoxyphenyl)-2-propanone (Series II)

(a) Acetylation of 1-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone.—The hydroxyketone was acetylated with acetyl chloride and pyridine,[24] yield, 1.6 g. (89%); $n^{25}D$ 1.5260. Fractional distillation showed that this acetate was a pure homogeneous product. *Anal.* Calcd. for $C_{13}H_{16}O_5$: C, 61.9; H, 6.4; OCH_3, 24.6. Found: C, 62.0; H, 6.3; OCH_3, 24.6.

2,4-Dinitrophenylhydrazone of 1-Acetoxy-1-(3,4-dimethoxyphenyl)-2-propanone.—Orange crystals from ethanol, m. p. 149–150°. *Anal.* Calcd. for $C_{19}H_{20}O_8N_4$: C,

(24) Smith and Bryant, THIS JOURNAL, **57**, 61 (1935).

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52.8; H, 4.7; OCH_3, 14.4. Found: C, 52.5; H, 4.8; OCH_3, 14.5.

(b) **Treatment of 1-(3,4-Dimethoxyphenyl)-2-propanone with Lead Tetraacetate.**—1-(3,4-Dimethoxyphenyl)-2-propanone (2.3 g.) was dissolved in glacial acetic acid (80 cc.) and freshly prepared lead tetraacetate (7 g.)[25] added. The mixture was heated for eight hours at 88° in a two-necked flask equipped with a mercury-sealed stirrer and a condenser. The solution was decanted into water (400 cc.) and the aqueous solution extracted with ether. The ether extract was washed with 5% sodium bicarbonate, then with water, and dried over sodium sulfate. Removal of the solvent left a dark-colored oil which distilled at 160–190° bath temperature (0.1 mm.); yield 2.2 g. (74%); $n^{25}D$ 1.5290. On fractional distillation (0.2 mm.) the greater part of this material distilled over as pure 1-acetoxy-1-(3,4-dimethoxyphenyl)-2-propanone. Its 2,4-dinitrophenylhydrazone when mixed with that prepared from the pure synthetic product (previous experiment) showed no depression in melting point.

Homoveratric Acid.—α-Chloro-homoveratric amide[12a] (6.0 g.) was dissolved in glacial acetic acid (20 cc.) and constant-boiling hydriodic acid (8 cc.) added. After standing for fifteen hours at room temperature the reddish-purple crystalline precipitate (22 g.) was filtered, dried *in vacuo* and added to a well-stirred, saturated solution of sodium bisulfite. Addition of ammonium hydroxide to the bisulfite solution precipitated the homoveratric amide (4.2 g., 82%) m. p. 141–144°. The amide was then hydrolyzed to homoveratric acid.[12a]

3-Bromo-1-(3,4-dimethoxyphenyl)-2-propanone (Series I).—Homoveratric acid was converted to the acid chloride, the latter treated with diazomethane and the resulting diazomethyl ketone allowed to react with hydrogen bromide in ether. The method used was identical with that employed for the preparation of 3-chloro-1-(3,4-dimethoxyphenyl)-2-propanone (Series I),[10] X = Cl. Yield of the bromide 80%; recrystallized from a mixture of ether and petroleum ether, m. p. 44–45°. *Anal.* Calcd. for $C_{11}H_{13}O_3Br$: OCH_3 22.7. Found: OCH_3, 22.5.

3-Acetoxy-1-(3,4-dimethoxyphenyl)-2-propanone (Series I).—Homoveratric acid (1.4 g.) was treated with pure thionyl chloride (2.0 cc.) for fifteen minutes at room temperature and then at 70° for an additional thirty minutes. The excess thionyl chloride was removed under reduced pressure and the residual product freed from last traces by two additions and removals of benzene. The light orange-colored oil was dissolved in ether and the solution added gradually to a cold solution of diazomethane in ether (prepared from 4 g. of nitrosomethyl urea). After standing at 0° for three hours, the ether was distilled off and the residual diazomethyl ketone refluxed with glacial acetic acid (20 cc.) for fifteen minutes. The acetic acid was removed under reduced pressure and the residue distilled at 165–190° (bath temperature) (0.1 mm.); yield of light-yellow oil, which solidified with difficulty, 1.44 g. (85%); white needle-like crystals from a mixture of ether and petroleum ether, m. p. 55–56°. *Anal.* Calcd. for $C_{13}H_{16}O_5$: C, 61.9; H, 6.4; OCH_3, 24.6. Found: C, 62.0; H, 6.4; OCH_3, 24.8.

Semicarbazone of 3-Acetoxy-1-(3,4-dimethoxyphenyl)-2-propanone.—White crystals from water and from ethanol–petroleum ether, m. p. 128–129°. *Anal.* Calcd. for $C_{14}H_{19}O_5N_3$: C, 54.4; H, 6.3; OCH_3, 20.1. Found: C, 54.4; H, 6.3; OCH_3, 20.2.

Synthesis of 1-(3,4-Dimethoxyphenyl)-1,2-propanedione.—To a hot solution of copper sulfate (1.45 g.) dissolved in pyridine (2.4 cc.) and water (1.2 cc.), was added 1-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone (Series II, X = −OH) (0.50 g.) and the resulting solution heated on the steam-bath for two hours. The reaction mixture was poured with stirring into 3 *N* hydrochloric acid (14 cc.) and the acid solution extracted with ether. Removal of the ether yielded a yellow solid (0.30 g.); recrystallized from a mixture of ether and petroleum ether, m. p. 69–70°. *Anal.* Calcd. for $C_{11}H_{12}O_4$: OCH_3, 29.8. Found: OCH_3, 29.7°. Oxidation of 2-hydroxy-1-(3,4-dimethoxyphenyl)-1-propanone (Series III), in a similar manner, yielded the same diketone.

Semicarbazone of 2-Hydroxy-1-(3,4-dimethoxyphenyl)-1-propanone.—A solution of 2-hydroxy-1-(3,4-dimethoxyphenyl)-1-propanone[5a] (0.1 g.), semicarbazide hydrochloride (0.1 g.) and potassium acetate (0.2 g.) in water (5 cc.) was heated at 70° for two hours and then allowed to stand at room temperature for one week; white crystals from water, m. p. 154–155°. *Anal.* Calcd. for $C_{12}H_{17}O_4N_3$: C, 53.9; H 6.4; OCH_3, 23.2. Found: C, 53.8; H, 6.5; OCH_3, 23.1.

Reaction of 1-Bromo-1-(3,4-dimethoxyphenyl)-2-propanone (Series II) with Silver Acetate and Ethanol.—1-Bromo-1-(3,4-dimethoxyphenyl)-2-propanone (2.0 g.) was dissolved in ethanol (150 cc.) and silver acetate (2.0 g.) added. The suspension was refluxed for twelve hours in an atmosphere of carbon dioxide. The silver bromide was filtered, the filtrate taken to dryness under reduced pressure and the residue distilled at 140–150° bath temperature (0.1 mm.); yield, 1.53 g. (88%). The 2,4-dinitrophenylhydrazone of this product, m. p. 141–142°, when mixed with the 2,4-dinitrophenylhydrazone of 1-ethoxy-1-(3,4-dimethoxyphenyl)-2-propanone[8] showed no depression, but when mixed with that of 2-ethoxy-1-(3,4-dimethoxyphenyl)-1-propanone showed a marked depression.

Reaction of 3-Chloro-1-(3,4-dimethoxyphenyl)-2-propanone (Series I) with Silver Acetate and Ethanol.—3-Chloro-1-(3,4-dimethoxyphenyl)-2-propanone was treated with silver acetate and ethanol in a similar manner. The resulting product was fractionally distilled (0.2 mm.) yielding 1-ethoxy-1-(3,4-dimethoxyphenyl)-2-propanone (Series II, X = $-OC_2H_5$) (approx. 60%) and a high alkoxyl-containing compound (alkoxyl, 43.5%) which was not investigated further.

Behavior of 1-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone (Series II) toward 2% Ethanolic Hydrogen Chloride.—1-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone (1.5 g.) was dissolved in a 2% solution of hydrogen chloride in ethanol (150 cc.) and the mixture refluxed for forty-eight hours under an atmosphere of carbon dioxide. The reaction product was neutralized with solid sodium bicarbonate, filtered and the filtrate taken to dryness under reduced pressure. The residual oil was dissolved in ether and the ether solution extracted with 10% sodium bisulfite. The ether solution was then dried and the solvent removed. The residue distilled at 120–130° bath temperature (0.05 mm.); yield of pale-yellow distillate, which soon solidified, 1.406 g. The product was treated with a small amount of warm petroleum ether, and the insoluble material (0.792 g.) filtered off and washed; recrystallized from dilute ethanol, m. p. 81–82°; no depression in melting point when mixed with an authentic sample of 2-ethoxy-1-(3,4-dimethoxyphenyl)-1-propanone (Series III).

The combined petroleum ether filtrate and washings were taken to dryness and the residual oil (0.561 g.) converted to the 2,4-dinitrophenylhydrazone; recrystallized from ethanol, m. p. 141–142°; no depression in melting point when mixed with the 2,4-dinitrophenylhydrazone of 1-ethoxy-1-(3,4-dimethoxyphenyl)-2-propanone (Series II).

The bisulfite extract from the original ether solution was neutralized, the sulfur dioxide removed, and the resulting solution extracted with ether. Removal of the ether left a small amount of bisulfite-soluble material (0.04 g.) which was not investigated.

Reaction of 3-Chloro-1-(3,4-dimethoxyphenyl)-2-propanone (Series I) with Aqueous Potassium Acetate, Barium Carbonate and Silver Oxide.—The chloroketone (3.3 g.) was refluxed with 5% aqueous potassium acetate (250 cc.) for five hours and the solution then extracted with chloroform. The extract was dried over sodium sulfate and the solvent removed. The residue was recrystallized from ether, yielding white crystalline material (1.5 g.), m. p., 76–77°; no depression in melting point when mixed with an authentic sample of 1-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone (Series II, X = −OH). The filtrates from the recrystallizations were taken to dry-

(25) Dimroth and Schweizer, *Ber.*, **56**, 1375 (1923).

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ness and the residue (A) fractionally distilled in the Cooke-Bower fractionating column[26] at 0.1-mm. pressure. About 20% (0.35 g.) of the starting material (A) was obtained as a yellow crystalline solid and after recrystallization from ether melted at 68–69°. A mixed melting point determination, with 1-(3,4-dimethoxyphenyl)-1,2-propanedione showed no depression. The remainder of the material was not identified.

Reaction of 3-Chloro-1-(3,4-dimethoxyphenyl)-2-propanone (Series I) with a Mixture of Potassium Acetate and Glacial Acetic Acid.—The chloroketone (8.0 g.) was dissolved in glacial acetic acid (35 cc.), freshly-fused potassium acetate (21 g.) added, and the resulting solution heated for eight hours at 90–100°. The reaction mixture was diluted with water (300 cc.), neutralized with sodium carbonate, and extracted with chloroform. The extract was dried, the solvent removed and the residue fractionally distilled under reduced pressure. Each of the fractions obtained was semicrystalline. The crystalline material (40%) was separated on a porous plate and recrystallized from a mixture of ether and petroleum ether, m. p. 65–66°; no depression when mixed with an authentic sample of 2-acetoxy-1-(3,4-dimethoxyphenyl)-2-propanone (Series III).

Reaction of 1-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone (Series II) with 5% Sulfuric Acid.—The hydroxyketone (0.4 g.) was heated at 70–80° with 5% sulfuric acid (100 cc.) for three and one-half hours and the solution extracted with chloroform. The chloroform extract was dried and the solvent removed. The residue was recrystallized from ether yielding the pure unchanged 1-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone (0.35 g.).

Reaction of 2-Hydroxy-1-(3,4-dimethoxyphenyl)-1-propanone (Series III) with Aqueous Potassium Acetate.—The hydroxyketone (0.5 g.) was refluxed for four hours with 5% aqueous potassium acetate (75 cc.). From the solution the starting material was recovered as the semicarbazone (m. p. 153–155°) in 40% yield. No 1-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone could be detected.

Reaction of 3-Chloro-1-(3,4-dimethoxyphenyl)-2-propanone (Series I) with Methanolic and Ethanolic Alkali.—The chloroketone (2.5 g.) was dissolved in methanol (15 cc.) and a solution of sodium (0.32 g.) in methanol (16 cc.) added dropwise at room temperature. The alkaline solution was acidified very slightly with hydrochloric acid, and then neutralized by addition of solid sodium bicarbonate, filtered and the filtrate taken to dryness under reduced pressure. The residue (1.75 g.) was recrystallized from petroleum ether (b. p. 30–50°) and then from aqueous ethanol; m. p. 40–41°. *Anal.* Calcd. for $(CH_3O)_2$—C_6H_3—$C_3H_4O(OCH_3)$: C, 64.3; H, 7.1; OCH_3, 41.5; mol. wt., 224. Found: C, 64.2; H, 7.0; OCH_3, 41.7; mol. wt. (Rast), 234.

Treatment of the same chloroketone with *methanolic* potassium hydroxide yielded the same compound in 80% yield.

The substitution of *ethanol* for *methanol* and sodium *ethylate* for sodium *methylate* in this experiment yielded the corresponding ethyl ether; b. p. 104° (0.04 mm.); $n^{25}D$ 1.5150; alkoxyl, calcd. for $(CH_3O)_2$—C_6H_3—$C_3H_4O(OC_2H_5)$, 39.1. Found, 39.2.

Treatment of these reaction products with semicarbazide or acidified 2,4-dinitrophenylhydrazine yielded no carbonyl derivatives.

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Summary

1. Four new substances, namely, 1-bromo-, 1-hydroxy-, 1-acetoxy- and 3-acetoxy-1-(3,4-dimethoxyphenyl)-2-propanone have been synthesized.

2. The allylic and dismutation rearrangement reactions attendant upon the conversion of the two halides, 1-bromo-1-(3,4-dimethoxyphenyl)-2-propanone and 3-chloro-1-(3,4-dimethoxyphenyl)-2-propanone to the corresponding alcohols, acetates and ethyl ethers have been studied under a variety of conditions.

3. The ease with which these rearrangements occur provides valuable confirmation of the theory of Hibbert that the ethanolysis products from wood are in reality stabilized end-products formed from more reactive lignin progenitors of the type represented by oxyconiferyl alcohol (β,γ-dioxyisoeugenol) or its keto isomer, and provides strong support for his views on the structure of native lignin.

MONTREAL, CANADA RECEIVED AUGUST 20, 1943

(26) Bower and Cooke, *Ind. Eng. Chem., Anal. Ed.*, **15**, 290 (1943).

[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

Studies on Lignin and Related Compounds. LXXV. Alkaline Nitrobenzene Oxidation of Plant Materials and Application to Taxonomic Classification[1]

BY R. H. J. CREIGHTON, R. DARNLEY GIBBS AND HAROLD HIBBERT

The two types of classification recognized by botanists for higher plants are (1) an *artificial* classification, or "key," compiled merely for the purpose of identification and based on any *obvious* characteristic, such as flower or leaf morphology, convenience being the sole criterion; (2) a *natural* one in which all available criteria should be employed[2] to indicate true relationships between species, genera, etc. In general, flower morphology is the most suitable basis for classification, but many other criteria (*e. g.*, morphology of other parts, cytology, comparative anatomy and chemistry) have been employed occasionally for its support.

Chemical methods have been employed in clarifying the relationships of many closely related species. Thus, Manske[3] has pointed

(1) This paper is a joint contribution from the Department of Botany and the Division of Industrial and Cellulose Chemistry, McGill University, Montreal, and represents part of a thesis submitted to the Faculty of Graduate Studies by R. H. J. Creighton, May, 1942, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Gilmour, *Nature*, **139**, 1040 (1937).

(3) Manske, *Can. Chem. Process Inds.*, **23**, 199 (1939).

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out that the structures of the alkaloids present in closely-related plants may serve to distinguish between species regarded as identical on the basis of morphology.

Miller[4] found the essential oils of three species of *Pycnanthemum*, *P. tullia*, *P. incanum* and *P. lanceolatum* (plants between which it is difficult to differentiate on morphological grounds) to differ markedly.

McNair's[5] studies of the essential oils from eighty-seven plants and families led him to conclude that their structure is closely related to the position of the plant in the phylogenetic scale.

Cole and Cardoso[6] isolated from members of the family *Flacourtiaceae* the five-membered ring fatty acids, gorlic acid, chaulmoogric acid, and several of the lower homologs of the latter. Of the eleven tribes or subfamilies which comprise the family *Flacourtiaceae*,[7] it is only from the *Oncobeae* (which according to Gilg is the central tribe) and the closely-related *Pangieae* that these acids have been isolated and identified. They contain an asymmetric carbon atom, and other members of the *Oncobeae* and *Pangieae* whose fatty acids have not yet been studied in detail have also yielded optically active fatty acids.

Reichert[8] has examined the starch grains from a large number of plant species and concludes that they "constitute a strictly scientific basis for the classification of plants." Both Reichert[8] and Carles[9] have carried out extensive investigations of the family *Iridaceae* which, as now classified, contains a number of genera, some of which (*e. g.*, *Moraea* and *Homeria*) differ so widely in the reactions of their starches as to suggest misclassification. In general, their results support the earlier classification of Tournefort[10] rather than the more modern one.[11]

A close relationship exists between the proteins in certain plant extracts and the plant species,[12] in that, as the degree of relationship between species diminishes, the number of common proteins present in the plant extracts decreases proportionately. Mez and co-workers[13] on the basis of their serological investigations have constructed a "family tree" of the vegetable kingdom. The indicated phylogenetic relationships are in general accepted by taxonomists. Where differences occur Mez's results may sometimes express the truer phylogenetic relationships, though some of his serological relationships are obviously false.

(4) Miller, Ph.D. Thesis, University of Minnesota, 1918.
(5) McNair, *Am. J. Botany*, **19**, 168 (1932); **21**, 427 (1934); *Bull. Torrey Botan. Club*, **62**, 515 (1935).
(6) Cole and Cardoso, THIS JOURNAL, **61**, 2349 (1939).
(7) Gilg in Engler and Prantl's "Die Natürliche Pflanzenfamilien," 1925.
(8) Reichert, *Carnegie Inst. Wash. Pub.*, No. 173.
(9) Carles, *Rev. gen. botan.*, **47**, 5, 87, 144, 215, 294 (1935).
(10) "Institutiones rei herbariae," Paris, 1701.
(11) Dykes, "The Genus Iris," Cambridge University Press, 1913.
(12) Chester, *Quart. Rev. Biol.*, **12**, 19 (1937).
(13) Mez and Zeigenspeck, *Botan. Arch.*, **12**, 163 (1925).

The role of lignin in plant taxonomy has been confined largely to lignin color reactions, of which the Mäule test[14] has been the most valuable.

Crocker,[15] employing a wide variety of botanical groups, found that the three genera included in the *Gnetales*, namely, *Gnetum*, *Ephedra* and *Welwitschia*, all gave strongly positive Mäule tests. In general, all of the *Coniferales* gave the expected negative test, but one of the *Podocarpus* species, namely, *P. amarus*, gave a strongly positive test. Crocker's work has recently been extended by Gibbs[16] and some of his findings are included here for comparison with the present results obtained by nitrobenzene oxidation.

Analytical data have shown that a marked difference exists between the lignins isolated from the gymnosperms or "softwoods" and those isolated from the angiosperms or "hardwoods." The lignins of the former type contain 14–16% methoxyl and the latter up to 20–22%. Holmberg,[17] employing thioglycolic acid as the lignin extraction agent, investigated the extracted lignins from over fifty plant species. His results showed that, while the lignins from all of the higher plants were essentially uniform in type, the carbon analyses of lignins isolated from the gymnosperms were generally 3–5% higher than those from the angiosperms, the oxygen values of the latter lignins being correspondingly higher, even in the case of certain monocotyledons in which low methoxyl values (16.9 to 17.1%) were found. Similar results were obtained by Klason,[18] in his analyses of β-lignin sulfonic acids from various woods. He found that the lignins from gymnosperms had the formula $C_{10}H_{10}O_3$ and those from angiosperms the formula $C_{10}H_{10}O_4$. More recently further confirmation of chemical differences between the lignins from gymnosperms and angiosperms, respectively, has been secured in analyses of products obtained in the ethanolysis of wood by Hibbert and co-workers.[19] They showed that the lignin from angiosperms differs from that from gymnosperms in that in the former there are present both the 4-hydroxy-3-methoxyphenyl and the 4-hydroxy-3,5-dimethoxyphenyl nuclei, whereas in the latter the 4-hydroxy-3-methoxyphenyl nucleus only is present. Thus spruce wood, when subjected to ethanolysis, yields a mixture of 2-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone (I), 1-ethoxy-1-(4-

(14) Mäule, *Fünfstück's Beitr. Wiss. Botan.*, **4**, 166 (1901).
(15) Crocker, *Bot. Gaz.*, **95**, 168 (1933).
(16) Gibbs, unpublished results.
(17) Holmberg, *Ing. Vetenskaps Akad., Hand.*, No. 131 (1934).
(18) Klason, *Ber.*, **63**, 1548 (1930); *Svensk Pappers Tidning*, **33**, 16 (1930); **35**, 224 (1932); **36**, 226 (1933).
(19) (a) Cramer, Hunter and Hibbert, THIS JOURNAL, **61**, 509 (1939); (b) Hunter, Cramer and Hibbert, *ibid.*, **61**, 516 (1939); (c) MacInnes, West, McCarthy and Hibbert, *ibid.*, **62**, 2803 (1904); (d) Kulka, Hawkins and Hibbert, *ibid.*, **63**, 2371 (1941); (e) Kulka and Hibbert, *ibid.*, **65**, 1180 (1943).

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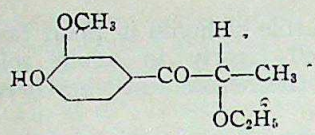
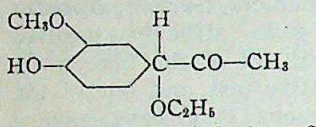
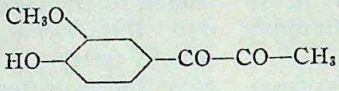


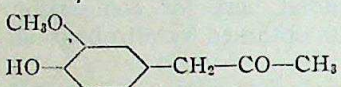
I. 2-Ethoxy-1-(4-hydroxy-3-methoxypheny)-1-propanone



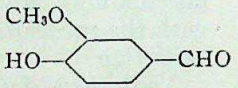
II. 1-Ethoxy-1-(4-hydroxy-3-methoxyphenyl)-2-propanone



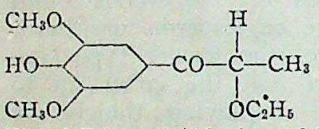
III. 1-(4-Hydroxy-3-methoxyphenyl)-1,2-propanedione



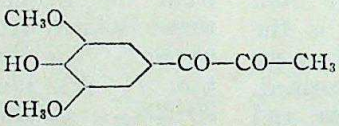
IV. 1-(4-Hydroxy-3-methoxyphenyl)-2-propanone



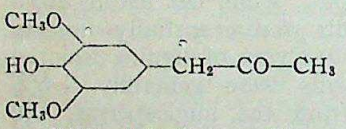
V. Vanillin



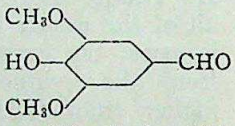
VI. 2-Ethoxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanone



VII. 1-(4-Hydroxy-3,5-dimethoxyphenyl)-1,2-propanedione



VIII. 1-(4-Hydroxy-3,5-dimethoxyphenyl)-2-propanone



IX. Syringaldehyde

hydroxy-3-methoxyphenyl)-2-propanone (II), 1-(4-hydroxy-3-methoxyphenyl)-1,2-propanedione (III), 1-(4-hydroxy-3-methoxyphenyl)-2-propanone (IV) and vanillin (V). Maple wood on similar treatment gives, in addition, the corresponding syringyl analogs (VI, VII, VIII and IX), the combined yields of pure products from angiosperms and gymnosperms amounting to 9.7 and *ca.* 3%, respectively. With certain monocotyledons, the presence of the syringyl compounds could not be definitely established.[19c]

More recently, employing the nitrobenzene oxidation technique of Freudenberg[20] spruce is found to give only vanillin upon oxidation, in a yield of 24% based on the initial Klason lignin, while maple and other dicotyledons give a combined yield of a mixture of vanillin and syringaldehyde of as high as 49%.[21] The ratio of vanillin to syringaldehyde in the isolated mixture was shown to be approximately 1:3. The monocotyledons investigated (consisting of several grasses) gave slightly lower yields of aldehydes (up to 30%), and the ratio of vanillin to syringaldehyde was approximately 1:1. A more recent investigation shows that the vanillin fraction isolated from these monocotyledons (all belonging to the grasses) contains a mixture of vanillin and *p*-hydroxybenzaldehyde.[22]

In the present investigation the above alkaline nitrobenzene oxidation technique has been applied to over fifty plant species and the results confirm in general those obtained in the earlier work. Certain exceptions were found, however, which suggest that the method may provide a possible aid to the taxonomist in establishing the true phylogenetic relationships of certain plant species.

The procedure was essentially that previously outlined.[21] Due to the difficulty in obtaining sufficiently large quantities of material in certain cases, a reduction in the amount of starting material was found necessary. In these cases the time of reaction could be reduced from three to two hours, and the tedious step of steam distillation eliminated, when only the bisulfite soluble fraction called for investigation. The mixture of aldehydes obtained in the case of the angiosperms was separated by means of fractional sublimation of the crude mixture.[21]

Whenever possible, fresh plant material was employed, although in certain cases, notably with *Podocarpus amarus*, *P. pedunculatus* (see below), *Paulownia imperialis*, *Drimys winteri*, *Trochodendron sp.*, *Zygogynum vieillardi* and *Belliolum haplopus* (Burtt), A. C. Smith, museum specimens were used. In all cases the air-dried chips were ground to 40-mesh in a Wiley mill and solvent-extracted before use.

Podocarpus pedunculatus is not recognized by Pilger[23] but is regarded as synonymous with *P. amarus*. The close agreement found in this investigation between the two species (Table I) lends support to his views.

The results of the alkaline nitrobenzene oxidation of fifty species are shown in Tables I, II and III.

Unless otherwise specified, the air-dried wood chips were ground to 40-mesh in the Wiley mill, the resulting wood meal extracted successively with 50:50 ethanol–benzene (forty-eight hours), ethanol (twenty-four hours) and hot water (twelve hours), then air-dried, and the moisture content determined by drying a 2-g. sample overnight at 105°. The Klason lignin was determined on the oven-dried sample by the method of Ritter, Seborg and Mitchell[24] involving the use of 72% sulfuric acid.

The commonly accepted gymnosperms (Table I, Expts. 1–12) gave only vanillin, in yields of 15–24% calculated on the Klason lignin content

(20) Freudenberg, Lautsch and Engler, *Ber.*, **73**, 167 (1940).

(21) Creighton, McCarthy and Hibbert, THIS JOURNAL, **63**, 3049 (1941).

(22) Creighton and Hibbert, *ibid.*, **66**, 37 (1944).

(23) Engler, "Das Pflanzenreich," 1903.

(24) Ritter, Seborg and Mitchell, *Ind. Eng. Chem., Anal. Ed.*, **4**, 202 (1932).

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TABLE I

NITROBENZENE OXIDATION OF PTERIDOPHYTES AND GYMNOSPERMS

Expt.	Plant	Klason lignin, %[a]	Total aldehydes, %[b]	Vanillin, %[b]	Syringaldehyde, %[b]	Ratio vanillin: syringaldehyde	Mäule test[c]
1	*Pteridium latiusculum* (Bracken)	28.1	21.8	20.5	None		−
2	*Cycas revoluta*	15.6	2.7	2.5	None		−
3	*Picea glauca* (White Spruce)	28.6	23.7	23.5	None		−
4	*Tsuga canadensis* (Hemlock)	31.1	23.2	22.1	None		−
5	*Pinus strobus* (White Pine)	34.9	20.1	18.5	None		−
6	*Thuja plicata* (Western Red Cedar)	33.9	24.6	24.0	None		−
7	*Sequoia sempervirens* (Redwood)	31.8	24.8	23.5	None		−
8	*Taxus canadensis* (Ground Hemlock)	32.5	22.0	20.7	None		−
9	*Agathis australis*	30.8	19.9	18.7	None		−
10	*Podocarpus neriifolius*		Present	Present	None		Variable,
11	*P. acutifolium*	34.9	20.2	19.8	None		some
12	*P. macrophyllus v. maki*	39.9	17.4	15.1	Trace (?)		times
13	*P. macrophyllus v. maki*	39.0	17.0	14.9	None		faintly +
14	*P. amarus*	32.1	30.7	12.5	12.5	1:1.0	+ or ++
15	*P. pedunculatus*	30.7	31.7	13.9	14.7	1:1.0	+
16	*Callitris rhomboidea*	34.8	19.7	18.8	None		−
17	*Tetraclinis articulata*	29.5	29.2	15.5	12.0	1:0.8	++
18	*Ginkgo biloba* (Maidenhair Tree)	32.8	25.7	25.3	None		−
19	*Ephedra trifurca*	23.3	39.6	9.3	27.7	1:3.0	++ or better
20	*E. sp.*	25.0	36.0	8.8	26.0	1:3.0	++
21	*Gnetum indicum*	24.7	26.8	6.8	16.5	1:2.5	+ or ++
22	*Welwitschia mirabilis*	16.5	4.9	2.0	2.4	1:1.2	+

[a] Based on dry wood weight. [b] Based on weight of initial Klason lignin. [c] A rough attempt is made to express results quantitatively.

TABLE II

NITROBENZENE OXIDATION OF DICOTYLEDONS

No.	Plant	Klason lignin, %[a]	Total aldehydes, %[b]	Vanillin, %[b]	Syringaldehyde, %[b]	Ratio vanillin: syringaldehyde	Mäule test
1	*Acer* (whole wood)	22.0	46.0	10.2	34.7	1:3.4	Not tested
2	*rubrum* (heart wood)	23.6	39.2	9.7	28.5	1:2.9	Not tested
3	(Red maple) (sapwood)	20.6	44.5	9.1	33.6	1:3.7	Not tested
4	*A. saccharinum* (Silver Maple)	18.8	51.0	12.7	35.2	1:2.8	+ or ++
5	*Populus* (Aspen)	17.4	44.7	9.4	32.1	1:3.4	+ or ++
6	*tremu-* (Aspen)[c]	17.0	43.3	9.1	33.4	1:3.7	Not tested
7	*loides* (Aspen)[d]	20.6	41.5	8.3	31.2	1:3.7	Not tested
8	*Sassafras sp.*	22.1	44.5	9.9	29.5	1:3.0	+[e]
9	*Quercus borealis v. maxima* (N. Red Oak)	18.4	47.2	10.5	34.3	1:3.3	Not tested
10	*Betula lutea* (Yellow Birch)	19.6	44.9	11.0	33.7	1:3.1	++
11	*Fraxinus americana* (White Ash)	18.5	48.6	10.5	37.2	1:3.5	++
12	*Ulmus fulva* (Slippery Elm)	23.0	41.7	9.0	29.1	1:3.2	+++
13	*U. americana* (American Elm)	21.3	40.9	9.8	30.7	1:3.1	+++
14	*Juglans cinerea* (Butternut)	19.0	45.2	11.1	31.0	1:2.8	+ or ++
15	*J. nigra* (Black Walnut)	20.9	39.3	10.5	26.5	1:2.5	+[e]
16	*Tilia americana* (Basswood)	23.8	35.2	8.9	23.8	1:2.7	+ or ++
17	*Corcho-* (Jute)	22.3	39.0	9.4	24.5	1:2.6	Not tested
18	*rus sp.* (fiber)	12.7	32.0	7.7	23.9	1:3.1	Not tested
19	*Sorbus americana*	18.5	49.0	9.5	37.8	1:4.0	Not tested
20	*Robinia pseudacacia*	21.2	39.8	9.4	27.6	1:2.9	++
21	*Paulownia imperialis*	18.9	44.6	10.6	32.8	1:3.1	+
22	*Liriodendron tulipifera*	20.0	49.2	11.0	36.5	1:3.2	+ to +++
23	*Trochodendron sp.*	24.0	40.4	9.5	29.5	1:3.1	++
24	*Drimys winteri*	24.3	35.3	8.2	22.0	1:2.7	+
25	*Belliolum haplopus*	36.9	29.6	13.9	16.2	1:1.1	+ or ++
26	*Zygogynum vieillardi*	35.5	32.8	14.3	16.8	1:1.2	+ or ++

[a] Based on dry wood weight. [b] Based on weight of initial Klason lignin. [c] Extracted forty-eight hours with ethanol, then twelve hours with water. [d] Extracted forty-eight hours with petroleum ether, then with ether. [e] Tested by Sharma (1922).

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TABLE III

NITROBENZENE OXIDATION OF MONOCOTYLEDONS

No.	Plant species	Klason lignin, %[a]	Total aldehydes, %[b]	Vanillin, %[b]	Syringaldehyde, %[b]	Ratio vanillin: syringaldehyde	Mäule test
1	*Dracaena fragrans* (?)	23.8	34.9	6.9	26.2	1:3.8	++ or +++
2	*Aloe abyssinica*	18.5	37.1	8.3	27.1	1:3.3	+++
3	Bamboo (unidentified)	22.5	28.5	15.1[c]	11.5	1:0.8	+ or ++[d]
4	Rye straw	20.2	30.5	14.1[c]	15.3	1:0.9	+ or ++[d]
5	Corn cobs	13.8	21.4	17.1[c]	6.0	1:0.4	+[d]
6	Corn stalks	19.9	17.8	9.5[c]	7.8	1:0.8	+ or ++[d]
7	*Saccharum officinarum*	16.4	16.3	5.3	9.0	1:1.7	+

[a] Based on dry wood weight. [b] Based on weight of initial Klason lignin. [c] "Vanillin fraction" consists of vanillin plus *p*-hydroxybenzaldehyde. [d] Ethanol–benzene extracted meal was used for these tests (all other Mäule tests were on *untreated* plant material).

of the wood, while the dicotyledons (Table II, Expts. 1–24) yielded 35–51% of a mixture of vanillin and syringaldehyde in an approximate ratio of 1:3. The monocotyledons (Table III, Expts. 1–7) gave lower yields of mixed aldehydes (16.3 to 37.1%). In the grasses (Table III, Expts. 4 and 6) (excepting *Saccharum officinarum*) the presence of a third non-methoxyl-containing aldehyde, admixed with the vanillin, was indicated from the lower methoxyl values. As shown in the following communication, the aldehyde was *p*-hydroxybenzaldehyde.

A number of interesting exceptions were found to the above chemical differentiation between gymnosperms and angiosperms. Three species belonging to the *Coniferales*, namely, *Podocarpus amarus*, *P. pedunculatus* and *Tetraclinis articulata* (Table I) and also members of all the genera included in the *Gnetales* (Table I, Expts. 19–22) were found to give not only vanillin but also high yields of syringaldehyde. These species also gave a positive Mäule test, and a comparison of the results of this with the nature of the aldehydes formed on oxidation shows that a close correlation exists between the occurrence of the syringyl nucleus in the lignin of plants and the red coloration obtained in the positive Mäule test. From *Podocarpus macrophyllus v. maki*, which was found to give a very weakly positive Mäule test, the presence of the syringyl grouping could not be definitely established. In one experiment (Table I, Expt. 12) fractional crystallization of the *m*-nitrobenzoylhydrazone of the last sublimation fraction gave a trace (0.003 g.) of a hydrazone (m. p. 191–193°) which showed no mixed melting point depression with the *m*-nitrobenzoylhydrazone of syringaldehyde (m. p. 192–193°). In repeating this experiment with larger amounts of material (from a different source) (Table I, Expt. 13) and fractionating the bisulfite fraction in a semi-micro Cooke–Bower fractionating column[25] no syringaldehyde could be found. It should be emphasized, however, that the Mäule test was only *very* faintly positive with this species. The case of *Tetraclinis articulata* is particularly interesting. It has recently been separated from *Callitris* by the taxonomists and this separation is clearly supported by the chemical evidence (Table I, Expts. 16 and 17).

With *Belliolum haplopus* and *Zygogynum vieillardi* (Table II, Expts. 25, 26) the ratio of vanillin to syringaldehyde was found to be 1:1.1 and 1:1.2, respectively, proving to be, in this respect, the sole exception met with in a wide variety of dicotyledons. Both species were found to contain large amounts of Klason lignin (35 and 37%, respectively), while the yields of aldehydes based on same were only 29.6 and 32.8%. The results are of interest since these two species belong to a group of primitive angiosperms comprising the families *Magnoliaceae*, *Winteraceae* and *Trochodendraceae*, all of which are characterized by the absence of vessels. According to the most recent classification of these groups, *Belliolum* and *Zygogynum* are included, along with *Drimys winteri* (Table II, Expt. 24) in the Winteraceae while *Liriodendron* (Table II, Expt. 22) and *Trochodendron* (Table II, Expt. 23) are placed in the Magnoliaceae and Trochodendraceae, respectively. The very marked difference in the chemical behavior of *Belliolum* and *Zygogynum*, as compared with *Drimys* and also with *Trochodendron* and *Liriodendron*, suggests that further work is necessary to clarify the classification of this group of plants.

Of marked interest concerning lignin structure are the many high yields of mixed aldehydes (ratio vanillin to syringaldehyde 1:3) obtained from angiosperms amounting to 51% of the Klason lignin in the case of silver maple. If, as suggested by one of us (H. H.), native maple lignin is derived essentially from a dimeric and polymeric mixture of oxyconiferyl and oxysyringyl alcohols, and assuming the dimer units are formed by the loss of a molecule of water, the above percentage in terms of these anhydropropylphenol building units would amount to approximately 61%. This provides substantial support for the view that native maple lignin is derived *entirely* from propylphenol building units, the variations in yield between the different species being due to variations in the amounts of the polymeric forms present.

(25) Bower and Cooke, *ibid.*, 15, 290 (1943).

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The very marked parallelism between the red color obtained on testing with the Mäule reagent and the definitely proven presence of the syringyl radical indicates the possibility of using the oxidation technique as a chemical means for checking taxonomic classification.[26]

Acknowledgment.—The authors wish to thank the numerous friends who so kindly provided much of the plant material used in this investigation and to express their appreciation of the valuable assistance rendered by Miss Jean Rosten in the preparation and analysis of the wood samples. One of us (R. H. J. C.) also desires to thank the Canadian Pulp and Paper Association for their financial assistance.

Summary

1. Alkaline nitrobenzene oxidation of forty-seven widely varying accepted forms of gymnosperms and angiosperms has shown that in practically all cases the former yield only vanillin, while the latter give both vanillin and syringaldehyde. This confirms the earlier findings of Hibbert and co-workers.

2. The yields of vanillin, in the case of the gymnosperms, vary between 15 and 24%, based on the Klason lignin. With the angiosperms the combined yield of vanillin and syringaldehyde amounts to 35–51%, the ratio of the former to the latter being approximately 1:3.

3. Considering the highest combined aldehyde yield (silver maple 51%) obtained, this amounts to 61% of the Klason lignin based on the assumption that the native maple lignin is derived essentially from a mixture of anhydro polymeric forms of coniferyl and syringyl alcohols.

4. Exceptions to the above ratio (1:3) of mixed aldehydes were found in the case of certain primitive angiosperms characterized by the absence of vessels, the ratio in this case being 1:1.

5. All genera of the *Gnetales* (a group of uncertain position) gave both vanillin and syringaldehyde on oxidation, a result in harmony with their high lignin and methoxyl values and behavior with the Mäule reagent. Their relationship to the angiosperms rather than to the gymnosperms is thus indicated.

6. Only a very few members of the *Coniferales* were found to yield, on oxidation, an aldehyde mixture containing *both* vanillin and syringaldehyde and to give a definite Mäule reaction.

7. The behavior on oxidation of all the plants investigated is in complete agreement with their color reaction (or its absence) when tested with the Mäule reagent, and thus offers a new chemical procedure for taxonomic classification.

(26) It is the authors' intention to isolate the red coloring matter obtained by treatment of angiosperms with the Mäule reagent with the object of establishing therein the presence of the syringyl nucleus.

MONTREAL, CANADA RECEIVED OCTOBER 20, 1943

[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, McGILL UNIVERSITY]

Studies on Lignin and Related Compounds. LXXVI. Alkaline Nitrobenzene Oxidation of Corn Stalks. Isolation of *p*-Hydroxybenzaldehyde

BY R. H. J. CREIGHTON[1] AND HAROLD HIBBERT

Alkaline nitrobenzene oxidation of a wide variety of woods[2] has been shown to give high yields of vanillin from gymnosperms and of a mixture of vanillin and syringaldehyde from dicotyledons.

Certain monocotyledons, notably corn (cobs and stalks), bamboo and rye straw, yielded, in addition to vanillin and syringaldehyde, a non-methoxylated carbonyl derivative which could not be separated from vanillin by sublimation. The absence of methoxyl was indicated in the much lower values found for the crude *m*-nitrobenzoylhydrazones derived from the bisulfite fraction[2] isolated from the oxidation products.

The bisulfite fraction from the nitrobenzene oxidation of corn stalks has been reinvestigated and a separation of the unknown product from vanillin effected, based on solubility differences

(1) This paper represents part of a thesis presented by R. H. J. Creighton to the Faculty of Graduate Studies and Research, McGill University, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, May, 1943.

(2) Creighton, Gibbs and Hibbert, THIS JOURNAL, 66, 32 (1944).

TABLE I

METHOXYL ANALYSES OF CRUDE *m*-NITROBENZOYL HYDRAZONES FROM THE BISULFITE FRACTION ISOLATED FROM THE ALKALINE NITROBENZENE OXIDATION PRODUCTS OF MONOCOTYLEDONS

Material	OCH_3 %
Dracaena sp. (stem)	14.5
Aloe abyssinica (stem)	14.3
Bamboo (unidentified) (stem)	10.8
Zea mays L. (Corn cobs)	5.5
Zea mays L. (Corn stalks)	7.5
Secale cereale L. (Rye straw)	12.1
Saccarhum officinarum L. (Sugar cane stem)	14.0
Dicotyledons (average 6 woods)	14.8
Quercus (Oak)	15.3
Populus (Aspen)	14.7
Juglans (Walnut)	15.0
Tilia (Basswood)	13.8
Robinia (pseudacacia) (Black Locust)	14.6
Liriodendron tulipifera (Yellow poplar)	15.6
Vanillin	9.8

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in cold benzene. The non-methoxyl-containing constituent has been identified as *p*-hydroxybenzaldehyde. The yields of the three aldehydes obtained in the oxidation of corn stalks are summarized in Table II.

TABLE II

SUMMARY OF YIELDS FROM THE ALKALINE NITROBENZENE OXIDATION OF CORN STALKS

Fraction	Crude product % Klason lignin	Recrystallized product % Klason lignin
Total aldehydes determined as *m*-nitrobenzoylhydrazones	18.7	
Crude bisulfite soluble oils	16.7	
Total distillable oils	10.3	
Vanillin	5.3	4.5
p-Hydroxybenzaldehyde	1.8	1.4
Syringaldehyde	3.2	2.6

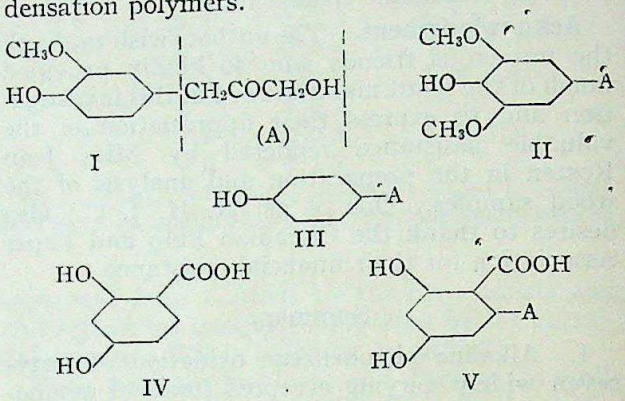
The presence of the *p*-oxyphenylmethane (—O—C_6H_4—C—) grouping in corn cob lignin has been shown previously by Phillips and Goss[3] who isolated anisic acid from the oxidation products of a methylated alkali corn-cob lignin, but obtained only oxalic acid from the unmethylated lignin. Phillips[4] also claims to have obtained anisic acid by permanganate oxidation of a fraction isolated from the dry distillation of an alkali corn cob lignin, presumably unmethylated. It seems likely that one of the products obtained in this same investigation, and characterized by them as a dimethoxycarboxylic acid, $C_8H_6O_2(OCH_3)_2$, was in reality acetosyringone, this having the same empirical composition and melting point, 120.5–121.5°.[5]

The experimental results may provide a means of distinguishing between mono- and dicotyledons. Substantial experimental evidence has been obtained by Hibbert and co-workers to show that the lignin complex in gymnosperms is derived from I; that in angiosperms from I and II.

It is possible that all monocotyledons may contain, in addition to lignins derived from I and II, a new type derived from III, oxidation of which would give *p*-hydroxybenzaldehyde.

On the other hand Raistrick's metabolic products obtained by the action of molds (*Penicillium brevi-compactum*) on glucose as sole substrate[6] contain the aromatic nucleus IV and presumably are also stabilized end products arising from V, the —COOH group being introduced as a secondary type reaction.

A common feature of all plants would seem to consist in their ability to synthesize metabolic products containing a similarly-functioning propyl side-chain (A) attached to a varying type of aromatic phenol unit. The products I, II, III, V, etc., may exist as such or in the form of condensation polymers.



Experimental

Corn-stalk meal (previously extracted successively with ethanol–benzene, ethanol and hot water) (50.0 g. containing 10.0 g. of Klason lignin), nitrobenzene (30 cc.) and aqueous sodium hydroxide (600 cc. of 2 *N*) were heated for three hours at 160° with vigorous agitation as outlined in the previous paper[2]; yield of crude bisulfite soluble oils, 1.503 g.

Separation of Syringaldehyde.—The crude oil (1.503 g.) on distillation yielded two crystalline fractions; (1) b. p. 130–160° (0.2 mm.); 0.825 g.; OCH_3 (of different portions) 12–17%; (2) b. p. 210–230° (0.25 mm.); 0.284 g. The second fraction was recrystallized from water and gave syringaldehyde; m. p. 110–112°; no mixed melting point depression.

Isolation of Vanillin and *p*-Hydroxybenzaldehyde.—Fraction (1) (0.825 g.) was mixed with 10 cc. of dry benzene and stirred for one hour at 20°, the mixture then centrifuged, the benzene-soluble portion evaporated to dryness and re-treated similarly with a further 5 cc. of benzene. The final benzene-soluble fraction left after the second treatment was recrystallized from water, and gave 0.451 g. of pure vanillin; m. p. 81–82°.

The benzene-insoluble fractions from the two treatments were combined, and recrystallized from water; yield, 0.126 g.; white crystalline product, m. p. 116–117°. A mixed melting point with *p*-hydroxybenzaldehyde showed no depression, as was also the case with the phenylhydrazones.

Summary

Oxidation of corn stalks by nitrobenzene and alkali gives, as actual pure products, vanillin, syringaldehyde and *p*-hydroxybenzaldehyde in yields of 4.5, 2.6 and 1.4%, respectively, based on the Klason lignin content of the corn stalks, the crude yields being 5.3, 3.2 and 1.8%, respectively.

This represents the first isolation of *free p*-hydroxybenzaldehyde from lignin. Its presence may serve as a distinguishing characteristic between the mono- and dicotyledons.

MONTREAL, CANADA RECEIVED AUGUST 20, 1943

(3) Phillips and Goss, THIS JOURNAL, **55**, 3466 (1933).
(4) Phillips and Goss, *Ind. Eng. Chem.*, **24**, 1436 (1932).
(5) Leger and Hibbert, THIS JOURNAL, **60**, 565 (1938).
(6) Oxford and Raistrick, *Biochem. J.*, **27**, 634, 1473 (1933).

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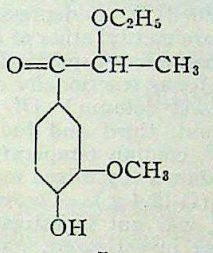
[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

Studies on Lignin and Related Compounds. LXXVII. Re-investigation of the Ethanolysis Products of Maple Wood

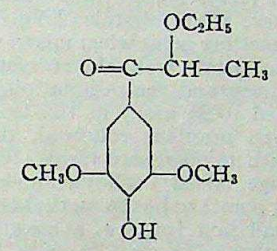
BY MARSHALL KULKA, HERBERT E. FISHER, SAMUEL B. BAKER AND HAROLD HIBBERT

Treatment of maple wood with a 2% solution of hydrogen chloride in ethanol yields around 25–30% of the lignin as a mixture of water-soluble, largely monomeric, propylphenol derivatives (termed ethanolysis oils) which are separable into bisulfite-soluble, alkali-soluble and neutral fractions.[1] The alkali-soluble fraction[2] consists of α-ethoxypropiovanillone [2-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone] (I) and α-ethoxypropiosyringone [2-ethoxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanone] (II). The amount of these two compounds isolated (approximately 5% based on the Klason lignin present in the original wood) constituted only about a third of the total alkali-soluble fraction of the ethanolysis oils.



I

2-Ethoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone



II

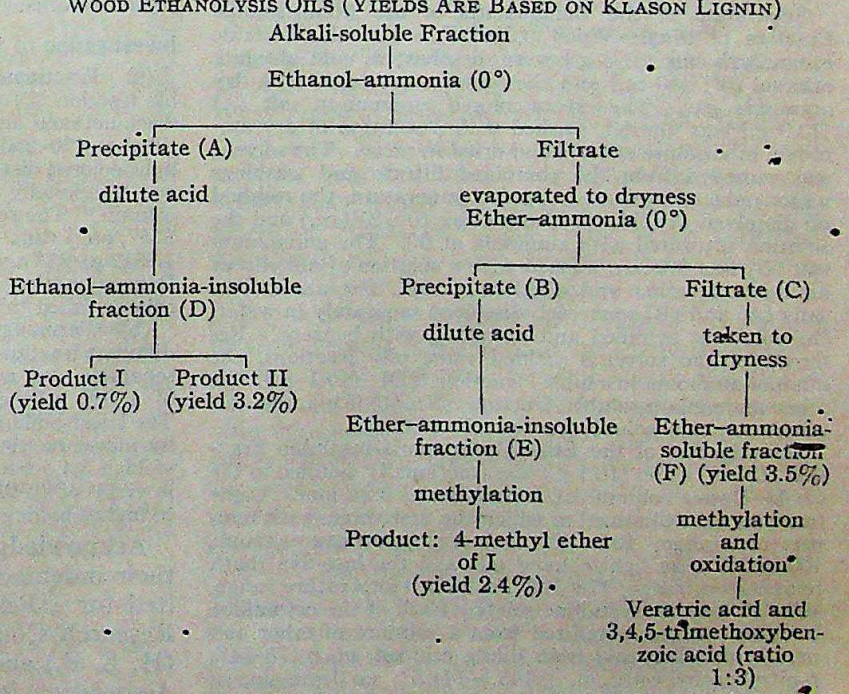
2-Ethoxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanone

The purpose of this re-investigation was to separate the components more completely and to identify the unknown components. While (I) and (II) have been isolated in increased yield (3.1 and 3.2%, respectively, based on the Klason lignin present in the original maple wood), due to the complexity of the remaining material no other components could be identified. The improved technique adopted provides a method applicable to a wide variety of plant products and is outlined in Chart I. Fraction D on rectification gave 2-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone (I) and 2-ethoxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanone (II) in yields of 0.7 and 3.2%, respectively.[3] The latter (II), previously isolated as a liquid, was now obtained as a light-colored crystalline compound. Since fraction E decomposes on distillation it was methylated with diazomethane, then fractionally distilled and heterogeneous fractions refractionated in a smaller column. The "crystalline fractions" isolated were identified as the methyl ether of (I) and represented 2.4% based on the Klason lignin present in the original wood.

An investigation of the ether-ammonia-soluble fraction (F) (methoxyl value 15.1%; ethoxyl value 22.8%) showed that only about one-half was precipitable as the 2,4-dinitrophenylhydrazone. This had an indefinite melting point and could not be purified by recrystallization; no other crystalline derivative could be isolated. The product (F) was not readily distillable at low pressures (0.001 mm.) but treatment with diazomethane gave a distillable methylated product from which, however, no pure products could be prepared. Attempts to effect a fractionation of (F) into homogeneous carbonyl- and non-carbonyl-containing fractions by oximation[4] followed by extraction with 10%

CHART I

SEPARATION OF COMPONENTS OF THE ALKALI-SOLUBLE FRACTION OF MAPLE WOOD ETHANOLYSIS OILS (YIELDS ARE BASED ON KLASON LIGNIN)



(1) West, MacGregor, Evans, Levi and Hibbert, THIS JOURNAL, 65, 1176 (1943).

(2) Hunter, Cramer and Hibbert, *ibid.*, 61, 516 (1939).

(3) All yields are based on the amount of Klason lignin present in the original wood.

(4) Bryant and Smith, THIS JOURNAL, 57, 57 (1935).

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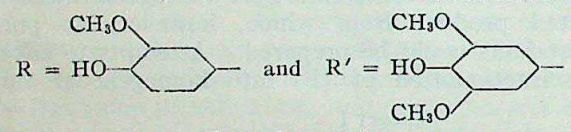
sodium hydroxide were unsuccessful. However, potassium permanganate oxidation of the methylated product (F) proved its aromatic nature and that its components contain the 3,4-dimethoxyphenyl- and 3,4,5-trimethoxyphenyl- nuclei.

The compounds isolated from the ethanolysis products to date and their yields are summarized in Table I.

TABLE I

COMPONENTS OF THE WATER-SOLUBLE ETHANOLYSIS OILS OF MAPLE WOOD

	Compound isolated	Wt. from 1000 g. of maple wood, g.	% based on Klason lignin
1.	R—CO—CH(OEt)—CH_3 (I)	6.2	3.1
2.	R′—CO—CH(OEt)—CH_3 (II)	6.4	3.2
3.	R—CO—CO—CH_3[5]	1.3	0.6
4.	R′—CO—CO—CH_3[5]	3.8	1.9
5.	R—CHO[6]	0.2	0.1
6.	R′—CHO[6]	1.3	0.6
7.	R—CH_2—CO—CH_3[6]	0.1	0.05
8.	R′—CH_2—CO—CH_3[6]	0.4	0.2
	Total identified products		9.75
9.	Unidentified but containing R and R′ nuclei	7.0	3.5
			Total 13.25



Experimental

Separation of the Components of the Alkali-soluble Fraction of Maple Wood (Chart I).—The alkali-soluble ethanolysis oils (31.6 g.) were dissolved in cold absolute ethanol (0°, 450 cc.) and the solution saturated with dry ammonia gas. The cream-colored ammonium salt (A) (10.9 g.) was filtered, washed with a solution of dry ammonia in absolute ethanol and dried *in vacuo*. The solvent was removed from the combined filtrate and washings under reduced pressure at room temperature, the residual oil dissolved in cold anhydrous ether (0°, 250 cc.) and the solution saturated with ammonia at 0°. The ammonium salt (B) was filtered, washed with a solution of anhydrous ammonia in ether and dried *in vacuo*. The ammonium salts (A) and (B) were each dissolved separately in water, the solutions acidified and extracted with benzene. Removal of the solvents yielded three oily fractions, the ethanol-ammonia-insoluble fraction (D) (10.1 g.), the ether-ammonia-insoluble fraction (E) (13.0 g.) and the ether-ammonia-soluble fraction (F) (7.0 g.).

Investigation of the Ethanol–Ammonia-insoluble Fraction (D).—The oil (10.1 g.) was fractionally distilled in the Cooke–Bower column[7] at a pressure of 0.25 mm. Eight fractions were obtained of which the first three (bath temperature range, 161–172°, column temperature range, 100–105°) were light-colored oils and the last five (bath temperature range, 178–193°, column temperature range, 107–112°) were crystalline solids. Each of the crystalline fractions was recrystallized from a mixture of ether and petroleum ether, and from dilute ethanol, m. p. 73–74°; *p*-nitrobenzoyl ester, m. p. 143.5–144.5°; no depression in melting point when mixed with the *p*-nitrobenzoyl ester of 2-ethoxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanone (II). The first three oily fractions were each again fractionally distilled from a smaller fractionating column (five plates), the resulting fractions methylated with diazomethane and the methylated products recrystallized from petroleum ether, m. p. 80–81°; no depression in melting point when mixed with the methyl ether of 2-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone (I). The amounts of each of the components found present in the ethanol-ammonia-insoluble fraction (D) were (I), 1.30 g.; (II), 6.35 g.; unidentified, 0.95 g.

Investigation of the Ether–Ammonia-insoluble Fraction (E).—The oil (E) (13.0 g.) was methylated with diazomethane and to insure complete reaction the non-methylated material was extracted with 5% sodium hydroxide and remethylated. The total methylated product was distilled and yielded two fractions, the first at bath temperature 150–200° (0.05 mm.) (8.6 g.) and the second at bath temperature 200–260° (0.025 mm.) (1.1 g.). The second fraction, a resinous oil, was not investigated further. The first fraction solidified on scratching the container and was recrystallized from a mixture of ether and petroleum ether; white crystals (2.5 g., m. p. 80–81°); no depression in melting point when mixed with pure methyl ether of (I). The filtrate from the recrystallization was evaporated to dryness and the residual oil (6.1 g.) was fractionally distilled (0.25 mm.) in the Cooke-Bower column.[7] Of the seven fractions collected, the second, third and fourth (bath temperature range, 168–180°, column temperature range, 90–92°) solidified and were shown (by mixed melting point) to be the methyl ether of (I) (2.4 g.). The very small first fraction, a colorless oil, was not investigated further. The last fraction, also not investigated, was a high-boiling resinous material probably dimeric or polymeric in type. The fifth and sixth fractions were combined and refractionated in a smaller column. The resulting fractions were of uniform composition ($n^{25}D$ 1.5200; alkoxyl (calcd. as methoxyl), 44.3%), but the 2,4-dinitrophenylhydrazone could not be purified by recrystallization and no other crystalline derivative could be isolated. The amounts of the components of the ether–ammonia–insoluble fraction (E) present were: (I), 4.9 g. (isolated as the pure methyl ether); unidentified, 3.8 g.; the remainder decomposed during fractionation.

Investigation of the Ether–Ammonia-soluble Fraction (F)

(a) **Fractional Distillation.**—The ether–ammonia-soluble fraction (F) (7.0 g.) was methylated completely with diazomethane and the methylated product (6.86 g.) distilled at 160–250° bath temperature (0.25 mm.); yield of light-colored distillate, 4.95 g. or 71%. This distillate (F′) was fractionally distilled (0.25 mm.) in the Cooke–Bower column.[7] The refractive indices of the fractions (F″, F‴, F⁗, etc.) thus obtained varied from 1.5200 to 1.5098 to 1.5312 at 25° and the alkoxyl values from 36.0 to 45.8%. Refractionation of several of these fractions in a smaller column failed to yield products of uniform composition.

(b) **Permanganate Oxidation.**—Portions (0.3 g.) of the different fractions F′, F″, F‴, etc., obtained in the above separation (a) were oxidized at 90–100° by slow addition of a 3% solution of potassium permanganate (50 cc.). The lower-boiling fractions yielded veratric acid (identified by mixed melting point) and the higher-boiling fractions yielded 3,4,5-trimethoxybenzoic acid (similarly identified) in yields of 20–25% by weight. The ratio of lower-boiling to higher-boiling material was approximately 1 to 3.

Acknowledgments.—The authors acknowledge their indebtedness to Canadian Industries Limited for a Fellowship (M. K.), to the National Research Council of Canada for a Studentship (H. E. F.) and to the Canadian Pulp and Paper Association for a Scholarship (S. B. B.).

Summary

1. The alkali-soluble fraction of the water-soluble lignin ethanolysis oils of maple wood has been re-investigated and the yields of its

(5) Kulka, Hawkins and Hibbert, THIS JOURNAL, 63, 2371 (1941).
(6) Kulka and Hibbert, *ibid.*, 65, 1180 (1943).
(7) Bower and Cooke, *Ind. Eng. Chem., Anal. Ed.*, 16, 290 (1943).

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known components, 2-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone and 2-ethoxy-1-(4-hydroxy - 3,5 - dimethoxyphenyl) - 1 - propanone have been increased to 3.1% and 3.2%, respectively, based on the Klason lignin present in the original wood.

2. 2-Ethoxy-1-(4-hydroxy-3,5-dimethoxyphenyl-1-propanone previously reported as being a liquid was isolated in pure form and found to be a well-defined crystalline solid.

3. The material left after removal of the two known components from the alkali-soluble fraction of the ethanolysis oils was found to be a complex mixture, inseparable by fractional distillation, the methylated product containing the 3,4-dimethoxyphenyl- and 3,4,5-trimethoxyphenyl- nuclei in the ratio of 1 to 3.

4. A summary of the work on ethanolysis of maple wood shows that the yield of *pure* compounds isolated was 9.8% of the Klason lignin present in the original wood. In view of the experimental difficulties involved in their separation and isolation this percentage represents a very conservative figure, the *actual* value undoubtedly being appreciably higher.

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[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

Studies on Lignin and Related Compounds. LXXVIII. Chromic Acid Oxidation of Lignin-type Substances, Wood Ethanolysis Products and Wood[1]

BY W. S. MACGREGOR, T. H. EVANS AND HAROLD HIBBERT

The importance in lignin chemistry of propylphenol (C_6—C—C—C) units related to coniferyl alcohol is evident from recent reviews on the subject.[2] This is exemplified in the isolation of a considerable amount of wood lignin as hydroxylated propylcyclohexane derivatives from the hydrogenation products of wood;[3] in the isolation from spruce wood ethanolysis products of 2 - ethoxy - 1 - (4 - hydroxy - 3 - methoxyphenyl)-1 - propanone[4] (I), 1 - (4 - hydroxy - 3 - methoxyphenyl)-1,2-propanedione[5] (II), 1-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-2-propanone[6] (III), 1-(4-hydroxy-3-methoxyphenyl)-2-propanone[7] (IV) and, in addition to these, the 4-hydroxy-3,5-dimethoxyphenyl analogs of I, II and IV from maple wood.

Theories concerning the mode of linkage of the propylphenol building-units in native lignin[2,8] are represented on the one hand by the Freudenberg[2a,8] postulate of spruce lignin as a mixture of polymers of the dehydrodiisoeugenol type and, on the other, by Hibbert's theory[2d,8] of native lignins as a series of polymers of dehydrodi-(oxyconiferyl alcohol) [dehydrodi-(β,γ-dioxyisoeugenol)] and dehydrodi-(oxysyringyl alcohol). Freudenberg's polymers are characterized by the presence of terminal methyl groups in the propyl side chains, while in Hibbert's the terminal groups are either primary alcohol groups or ether linkages —O—CH_2—O—, methyl groups being absent. Upon cleavage of these latter types of polymers the side chains would become free to rearrange from the labile —CH_2—$COCH_2OH$ form to the more stable configurations isolated (I-IV). The actual presence of terminal carbinol groups, or end —CH_2—O—CH_2— linkages in native lignin, is proven by the isolation of 1-(4-hydroxycyclohexyl)-3-propanol[3a,3b] and of 1-cyclohexyl-3-propanol[3c] upon hydrogenation of wood. Further, the ease with which the postulated rearrangements of RCH_2COCH_2OH to units I-IV (the latter characterized by the presence of terminal methyl groups)[8] are known to occur also forms supporting evidence for the views of Hibbert[2d,8] that these latter represent stabilized end-products formed from the more reactive R—CH_2COCH_2OH type.

By oxidizing organic substances containing methyl groups with hot, concentrated, aqueous chromic acid and simultaneous steam distillation of the acetic acid formed, Kuhn and l'Orsa[9] were able to account for the total carbon in many compounds as carbon dioxide, or as acetic acid, the yield of the latter being above 85% of theoretical for many structures containing methyl groups, such as CH_3COCH_2—, $CH_3CHOHCH$-OH—, CH_3CH_2O—, and CH_3CH=CH—. Freudenberg[10] oxidized spruce "cuproxam lignin" by the same method and obtained a 6% yield of acetic acid. This low yield, amounting to only twenty per cent. of that theoretically obtainable from his structural lignin polymer,[2a,8] was regarded by him as due to the inadequacy of the experimental technique employed.

(1) This paper represents part of a thesis submitted to the Faculty of Graduate Studies and Research, McGill University, by Warren S. MacGregor, in partial fulfillment of the requirements for the degree of Doctor of Philosophy, May, 1943.

(2) (a) Freudenberg, *Ann. Rev. Biochem.*, **8**, 88 (1939); (b) Erdtman, *Svensk. Papperstidn.*, **44**, 243 (1941); (c) Hibbert, *Paper Trade J.*, **113**, No. 4, 35 (1941); (d) Hibbert, *Ann. Rev. Biochem.*, **11**, 183 (1942); (e) *Chem. Soc. London, Ann. Reports*, **39**, 142 (1943).

(3) (a) Harris, D'Ianni and Adkins, THIS JOURNAL, **60**, 1467 (1938); (b) Godard, McCarthy and Hibbert, *ibid.*, **63**, 3061 (1941); (c) Bower, Cooke and Hibbert, *ibid.*, **65**, 1192 (1943).

(4) Cramer, Hunter and Hibbert, *ibid.*, **61**, 509 (1939).

(5) Kulka, Hawkins and Hibbert, *ibid.*, **63**, 2371 (1941).

(6) West, MacInnes and Hibbert, *ibid.*, **65**, 1187 (1943).

(7) Kulka and Hibbert, *ibid.*, **65**, 1185 (1943).

(8) Eastham, Fisher, Kulka and Hibbert, *ibid.*, **66**, 26 (1944).

(9) Kuhn and l'Orsa, *Z. angew. Chem.*, **44**, 847 (1931).

(10) Freudenberg, *Ber.*, **66**, 262 (1933).

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In the present investigation the chromic acid oxidation technique has been applied to lignin-type substances, wood ethanolysis products, extracted lignins and woods, in order to obtain further information concerning the structures of native and isolated lignins, and especially to determine the amount of terminal methyl groups present, if any, in the two latter.

TABLE I

OXIDATION OF LIGNIN BUILDING UNITS AND RELATED COMPOUNDS

(R) = (4-hydroxy-3-methoxyphenyl)

Expt.	Substance	Acetic acid % obtained	Acetic acid % of theory
1	Isoeugenol	30.9 28.6	84 78
2	Dehydrodiisoeugenol	31.7 30.9	86 84
3	1-(R)-propane	31.2	85
4	1-(R)-2-propanone	29.8 29.5	90 89
5	1-(3,4-Dimethoxyphenyl)-1-propanone	30.4	97
6	2-Hydroxy-1-(R)-1-propanone	28.4 25.6	93 84
7	2-Ethoxy-1-(R)-1-propanone	50.2 48.8	94 91
8	3-Ethoxy-1-(R)-1-propanone	23.1	87
9	1-(R)-1,2-propanedione	28.0 29.2	92 96
10	Semicarbazone of 2-ethoxy-1-(R)-1-propanone	39.6	93
11	Semicarbazone of 1-ethoxy-1-(R)-2-propanone	40.5	95
12	3-Hydroxy-1-(R)-1-propanone	0.7 0.4	.. ..
13	1-(R)-2,3-propanediol	0.7	..
14	Eugenol	0.6	..
15	Vanillin semicarbazone	0.5	..
16	Acetovanillone	33.2 32.9	92 91
17	2-(3,4-Dimethoxyphenyl)-2-propanol	11.1 13.6	36 44
18	Acetophenone[9]		10

As shown in Table I, oxidation with chromic acid of (4-hydroxy-3-methoxyphenyl)-propane derivatives containing a terminal methyl group (Expts. 1–9) yields, in agreement with the observations of Kuhn and l'Orsa,[9] at least 80% of the theoretical amount of acetic acid. The ethoxyl group is also oxidized practically quantitatively to acetic acid (Expts. 7, 8, 10 and 11). Where the terminal methyl group either is replaced by carbinol (Expts. 12 and 13) or is absent (Expts. 14 and 15) no acetic acid is obtained. The procedure is therefore suitable for the detection of terminal methyl groups in lignin-type compounds.

The effect of aromatic ring stability on yield of acetic acid is shown clearly in Expts. 16, 17 and 18 where, in each case, the methyl group is attached to a carbon atom in the position α to the ring. Where the ring is *stable* (Expt. 18), oxidation results in formation of aromatic carboxylic acids in good yield with accompanying oxidation of the methyl group to carbon dioxide and water. However, as the stability of the ring *decreases* (Expts. 16 and 17) oxidation is accompanied by ring opening permitting of cleavage and formation of acetic acid.

With the remaining products of Table I, the methyl group (where present) is part of the skeletal form $R-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-$, the methyl group being attached to a carbon atom in the position β to the ring. Since the tendency to cleave is through the α position (carboxylic acid formation) the yield of acetic acid will be high even in the case of $R-CH_2-CH_2-CH_3$.

The acetic acid yield from similarly situated methyl groups appears to be the same irrespective of whether the structure be mono- or polymolecular. This is evidenced in the high yield of acetic acid from dehydrodiisoeugenol (Table I, Expt. 2), the yield in this case being enhanced by the labilizing effect of the phenolic hydroxyl group (that is, oxidation of dehydrodiisoeugenol parallels that of acetovanillone). On the other hand, it is to be expected that this same effect will be inhibited in a chain polymer of the dehydrodiisoeugenol type due to the phenolic ether linkages (with the exception of the methyl group attached to the terminal member) so that yields of 40–50% of theoretical are to be anticipated (*cf.* Table I, Expt. 17). On this basis a polymer of the Freudenberg type V should give at least 40–50% of the theoretical amount of acetic acid, or approximately twice the amount found by Freudenberg, and it is very likely that the acetic acid obtained in his experiment originated solely from methyl groups on terminal units.

When spruce and maple woods (previously extracted successively with benzene–alcohol and water) were oxidized (Table II, Expts. 4 and 5), the acetic acid obtained was that due solely to the ester acetyl groups. Thus native lignin in these woods contains only a small percentage (if any) of end methyl groups. Cellulose and holocelluloses (Expts. 1, 2 and 3) gave no acetic acid other than that from the acetyl groups present.

The yields of acetic acid from the lignin ethanolysis products from spruce and maple woods were determined in similar fashion (Table II, Expts. 6, 7, 8, 9, 10). The low molecular weight lignin water-soluble ethanolysis oils from these two woods yielded 7.3 and 10.8% acetic acid, respectively, in excess of that arising from the introduced ethoxyl groups (Table II, Expts. 7 and 10). By chemical fractionation of the same oils, methyl-containing C_6-C_3 units have been isolated in quantity sufficient to account for 68% of the acetic acid from the spruce ethanolysis

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TABLE II

OXIDATION OF WOODS AND ISOLATED LIGNIN FRACTIONS

Expt.	Substance	Klason lignin, %	Ethoxyl, %	Methoxyl, %	% Acetic acid: Total obtained, %	From acetyl groups, %	From ethoxyl groups,[a] %	From lignin terminal methyl groups, %
1	Cellulose	0.0	..	..	0.05	0	0	..
2	Spruce holocellulose	0.0	..	..	2.2	2.4	0	..
3	Maple holocellulose	0.0	..	..	4.9	5.4	0	..
4	Spruce wood	27.9	..	..	2.4 2.3 2.2	2.6	0	..
5	Maple wood	21.0	..	..	6.4 5.5 5.3	5.6	0	..
6	Spruce water-insoluble ethanol lignin[b]	..	11.0	14.1	20.7 19.7	...	13.6	6.6
7	Spruce water-soluble ethanolysis oils[b]	..	20.7	8.6	32.7 33.3	...	25.7	7.3
8	Maple ether-insoluble ethanol lignin[b]	..	9.1	19.2	10.3 10.8	...	11.3	..
9	Maple ether-soluble ethanol lignin[b]	..	13.2	17.8	16.9 15.7 16.7	...	16.4	..
10	Maple water-soluble ethanolysis oils[b]	..	12.5	18.4	25.2 27.3	...	15.5	10.8

[a] 93% of theoretical (*cf.* Table I). [b] Fractions designated as in previous communication, Pt. LXVI, THIS JOURNAL, 65, 1176 (1943).

TABLE III

YIELD OF ACETIC ACID DERIVED FROM MONOMOLECULAR COMPOUNDS ISOLATED FROM ETHANOLYSIS OILS

Substance	Percentage of total oil	Calcd. yield[a] of acetic acid, %	Calcd. yield[b] of acetic acid from end methyl groups, %
Spruce ethanolysis oils			
2-Ethoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone	14.7	7.3	3.6
1-Ethoxy-1-(4-hydroxy-3-methoxyphenyl)-2-propanone	4.3	2.1	1.0
1-(4-Hydroxy-3-methoxyphenyl)-1,2-propanedione	1.4	0.4	0.4
1-(4-Hydroxy-3-methoxyphenyl)-2-propanone	0.12	0.04	0.04
Total	20.5	9.8	5.0
Maple ethanolysis oils			
2-Ethoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone	11.8	5.9	2.9
2-Ethoxy-1-(4-hydroxy-3,5-dimethoxyphenyl)-1-propanone	8.5	3.7	1.8
1-(4-Hydroxy-3-methoxyphenyl)-1,2-propanedione + 1-(4-Hydroxy-3,5-dimethoxyphenyl)-1,2-propanedione	8.3	2.1	2.1
1-(4-Hydroxy-3,5-dimethoxyphenyl)-2-propanone	0.6	0.1	0.1
1-(4-Hydroxy-3-methoxyphenyl)-2-propanone	0.3	0.1	0.1
Total	29.5	11.9	7.0

[a] Calculated from the yields of acetic acid obtained upon oxidation of the pure compounds (Table I), *e. g.* 11.8 × 0.50 = 5.9. [b] The acetic acid (93% of theory) from ethoxyl groups has been deducted.

oils[4,5,6,7] (7.3 × 68/100 = 5.0) and 65% of that from the maple ethanolysis oils[11] (10.8 × 65/100 = 7.0) as shown in Table III. The acetic acid is therefore derived from these isolable units.

The oxidation of amorphous water-insoluble *spruce* and *maple* ethanol lignins varied markedly, in that the former gave a 6.6% yield of acetic acid, derived from terminal methyl groups (Table II, Expt. 6), while the acetic acid derived from the maple water-insoluble lignin fractions is entirely accounted for by ethoxyl groups present in these materials (Table II, Expts. 8 and 9), thus indicating a pronounced difference in structure between the two types. This was further emphasized by the fact that the water-soluble lignin ethanolysis oils from maple wood (Table II, Expt. 10) contained *all* of the constituents characterized by the presence of terminal methyl groups. Occasionally, due to variations in the ethanolysis reaction, cleavage of the native maple lignin polymers was not always complete and in one case a *water-insoluble* maple ethanol lignin fraction yielded, upon oxidation, 1.5% of acetic acid from terminal methyl groups.

Re-ethanolysis of an ether-soluble spruce lignin fraction resulted in only a slight decrease in the methyl groups in the *recovered* petroleum ether-insoluble lignin as shown by the decrease in yield of acetic acid from 6.1 to 5.4% (Table IV). However, the oily, petroleum ether-soluble lignin fraction isolated simultaneously (amounting to 31% of the total re-ethanolysis products) yielded 16.1% acetic acid from terminal methyl groups on oxidation (Table IV). The effect of the re-ethanolysis treatment of the *ether-soluble* spruce ethanol lignin was to increase the yield of acetic acid from end methyl groups from 6.1 to 8.4% (see footnote, Table IV).

This actual formation of methyl groups during ethanolysis of spruce wood lignin is in accord with Hibbert's oxyconiferyl alcohol theory of lignin structure.[2d,8]

(11) Kulka, Fisher, Baker and Hibbert, THIS JOURNAL, 66, 39 (1944).

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TABLE IV

RE-ETHANOLYSIS OF ETHER-SOLUBLE SPRUCE ETHANOL LIGNIN

	Substance	Weight, g.	Acetic acid: Total obtained, %	Acetic acid: From ethoxyl groups, %	Acetic acid: From terminal methyl groups (by diff.), %	Acetic acid: From terminal methyl groups, g.	
I	Spruce ether-soluble ethanol lignin	9.7	22.8	16.7	6.1	0.59	
II	Petroleum ether-*insoluble* fraction from re-ethanolysis of I	6.4	17.6	12.2	5.4	0.35	0.82[a]
III	Petroleum ether-*soluble* fraction from re-ethanolysis of I	2.9	29.2	13.0	16.1	0.47	

[a] 0.82 g. acetic acid represents a combined yield of 8.4% based on the original weight (9.7 g.) of the ether-soluble spruce ethanol lignin.

Experimental

Preparation of Samples.—The wood samples were ground in a Wiley mill to 40-mesh, extracted forty-eight hours with 1:1 alcohol–benzene, twenty-four hours with alcohol, thoroughly washed with water, and dried under reduced pressure. The holocelluloses were prepared from the same wood samples by the procedure of Van Beckum and Ritter.[12] The ethanol lignin fractions were obtained by the standardized procedure used in these Laboratories.[13]

Oxidation.—The sample (0.2–0.5 g.) was placed in a 500-cc. flask fitted with dropping funnel, nitrogen inlet, and distillation outlet.[9] Twenty grams of chromium trioxide in 50 cc. of water was then introduced from the dropping funnel, and a slow stream of nitrogen (1 to 2 bubbles per second) passed through the reaction mixture. Heating in a wax-bath, maintained at 160°, was commenced and 25-cc. portions of water were added at half-hour intervals until all the acetic acid was removed (seven additions were generally sufficient). The distillate, which comprised a solution of acetic acid plus a small amount of acidity derived from chromic acid, was transferred to an Erlenmeyer flask, boiled to remove dissolved carbon dioxide, and titrated with 0.1 *N* sodium hydroxide.

In each analysis the "corrected value" for acetic acid in the distillate was determined as follows: Two cc. excess 0.1 *N* alkali was added to the titrated solution and the solution concentrated to 2 to 4 cc. The acetate in the solution was then determined by the method of Clark.[14] This latter value for acetic acid is recorded in the tables. Blank determinations showed an acidity equivalent to 0.2 cc. of 0.1 *N* sodium hydroxide due to chromic acid.

In the oxidation of wood and holocelluloses 1 to 2 g. samples were taken and oxidized with a solution of 50 g. of chromium trioxide in 70 cc. of water.

Re-ethanolysis of Spruce Ethanol Lignin.—Spruce ether-soluble ethanol lignin (9.7 g.) dissolved in 350 cc. of 2% ethanolic hydrogen chloride was refluxed forty-eight hours in an atmosphere of carbon dioxide. The resulting solution was neutralized with the calculated amount of sodium bicarbonate, filtered and the filtrate concentrated under reduced pressure to 50 cc. This solution was then added in a fine stream to 1500 cc. of petroleum ether (b. p. 60–70°) with rapid stirring, and the amorphous precipitate removed by filtration, giving a brownish powder (6.4 g.). The petroleum ether filtrate was evaporated under reduced pressure, the residual oil dissolved in 25 cc. of benzene, and the benzene distilled to remove any adhering petroleum ether. The process was repeated and the residual oil brought to constant weight under reduced pressure at 70°, removal of the solvent being facilitated by bubbling carbon dioxide through the oil during this process. After a total evaporation time of twelve hours the material reached a constant weight of 3.9 g. The samples for analysis and oxidation were aliquots of this material. 71.2 mg. of this oil was dried thirty hours in an oven at 105°. The final weight was 52.6 mg.; the true yield of oil was, therefore, 2.9 g.

Acknowledgments.—The authors wish to acknowledge the grant of a bursary from the Canadian Pulp and Paper Association to one of them (W. S. M.) during the tenure of which this work was carried out.

Summary

1. Chromic acid oxidation of oxygenated side-chain phenylpropane derivatives related to lignin yielded 80 to 95% of the theoretical amount of acetic acid, thereby providing a method for the quantitative determination of

groupings in such products.

2. Oxidation of spruce and maple woods showed that the native lignin present in each wood contains no appreciable quantity of end methyl groups.

3. A difference between extracted, amorphous spruce and maple ethanol lignins was observed, in that the former was found to contain an appreciable quantity of —C—CH_3 groupings (one for each four or five C_6—C_3 units) whereas the latter contained few or no such groups.

4. Re-ethanolysis of spruce ethanol lignin effected an increase in the proportion of terminal methyl groups.

5. Strong experimental support is thus found for the theory of Hibbert that native lignin is characterized by the absence of terminal methyl groups and that their presence in extracted lignins is the result of intramolecular changes undergone by very reactive side chains such as are present in oxyconiferyl alcohol.

MONTREAL, CANADA RECEIVED AUGUST 20, 1943

(12) Van Beckum and Ritter, *Paper Trade J.*, **104**, 257 (1937).

(13) Patterson, West, Lovell, Hawkins and Hibbert, THIS JOURNAL, **63**, 2065 (1941).

(14) Clark, *Ind. Eng. Chem., Anal. Ed.*, **8**, 487 (1936).

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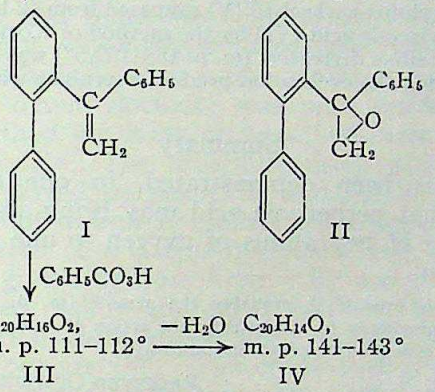
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DUKE UNIVERSITY]

The Anomalous Oxidation of an Ethylene Derivative by Perbenzoic Acid

BY CHARLES K. BRADSHER[1]

The classical reaction of an olefin with perbenzoic acid leads to the formation of an olefin oxide. So well established is this fact, that it forms the basis of a quantitative method for the estimation of olefin linkages.[2]

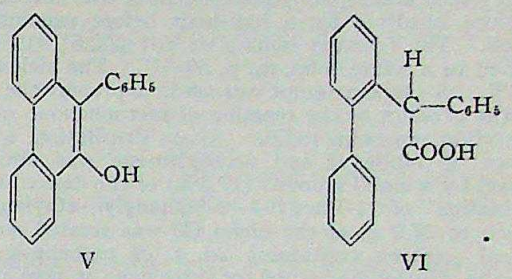
In connection with another problem, we attempted the preparation of the oxide (II) of 1-phenyl-1-(2-biphenylyl)-ethylene by perbenzoic acid oxidation of the corresponding olefin (I).



Despite the use of a 32% excess of the oxidizing agent, after three days standing at 0–10° the solution gave a negative test for perbenzoic acid.[3] Worked up in the usual way, there was obtained a quantity of crystals which, upon analysis, proved to be not the expected oxide, but a compound (III) which apparently contained two oxygen atoms. This "dioxide"[4] (III), upon heating with hydrobromic acid, sulfuric acid or potassium bisulfate, lost one molecule of water to yield a compound (IV) melting at 141–143°. When the dehydration product (IV) was refluxed with acetyl chloride, it gave a derivative melting some 20° higher.

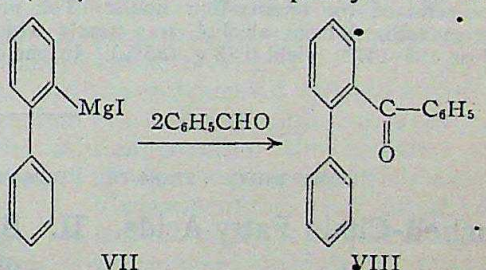
The properties and composition of the dehydration product (IV) correspond to those reported by Koelsch[5] for 9-phenylphenanthrol-10 (V) which he had synthesized by cyclization of the acid chloride of (2-biphenylyl)-phenylacetic acid (VI). A sample of the phenanthrol (V) prepared by Koelsch's directions was found to be identical with the dehydration product (IV) obtained from the "dioxide."

It should be pointed out that though (2-biphenylyl)-phenyl-acetic acid (VI) is isomeric, it



is not identical with the "dioxide" which has no acidic properties and which melts some 60° lower than the acid.

The olefin (I) used in the reaction was prepared from *o*-phenylbenzophenone[6] (VIII) by the action of methylmagnesium iodide essentially as described by Bergmann and Bondi.[7] The *o*-phenylbenzophenone has been prepared in a new way which makes possible the use of commercially available starting materials. The Grignard reagent (VII) from 2-iodobiphenyl was treated



with over two moles of benzaldehyde in benzene solution and the mixture refluxed overnight, resulting in a 69% yield of the desired ketone (VIII). This use of an excess of aldehyde as an oxidizing agent has been much investigated from a theoretical standpoint,[8] but has as yet found little synthetic application.[9]

Experimental

***o*-Phenylbenzophenone.**—A Grignard reagent was prepared from 56 g. of 2-iodobiphenyl and 4.86 g. of magnesium. A solution of 22 cc. of benzaldehyde in 40 cc. of benzene was added slowly. When addition was complete, two-thirds of the ether was distilled off and 100 cc. of benzene and 40 cc. of benzaldehyde added. The mixture was refluxed for twenty-two hours, after which it was decomposed by the addition of ammonium chloride solution. The ether–benzene layer was dried, concentrated, and the residue distilled under reduced pressure. The entire fraction boiling at 195–232° (19 mm.) was collected and crystallized from methyl alcohol giving 35.8 g. (69.5%)

(1) National Research Fellow (participating basis) 1941–1942.

(2) Nametkin and Brussoff, *J. prakt. Chem.*, **112**, 169 (1926).

(3) An earlier communication (Bradsher and Rapoport, THIS JOURNAL, **65**, 1646 (1943)) cited an example of an unsaturated hydrocarbon which reacted with more than the theoretical quantity of perbenzoic acid. This cannot be accounted for on the basis of the normal rate for the spontaneous decomposition of perbenzoic acid.

(4) In the use of the term "dioxide," we seek to imply nothing more than the composition of the product. We hope to make the structure of this compound the subject of a further investigation.

(5) Koelsch, THIS JOURNAL, **56**, 482 (1934).

(6) Schlenk and Bergmann, *Ann.*, **464**, 1, 34 (1928).

(7) Bergmann and Bondi, *Ber.*, **64**, 1455, 1476 (1931).

(8) *E. g.*, Marshall, *J. Chem. Soc.*, **105**, 527 (1914); **107**, 309 (1915); **127**, 2184 (1925); Meisenheimer, *Ann.*, **442**, 180 (1925); **446**, 76 (1926); Hess, *ibid.*, **437**, 256 (1924); Rheinholdt, *J. prakt. Chem.*, **109**, 175 (1925); Gomberg and Bachmann, THIS JOURNAL, **52**, 4967 (1930); Shankland and Gomberg, *ibid.*, **52**, 4973 (1930).

(9) A notable exception is to be found in the work of Bachmann, *ibid.*, **56**, 1363 (1934).

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of white crystals, m. p. 86–87°. This material was identical with a sample prepared from the nitrile by the method of Schlenk and Bergmann.[6]

1-Phenyl-1-(2-biphenylyl)-ethylene (I) was prepared as described by Bergmann and Bondi[7] with the exception that the product of the reaction between methylmagnesium iodide and *o*-phenylbenzophenone was heated with potassium bisulfate for a half-hour before vacuum distillation. The fraction boiling at 201–202.5° (12 mm.) solidified to a white solid, m. p. 59–61°. The yields were 56–73%. A single attempt was made to prepare the olefin from the product of the reaction of acetophenone with 2-biphenylylmagnesium iodide. Upon distillation, a large fore-run of biphenyl and acetophenone was obtained, followed by a small amount (17.5%) of the desired olefin.

Oxidation of 1-Phenyl-1-(2-biphenylyl)-ethylene.—A solution of 27.9 g. of the olefin (I) was treated with an ethereal solution containing 20 g. of perbenzoic acid. After the solution had stood for three days, it gave a negative test for excess oxidant. The solution was washed free of acid with sodium bicarbonate solution and dried over sodium sulfate. Upon concentration of the solution and addition of petroleum ether, 14 g. (46%) of nearly colorless crystals was obtained, m. p. 107–109°. An analytical sample was prepared by repeated recrystallization, m. p. 111–112°.

Anal. Calcd. for $C_{20}H_{16}O_2$: C, 83.32; H, 5.60. Found: C, 83.37; H, 5.68.

Dehydration of the "Dioxide" (III).—(a) By hydrobromic and acetic acids: one-half gram of the "dioxide" (III) was suspended in a boiling mixture containing 5 cc. of acetic and 5 cc. of 34% hydrobromic acids and the mixture refluxed for twenty-four hours. The product, once recrystallized from alcohol, was nearly white and melted at 139–141°; yield 0.33 g. (35%). In one case in which the "dioxide" had been heated previously for a few minutes at its boiling point (22 mm.) the yield was 56%.

(b) By the action of potassium bisulfate: one gram of the "dioxide" was heated at 170–180° for ten minutes with 2 g. of potassium bisulfate. The product was extracted with ether and recrystallized as above; yield 0.33 g. (35%).

(c) By the action of concentrated sulfuric acid: one-half gram of the "dioxide" was heated on the steam-bath for two minutes with 3 cc. of concentrated sulfuric acid. Poured into water and once recrystallized, it gave 0.30 g. (64%) of white needles, m. p. 141–143°.

The products obtained by all of these methods were shown to be identical by mixed melting point determinations.

Anal. Calcd. for $C_{20}H_{14}O$: C, 88.86; H, 5.22. Found: C, 88.94, 88.73; H, 5.30, 5.23.

The products were shown to be identical with a sample of 9-phenylphenanthrol-10 (V) prepared from (2-biphenylyl)-phenylacetic acid (VI) by the method of Koelsch.[5]

A crystalline derivative (m. p. 158–159.5°) was obtained by refluxing the cyclization product overnight with acetyl chloride.[10]

Summary

It has been demonstrated, in one case at least, that perbenzoic acid may bring about the addition of two atoms of oxygen to one mole of an olefin.

(10) This product is probably the acetate (m. p. 153–155°) prepared previously by Koelsch[5] by the action of acetic anhydride and sulfuric acid on 9-phenylphenanthrol-10.

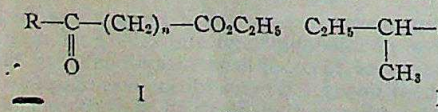
DURHAM, N. C. RECEIVED OCTOBER 4, 1943

[CONTRIBUTION FROM THE FURMAN CHEMICAL LABORATORY, VANDERBILT UNIVERSITY]

Branched-Chain Fatty Acids. II. Syntheses in the C_{19} and C_{25} Series. Preparation of Keto Esters

BY JAMES CASON AND FRANKLIN S. PROUT[1]

In continuation of the program of synthesizing methyloctadecanoic acids,[2] the 16-methyl isomer has been prepared by the general method used for synthesis of 17-methyloctadecanoic acid.[2] This procedure involves preparation of a keto ester (I) by reaction between a dialkylcadmium



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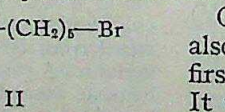

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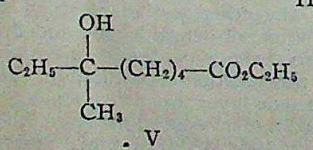

V

compound and an ω-carbethoxyalkoyl chloride, reduction of the keto ester by the Clemmensen method and hydrolysis of the reduced ester. For synthesis of 16-methyloctadecanoic acid the required alkyl halide is 1-bromo-6-methyloctane (II). This bromide has been prepared by Levene and Marker[3] from the corresponding alcohol which was obtained by reduction of ethyl 6-methyloctoate (IV). These workers prepared 6-methyloctoic acid[4] by extending the chain of 1-bromo-4-methylhexane by use of the malonic ester synthesis.

Our preparation of 1-bromo-6-methyloctane also utilizes ethyl 6-methyloctoate, which was first prepared by us as in the scheme shown. It was hoped that the small amount of isoamyl alcohol present in the *s*-butylcarbinol[5] used as starting material would not interfere with obtaining a pure product in the final stages of the synthesis; however, such was not the case. Reduction of the keto ester, III, by the Clemmensen method proved more difficult than reduction of the 7-methyl isomer[2]; therefore, the concentration of the undesired 7-methyl isomer, arising from isoamyl bromide, was considerably increased at this step. 16-Methyloctadecanoic

(1) Taken in part from the M.S. thesis of Franklin S. Prout.

(2) Cason, THIS JOURNAL, 64, 1106 (1942).

(3) Levene and Marker, *J. Biol. Chem.*, 103, 299 (1933).

(4) Levene and Marker, *ibid.*, 95, 153 (1932).

(5) Fractionated through a 3-foot packed column, b. p. 127.5–128.5°.

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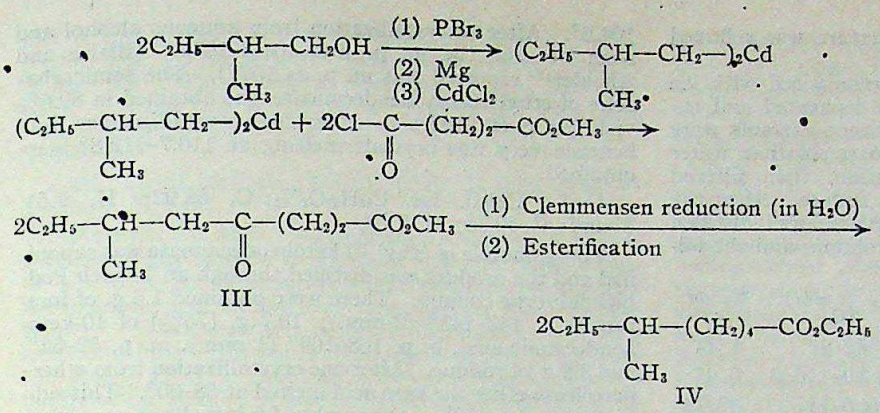

III

IV

acid obtained from 1-bromo-6-methyloctane prepared by this route was contaminated with the less soluble 17-methyloctadecanoic acid and could not be isolated in a pure state.

Ethyl 6-methyloctoate was next synthesized by a method involving no branched-chain starting materials. The procedure used, which has been employed by Schneider and Spielman[6] for synthesis of several 10-methyl acids, depends on the reaction of a Grignard reagent with a keto ester to give a hydroxy ester. By use of ethylmagnesium iodide and ethyl 6-ketoheptoate in this reaction, there was obtained ethyl 6-hydroxy-6-methyloctoate (V). The crude hydroxy ester was dehydrated by heating with iodine and the unsaturated ester was hydrogenated to the desired ethyl 6-methyloctoate. The over-all yield from ethyl 6-ketoheptoate was 19–30%. When 1-bromo-6-methyloctane prepared from this ester was used in the synthesis of 16-methyloctadecanoic acid a readily purified product was obtained. 16-Methyloctadecanoic acid melts at 49.9–50.6°, about seventeen degrees below the 17-methyl isomer.

Since 6-methyl- and 10-methyltetracosanoic acids were desired for biological testing,[7] they have been prepared by the general method of Schneider and Spielman,[6] as described above for preparation of ethyl 6-methyloctoate. The reaction between myristylmagnesium bromide and ethyl 10-ketohendecanoate was carried out essentially as described by Schneider and Spielman; however, the resulting hydroxy ester was used for dehydration, rather than the acid, as used by the above authors. The unsaturated ester was hydrogenated over platinum and, in order to insure as pure a product as possible, the saturated C_{25} ester was distilled through an 18-inch Vigreux type column. The over-all yield of recrystallized 10-methyltetracosanoic acid, obtained after saponification of the ester, was 39%. Schneider and Spielman obtained this acid in 34% yield. 6-Methyltetracosanoic acid was obtained by a similar procedure, starting with octadecyl bromide and ethyl 6-ketoheptoate, in an over-all yield of 26%.

The keto esters prepared in the course of the syntheses described above were obtained by the reaction between a dialkylcadmium compound and an ω-carbethoxyalkoyl chloride. The method of Cason[2] has been improved so that yields of 75–85% were obtained, and this procedure now appears to be the most efficient yet devised for synthesis of aliphatic keto esters. The improvement was effected by removing as much ether as possible from the reaction mixture after preparation of the dialkylcadmium compound from the corresponding Grignard reagent. This process greatly reduces the yield of di-ester, arising from reaction of the ester acid chloride with ether, and the yield of keto ester is nearly doubled. If a dialkylcadmium derivative other than dimethylcadmium is used, the small amount of di-ester may be removed by fractional distillation; however, when dimethylcadmium is used the di-ester and keto ester have nearly identical boiling points. In this case, a pure product may be obtained by distillation of the keto acid.

When the above-described method of running the cadmium reaction was applied to a secondary bromide, 2-bromopentane, the reaction failed completely. However, when the cadmium derivative of 2-bromopentane was prepared in ether at −5 to −7° and allowed to react with β-carbomethoxypropionyl chloride at this temperature a 21.5% yield of methyl 4-keto-5-methyloctoate was obtained.

It has been previously reported[2] that when diisoamylcadmium is allowed to react with succinic anhydride in ether the yield of 4-keto-7-methyloctoic acid is only 5–10%. In a trial run, this reaction was carried out in boiling benzene solution, and a yield of 31% was obtained.

Experimental[8]

Keto Esters and Acids

Methyl 4-Keto-7-methyloctoate.[2]—The Grignard solution prepared in an atmosphere of nitrogen from 7.3 g. of magnesium and 45.3 g. of isoamyl bromide (b. p. 120.0–120.2°) in 150 cc. of ether was cooled in an ice-bath and 29.3 g. of dried C. P. cadmium chloride was added in one portion. After removal of the ice-bath the mixture was stirred for five minutes, then ether was distilled rapidly from the solution by heating on a steam-bath, while stirring was continued. Distillation was continued until a dark semi-solid residue remained, then 100 cc. of dry thiophene-free benzene was added and distillation resumed until benzene had practically ceased to distil. After 100 cc. of benzene had been added to the residue the mixture was stirred and refluxed until the cake had been broken up and dispersed through the mixture. There was then added during ten minutes a solution of 36.1 g. of β-carbomethoxypropionyl chloride[9] in 50 cc. of benzene. After the exo-

(6) Schneider and Spielman, *J. Biol. Chem.*, **142**, 345 (1942).

(7) These acids were prepared at the request of Dr. Bruno Gerstl of the Yale University Medical School and are being tested by him for biological activity.

(8) All melting points corrected.

(9) Ruggli and Maeder, *Helv. Chim. Acta*, **25**, 943 (1943).

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thermic reaction had subsided the mixture was refluxed with stirring for one hour.

The organometallic complex was decomposed with ice and sulfuric acid, and the water was separated and extracted twice with benzene. The benzene extracts were washed with water, 5% sodium carbonate solution, water and saturated sodium chloride solution, then filtered through a layer of anhydrous sodium sulfate. After the solvent had been flashed off, the residue was distilled through an 18-inch Podbielniak type column, and the following fractions were obtained

Fraction	B. p. (8 mm.), °C.	Weight, g.
Methyl ethyl succinate[2]	82–89	1.44
Intermediate fraction	89–116.5	0.98
Methyl 4-keto-7-methyloctoate	116.5–117	32.74

The yield of keto ester is 73.5% of theory based on ester acid chloride or 58.8% based on isoamyl bromide.

When this reaction was run as above except that only 29.3 g. of β-carbomethoxypropionyl chloride was used the yield of keto ester was 74–76% based on ester acid chloride or 48.3–49.5% based on isoamyl bromide. When the reaction was carried out in ether, using the above quantities (29.3 g. of acid chloride), there were obtained 3.70 g. of methyl ethyl succinate and 15.40 g. (42.5% based on ester acid chloride) of methyl 4-keto-7-methyloctoate.

4-Keto-7-methyloctoic Acid.[2]—A solution of diisoamylcadmium in 200 cc. of benzene was prepared from 0.3 mole of isoamyl bromide as described in the preparation of methyl 4-keto-7-methyloctoate. After addition of 22.5 g. of succinic anhydride, which had been ground and washed with carbon bisulfide and ether,[9] the mixture was stirred under reflux for four hours. The reaction mixture was decomposed with ice and sulfuric acid, and the benzene phase was separated and extracted with 300 cc. of 5% sodium carbonate solution in four portions. The material obtained from the carbonate extract after acidification was distilled from a Claisen flask at 4 mm. pressure. The entire distillate, consisting of 4-keto-7-methyloctoic acid, boiled at 152–153° and crystallized rapidly in the receiver; yield, 11.9 g. (30.8%).

On working up the benzene solution containing the neutral material from this reaction only 2.0 g. of material was obtained. This yielded, on distillation at 4 mm. pressure, 0.94 g. boiling at 100–110° and 0.93 g. boiling at 147–150°. These fractions were not further investigated.

Ethyl 10-keto-13-methyltetradecanoate was prepared in a 0.3-mole run from isoamyl bromide and ω-carbethoxynonoyl chloride[2,10] by the procedure described for methyl 4-keto-7-methyloctoate, except that the ester acid chloride was added in 100 cc. of benzene. This keto ester was obtained in a yield of 58.2 g. (85% based on acid chloride); b. p. 180–182° (3 mm.).

Anal. Calcd. for $C_{17}H_{32}O_3$: C, 71.80; H, 11.34. Found: C, 71.76; H, 11.66.

Ethyl 6-ketoheptoate,[11] b. p. 143–145° (33 mm.), and **ethyl 10-ketohendecanoate,**[6,12] b. p. 137–138° (2 mm.), were prepared by the procedure described for methyl 4-keto-7-methyloctoate. In both cases the yields in 1.0-mole runs were 76%. Since some dimethylcadmium is lost by volatilization during distillation of benzene and since it is desirable to reduce di-ester formation to a minimum in these cases, only 0.5 mole equivalent of ω-carbethoxyvaleryl chloride[13] and of ω-carbethoxynonoyl chloride were used for these preparations. The purity of these keto esters was indicated to be 80–90% by conversion to semicarbazones. From ethyl 6-ketoheptoate there was obtained an 86.5% yield of semicarbazone, m. p. 100.2–104.2°. After recrystallization from aqueous alcohol and from benzene the m. p. was 104.8–107.0° (Blaise and Koehler[11a] reported this m. p. as 107°). The semicarbazone of ethyl 10-ketohendecanoate was obtained in 89.6% yield (m. p. 90.2–99.4°). After three crystallizations from benzene very fine crystals melting at 110.7–112.8° were obtained.

Anal. Calcd. for $C_{14}H_{27}O_2N_2$: C, 58.92; H, 9.54. Found: C, 59.35; H, 9.70.

A 30-g. sample of ethyl 10-ketohendecanoate was saponified and the product was distilled through an 18-inch Podbielniak type column. There were obtained 1.5 g. of forerun, b. p. 143–145° (2 mm.); 19.7 g. (75%) of 10-ketohendecanoic acid, b. p. 168–169° (1 mm.), m. p. 52–59°; and 3.2 g. of residue. After one crystallization from ether–petroleum ether the keto acid melted at 58–60°. This substance appears to be polymorphic, for it melts at once when placed in a bath at 59°, partially resolidifies and melts completely at 60°. It has been reported as melting at 57.5°,[6] 58.5–59.5°,[14] 53–55°.[15]

The residue (3.2 g.) from the above distillation was extracted with 200 cc. of boiling water, and after considerable salve-like material had been removed by filtration the clear filtrate was concentrated to 100 cc. On cooling there crystallized 0.99 g. of sebacic acid, m. p. 121–129°. After one crystallization from acetone-benzene, this product melted at 131.5–132.5° and gave no depression on mixing with pure sebacic acid of the same melting point. If this weight of sebacic acid is increased by 0.10 g. to allow for that remaining in the mother liquor, it corresponds to 1.4 g. or 4.7% of diethyl sebacate in the sample of keto ester.

The fore-run (1.5 g.) from 10-ketohendecanoic acid solidified when cooled in ice and salt, so it was recrystallized from petroleum ether (b. p. 30–40°). After three crystallizations there was obtained 30 mg. of a substance crystallizing as clusters of feathery needles and melting at 67.4–67.8°. It reacts with 2,4-dinitrophenylhydrazine and the analytical figures suggest that it is **dodecanedione-2,11.** This would arise from reaction of dimethylcadmium with the ester group of ethyl 10-ketohendecanoate.

Anal. Calcd. for $C_{12}H_{22}O_2$: C, 72.71; H, 11.19. Found: C, 72.48; H, 11.28.

Methyl 4-keto-5-methyloctoate could not be obtained by the procedure described above for preparing keto esters, presumably due to the instability of di-(2-amyl)-cadmium. For preparation of this keto ester, the Grignard reagent from 0.3 mole of 2-bromopentane in 150 cc. of ether was cooled to −7° and treated with 29.3 g. of dried cadmium chloride at such a rate as to allow the temperature to remain below −5°. After the resultant mixture had been stirred for one and one-half hours at −5 to −7° a solution of 33.8 g. of β-carbomethoxypropionyl chloride in 75 cc. of ether was added during twenty minutes at −5 to −7°. After addition was complete the reaction mixture was stirred four hours at the same temperature. When the reaction was worked up as described for methyl 4-keto-7-methyloctoate there was obtained 8.07 g. (21.5% based on ester acid chloride) of methyl 4-keto-5-methyloctoate, b. p. 130.5–130.7° (21 mm.). No fraction corresponding to methyl ethyl succinate was obtained.

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.50; H, 9.75. Found: C, 63.87; H, 9.93.

16-Methyloctadecanoic Acid

Methyl 4-keto-6-methyloctoate was prepared from 1-bromo-2-methylbutane (b. p. 119–121°) and *p*-carbomethoxypropionyl chloride in the manner described for preparation of methyl 4-keto-7-methyloctoate, except that only about half the ether was distilled after preparation of the cadmium compound; b. p. 132–134° (16 mm.); yield, 60%. When the preparation was carried out in ether solution the yield was only 24–27%.

Since this ester is contaminated with the 7-methyl iso-

(10) By distilling this ester acid chloride at a pressure of 5 mm. or less a yield of 90–95% may be obtained.

(11) (a) Blaise and Koehler, *Bull. soc. chim.*, (4) **7**, 222 (1910); (b) Lease and McElvain, THIS JOURNAL, **55**, 806 (1933).

(12) Ruzicka and Stoll, *Helv. Chim. Acta*, **10**, 692 (1927).

(13) Prepared in same manner and in same yield as ω-carbethoxynonoyl chloride.

(14) Chuit, Boelsing, Hauser and Malet, *Helv. Chim. Acta*, **9**, 1074 (1926).

(15) Abraham, Morvat and Smith, *J. Chem. Soc.*, 948 (1937).

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mer it was saponified, and the semicarbazone of the resultant 4-keto-6-methyloctoic acid was prepared. It crystallizes from 50% ethanol as thin blades, m. p. 137–138° (dec.). When this semicarbazone was mixed with that from 4-keto-7-methyloctoic acid the m. p. was depressed to 128–131°.

Anal. Calcd. for $C_{10}H_{19}O_3N_3$: C, 52.39; H, 8.35. Found: C, 52.64; H, 8.39.

6-Methyloctoic Acid.[4]—Clemmensen reduction of methyl 4-keto-6-methyloctoate in alcoholic solution[6] gave yields of only 10–16%; so reduction was accomplished in aqueous hydrochloric acid as has been described for the 7-methyl isomer.[2] When reduction of 45.2 g. of keto ester was continued for forty-eight hours there was obtained in the best run 22.4 g. (76.7%, based on keto ester consumed) of 6-methyloctoic acid, b. p. 98–105° (1–2 mm.) and 10.1 g. of 4-keto-6-methyloctoic acid, b. p. 125–129° (1–2 mm.).

6-Methyloctamide was prepared from a sample of pure acid recovered from reduction of the ester (see below). The method used was that previously described for 7-methyloctoic acid.[2] This amide crystallizes from benzene as small plates, m. p. 90.4–91.6°.

Anal. Calcd. for $C_9H_{19}ON$: C, 68.74; H, 12.18. Found: C, 68.52; H, 12.44.

Ethyl 6-Methyloctoate.[3]—A Grignard reagent was prepared from 23.4 g. of ethyl iodide (b. p. 72.5–72.9°) in 100 cc. of ether and forced from the flask under nitrogen pressure into a nitrogen-filled separatory funnel. This solution was added during one hour to a stirred solution of 21.5 g. of ethyl 6-ketoheptoate in 100 cc. of ether, which was cooled in an ice–salt mixture. After addition was complete the mixture was stirred for an additional hour with continued cooling. The Grignard complex was then decomposed in the usual way and the aqueous phase was extracted with two portions of ether. The extracts were washed with water, 5% sodium carbonate solution, water and saturated sodium chloride solution, then filtered through a layer of anhydrous sodium sulfate. The residue remaining after removal of solvent was heated for thirty minutes with a crystal of iodine at 180–190°, and the unsaturated ester was distilled from a Claisen flask, b. p. 83–100° (3 mm.). This ester was readily hydrogenated in 100 cc. of 95% ethanol in the presence of 0.3 g. of platinum oxide catalyst. The resulting ethyl 6-methyloctoate was distilled through an 18-inch Podbielniak type column at 36 mm. pressure; b. p. 125.5–127.5°; yield in the best run, 7.0 g. (30%). The average yield of several runs was 20%.

In an effort to improve the yield, the hydroxy ester was dehydrated by other methods: with phosphorus tribromide followed by alcoholic potassium hydroxide[16] the yield was 21%; with phosphorus pentachloride followed by alcoholic potassium hydroxide[17] the yield was 16%; with phosphorus oxychloride[18] the yield was 17%; and with acetic anhydride the yield was 20.5%. Since these processes are relatively more laborious the use of iodine was adopted as most satisfactory.

1-Bromo-6-methyloctane.[3]—6-Methyloctanol-1 was prepared by reduction of ethyl 6-methyloctoate with sodium and alcohol according to Manske.[19] From 25.9 g. of ester there was obtained 10.8 g. of 6-methyloctanol-1, b. p. 108–111° (22 mm.). Since 7.3 g. of 6-methyloctoic acid, b. p. 139–143° (17 mm.), was recovered the yield on the basis of acid consumed was 83%. By treating 14.5 g. of the alcohol with anhydrous hydrogen bromide[20] there was obtained 13.0 g. (62.5%) of bromide, b. p. 105–108° (21 mm.). There was 1.0 g. of lower-boiling material and 1.8 g. of higher-boiling material (distillation through 18-inch column).

Ethyl 10-keto-16-methyloctadecanoate, prepared by the general method described above for methyl 4-keto-7-methyloctoate, was distilled through an 18-inch Podbielniak type column, with no head and with the take-off just above the heating jacket. The keto ester, which was collected at 192–195° (2 mm.), weighed 11.5 g. (76.5% based on acid chloride, 53.7% based on bromide).

Anal. Calcd. for $C_{21}H_{40}O_3$: C, 74.07; H, 11.84. Found: C, 73.54; H, 12.30.

The fore-run from the keto ester consisted of 1.2 g. of material boiling at 71.5–73° (3 mm.) and 2.0 g. of material boiling almost entirely at 130° (2 mm.). The latter fraction was saponified and the product separated into neutral and acidic portions. After crystallization from water the acidic fraction weighed 0.44 g. and melted at 126–128°. After an additional crystallization from acetone–benzene it melted at 128–130.5° and gave no depression on mixing with pure sebacic acid. The liquid neutral fraction weighed 1.2 g. and was insoluble in concentrated sulfuric acid. The analysis corresponds to that of **3,14-dimethylhexadecane** (from coupling of the Grignard reagent).

Anal. Calcd. for $C_{18}H_{38}$: C, 84.95; H, 15.05. Found: C, 85.04; H, 15.20.

10-Keto-16-methyloctadecanoic acid was prepared by saponification of 0.68 g. of the ester according to the method described for the 17-methyl isomer.[2] The yield of material melting at 50.3–53.6° was 0.54 g. (86%). After three crystallizations from ligroin (b. p. 35–39°) this keto acid was obtained as fine feathery crystals melting at 52.7–54.1°.

Anal. Calcd. for $C_{19}H_{36}O_3$: C, 73.03; H, 11.62. Found: C, 73.06; H, 11.67.

Ethyl 16-methyloctadecanoate was prepared by Clemmensen reduction of the above-described keto ester in alcoholic solution.[6] From 10.7 g. of keto ester there was obtained, after distillation through the Podbielniak type column, 8.1 g. (78.6%) of reduced ester, b. p. 170–175° (1.5 mm.).

Anal. Calcd. for $C_{21}H_{42}O_2$: C, 77.24; H, 12.97. Found: C, 77.10; H, 13.11.

16-Methyloctadecanoic Acid.—From saponification of 8.0 g. of the ester there was obtained 7.3 g. (99%) of 16-methyloctadecanoic acid melting at 45.7–49.3°. After one crystallization from acetone and two from methanol there was obtained 5.22 g. of translucent blades melting at 49.9–50.6°, $n^{70}D$ 1.4342, $n^{65}D$ 1.4361, $n^{60}D$ 1.4379, $n^{55}D$ 1.4400.

Anal. Calcd. for $C_{19}H_{38}O_2$: C, 76.45; H, 12.83; mol. wt., 298.5. Found: C, 77.00; H, 12.73; mol. wt., 297.0.

When 16-methyloctadecanoic acid was prepared from 1-bromo-6-methyloctane obtained from *s*-butylcarbinol as starting material, the crude acid precipitated from the saponification mixture melted at 43–49°. After a 5.1-g. sample had been fractionally crystallized ten times there was obtained 0.25 g. of 17-methyloctadecanoic acid melting at 66.7–67.3°.

For preparation of the amide, the acid chloride from 1.54 g. of acid was dissolved in 15 cc. of dioxane and added with stirring to 25 cc. of cold concentrated ammonium hydroxide. The precipitated amide weighed 1.53 g. (99%) and melted at 89.4–91.8°. After three crystallizations from ligroin (b. p. 80–100°) there was obtained 1.23 g. of transparent blades melting at 92.5–93.0°.

Anal. Calcd. for $C_{19}H_{39}ON$: C, 76.71; H, 13.21. Found: C, 76.94; H, 13.52.

A 1.0-g. sample of this amide was saponified by refluxing for thirty-six hours with a mixture of 10 cc. of ethanol and 30 cc. of 10% aqueous sodium hydroxide, 20-cc. portions of 10% sodium hydroxide being added at twelve-hour intervals. On acidification there was obtained 0.99 g. of 16-methyloctadecanoic acid melting at 48.0–49.9°. After three crystallizations from acetone the constant m. p. of 49.9–50.6° was reached.

The **tribromoanilide** was prepared in 89% yield (m. p. 103.8–105.8°) from 0.51 g. of the acid, using the method previously described by one of us.[2] After three crystallizations from ligroin (b. p. 80–100°) the constant m. p. of 106.8–106.9° was reached.

(16) Noller and Adams, THIS JOURNAL, **48**, 1074 (1926).
(17) Modification of the method of Noller and Adams.
(18) Butenandt and Schmidt-Thomé, *Ber.*, **71**, 1487 (1938); Butenandt and Peters, *ibid.*, **71**, 2688 (1938).
(19) Manske, *Org. Syn.*, **14**, 20 (1934).
(20) Reid, Ruhoff and Burnett, *ibid.*, **15**, 94 (1935).

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Anal. Calcd. for $C_{25}H_{49}ONBr_3$: C, 49.21; H, 6.60. Found: C, 49.64; H, 6.91.

C_{25} Acids

6-Methyltetracosanoic Acid.—Octadecyl bromide was prepared from commercial octadecyl alcohol with anhydrous hydrogen bromide.[20] On distillation through an 18-inch Vigreux type column there was obtained an 81% yield of product boiling at 177.5–179° (3 mm.). The Grignard reagent prepared from 8.56 g. of this bromide in 50 cc. of ether was added during fifty minutes to a solution of 3.45 g. of ethyl 6-ketoheptoate in 50 cc. of ether. During addition the mixture was stirred at 0°, and after addition was complete the mixture was stirred under reflux for one hour. After decomposition of the organometallic complex with ice and sulfuric acid the ether layer was separated and filtered to remove 0.6 g. of suspended hexatriacontane (m. p. after crystallization from ligroin, 75.2–76.1°). The aqueous phase was extracted twice with ether and the ether extracts were washed with water, 5 % sodium carbonate solution, water and saturated sodium chloride solution, then filtered through a layer of anhydrous sodium sulfate. The total ether solution was concentrated to about 25 cc. and allowed to stand overnight in the refrigerator, whereupon a small additional amount of hexatriacontane separated. After removal of the hexatriacontane and distillation of the remaining solvent, the residual hydroxy ester was heated for thirty minutes at 180–190° with a crystal of iodine. The mixture was then heated to 150° under 1 mm. pressure to remove about 3 cc. of low-boiling material. The residue was treated with Norit in ether, then hydrogenated over platinum oxide in 100 cc. of alcohol. Hydrogenation was slow and several 0.1-g. portions of catalyst were required. The reduced ester was distilled through an 18-inch Podbielniak type column. After a forerun of 2.1 g., **ethyl 6-methyltetracosanoate** was collected at 211–214° (*ca.* 0.5 mm.); yield, 2.4 g. (29.2%).

Anal. Calcd. for $C_{27}H_{54}O_2$: C, 78.76; H, 13.47. Found: C, 79.33; H, 13.29.

Saponification of 2.3 g. of the ester gave 1.92 g. (90%) of acid melting at 57.5–60.5°. After three crystallizations from ligroin (b. p. 72–80°), the constant m. p. of 55.8–56.6° was reached. Slightly impure samples usually melted higher than the pure substance.

Anal. Calcd. for $C_{25}H_{50}O_2$: C, 78.46; H, 13.17; mol. wt., 382.6. Found: C, 78.77; H, 13.35; mol. wt., 384.6.

In one run the unsaturated ester was saponified and the potassium salt of the acid was purified by washing with ether. The unsaturated acid was hydrogenated in acetic acid and the reduced acid was crystallized from acetic acid twice and from ligroin twice. The product obtained in this way melted at 55.2–56.4°. Crude samples of 6-methyltetracosanoic acid could not be purified by crystallization from acetone, methyl alcohol, acetic acid or petroleum ether (b. p. 30–40°).

The **amide**, prepared in 80% yield by the method described for 16-methyloctadecanoic acid, was crystallized four times from methanol and once from ligroin (b. p. 72–80°); m. p. 83.9–85.3°.

Anal. Calcd. for $C_{25}H_{51}ON$: C, 78.67; H, 13.47. Found: C, 78.56; H, 13.60.

The **tribromoanilide**, after crystallization from ligroin (b. p. 72–80°), acetone and ethanol, melted at 94.4–97.2°.

Anal. Calcd. for $C_{31}H_{52}ONBr_3$: C, 53.87; H, 7.58. Found: C, 54.00; H, 8.22.

6-Hydroxy-6-methyltetracosanoic Acid.—Ethyl 6-hydroxy-6-methyltetracosanoate was prepared from 17.1 g. of octadecyl bromide as described in the above section. The crude hydroxy ester was saponified with boiling alcoholic potassium hydroxide. After dilution of the alcoholic solution with hot water the soap was salted out with sodium chloride and, after filtration from the cooled solution, was washed well with saturated salt solution and ether. The crude hydroxy acid obtained by treating this soap with dilute hydrochloric acid weighed 5.19 g. (30.3%). After repeated crystallization from ligroin (b. p. 39–55°) this acid melted constantly at 46.0–47.3°.

Anal. Calcd. for $C_{25}H_{50}O_3$: C, 75.32; H, 12.64. Found: C, 75.46; H, 12.87.

10-Methyltetracosanoic Acid.—Myristyl bromide, prepared[20] from 100 g. of commercial myristyl alcohol (E. K. Co.), was distilled through an 18-inch Vigreux type column at 2 mm. pressure. There was obtained 4.4 g. of material boiling at 123–125°, 70.8 g. of myristyl bromide boiling at 135–137° and 24.8 g. of material boiling at 154–155°. Thus, the alcohol used apparently contained about 4% lauryl alcohol and 20% cetyl alcohol.

Starting with myristyl bromide and ethyl 10-ketohendecanoate, **ethyl 10-methyltetracosanoate** was prepared by the same general procedure described for the 6-methyl isomer; yield in a 0.15-mole run, 44.0%; b. p. 218–222° (*ca.* 0.5 mm.).

Anal. Calcd. for $C_{27}H_{54}O_2$: C, 78.76; H, 13.47. Found: C, 79.43; H, 13.25.

By saponification of the ester and crystallization of the crude acid from acetone an 89.5% yield of 10-methyltetracosanoic acid melting at 49.5–51.5° was obtained. After two additional crystallizations fine crystals were obtained which melted constantly at 50.5–51.5° (Schneider and Spielman,[6] 51.0–51.5°).

The **amide**, prepared in 96% yield, after crystallization from acetone, melted at 77.5–78.5° (literature,[6] 79–79.5°).

The **tribromoanilide**, prepared in 72% yield, crystallized from ethanol as fine white crystals, m. p. 84.2–84.8°.

Anal. Calcd. for $C_{31}H_{52}ONBr_3$: C, 53.87; H, 7.58. Found: C, 54.02; H, 8.18.

The authors wish to express their appreciation for a grant from the Natural Science Research Fund of Vanderbilt University.

Summary

16-Methyloctadecanoic acid has been synthesized from the intermediate ethyl 10-keto-16-methyloctadecanoate. This and four other keto esters were prepared in yields of 75–85% by the reaction between the appropriate ester acid chlorides and dialkylcadmium derivatives.

6-Methyltetracosanoic acid has been prepared from the corresponding 6-hydroxy acid. The ester of the hydroxy acid was prepared from octadecylmagnesium bromide and ethyl 6-ketoheptoate. Schneider and Spielman's synthesis of 10-methyltetracosanoic acid has been repeated and modified slightly.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF CIBA PHARMACEUTICAL PRODUCTS, INC.]

The Synthesis of 3,4-Dicarboxy-2-furanvaleric Acid and Some of Its Derivatives

BY KLAUS HOFMANN[1]

Synthetic work on substances related to biotin, which is at present under way in this Laboratory called for the preparation of 3,4-dicarboxy-2-furanvaleric acid. Alder and Rickert[2] have described a procedure for the preparation of furan-3,4-dicarboxylic acid which we have successfully applied to the synthesis of 3,4-dicarboxy-2-furanvaleric acid. The starting material for the present investigation was 2-furanvaleric acid which was prepared by a modification of the method of Asano and Nakatomi.[3] Furylacrolein (I) and malonic acid were condensed to 4-(2-furyl)-1,3-butadiene-1,1-dicarboxylic acid (II). Attempts to decarboxylate this substance according to the procedure of the Japanese workers resulted in the formation of tarry products and in no instance was it possible to obtain 4-(2-furyl)-1,3-butadiene-1-carboxylic acid (III). The original procedure was therefore modified. The crude condensation product (II) was dissolved in methanol and was hydrogenated with palladium black as the catalyst until approximately 3 moles of hydrogen had been absorbed. Decarboxylation of the resulting product in pyridine solution at 130–140° resulted in the formation of 2-furanvaleric acid (IV) which was obtained in 50% yield as a white crystalline mass melting at 42–43°. The acid was further characterized by the preparation of its anilide which melted at 75–76°.

When equimolar amounts of this acid and diethyl-acetylene-dicarboxylate were heated on the steam-bath the diene addition compound (V) was obtained as a viscous oil. This oil when hydrogenated in the presence of palladium black, absorbed one mole of hydrogen and was transformed into the partially hydrogenated substance (VI). Heating of this product to 190–200° caused its decomposition into ethylene and 3,4-dicarbethoxy-2-furanvaleric acid (VII) which was obtained in 60–70% yield as a viscous oil boiling at 204–206° at 0.02 mm. Saponification of (VII) yielded 3,4-dicarboxy-2-furanvaleric acid (VIII) melting at 188–190°. The presence of the furan nucleus in this acid was demonstrated spectroscopically. The ultraviolet absorption spectrum of (VIII) was compared with the absorption curve of 3,4-dicarboxy-furan prepared according to Reichstein, *et al.*[4] As may be seen from Fig. 1 the two absorption curves are almost identical, demonstrating the furan nature of the tricarboxylic acid (VIII).

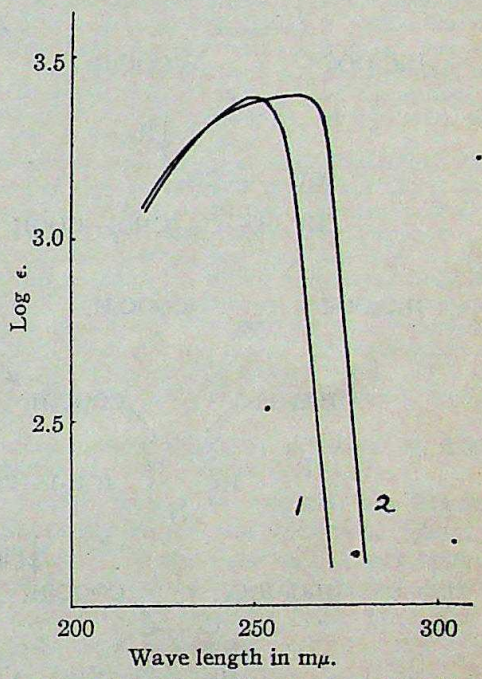

Fig. 1.—Ultraviolet absorption spectra of 3,4-dicarboxy-furan (curve 1) and 3,4-dicarboxy-2-furanvaleric acid (curve 2) in absolute alcohol.

The application of the Alder–Rickert synthesis made it possible to prepare derivatives of 3,4-dicarboxy-2-furanvaleric acid containing various substituents at the furan carboxyls as well as at the acid group at the end of the aliphatic side-chain. Thus treatment of the ester acid (VII) with thionyl chloride gave the acid chloride (X) which, when coupled with piperidine, formed the oily ester piperidide (XI). Treatment of this derivative with alcoholic potassium hydroxide removed the ester groups in positions 3 and 4 with the formation of 3,4-dicarboxy-2-furanvaleric acid piperidide (XII) melting at 133–134°. In contrast to the aliphatic carboxyl group, which is blocked by the piperidine residue, the ring carboxyl groups in compounds (XI) and (XII) are available for further transformations.

As may be seen in the experimental section, the triethyl ester (IX) of (VIII) has likewise been prepared.

It has been possible to hydrogenate some of the above compounds and thus to prepare the corresponding tetrahydrofuran derivatives. The results of these studies will be presented in a forthcoming publication from this Laboratory.

(1) The author wishes to express his thanks to Ciba Pharmaceutical Products, Inc., Summit, New Jersey, for their generous support of this work.

(2) Alder and Rickert, *Ber.*, **70**, 1354 (1937).

(3) Asano and Nakatomi, *J. Pharm. Soc.* (Japan), **53**, 176 (1933).

(4) Reichstein, Grüssner, Schindler and Hardmeier, *Helv. chim. acta*, **16**, 276 (1933).

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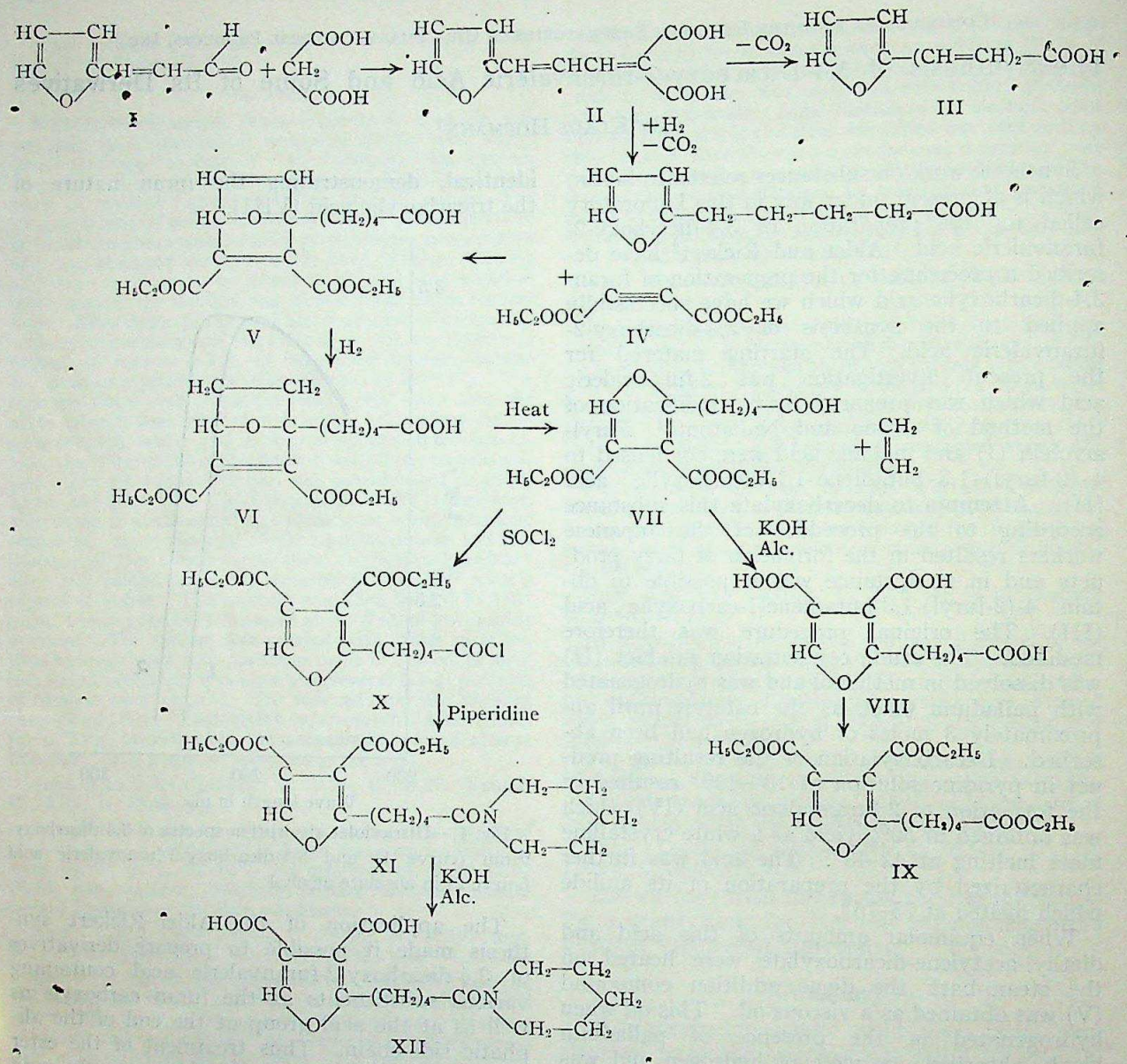

Experimental

All melting points are corrected.

4-(2-Furyl)-1,3-butadiene-1,1-dicarboxylic Acid (II).—325 grams of furyl-acrolein, prepared according to Burdick and Adkins,[5] and 600 g. of malonic acid were dissolved in 890 cc. of pyridine; 1 cc. of piperidine was then added and the solution was heated on the steam-bath for four hours in a stream of carbon dioxide. The resulting dark red solution was poured on cracked ice and acidified to congo red with concentrated hydrochloric acid. The reaction product began to crystallize and the crystallization was complete after the solution was kept in the refrigerator overnight. The crystalline material was then collected on a Büchner funnel, was washed with dilute hydrochloric acid and water and was dried at 100° *in vacuo*; 337 g. of the crude product was obtained in the form of orange needles. This material, which consists of a mixture of isomers, was used for the next step without further purification. A sample was recrystallized from dilute methanol. Red needles were obtained, which decomposed at 190–195° without melting.

Anal. Calcd. for $C_{10}H_8O_5$: C, 57.68; H, 3.87. Found: C, 57.80; H, 4.01.

(5) Burdick and Adkins, THIS JOURNAL, **56**, 441 (1934).

2-Furanvaleric Acid (IV).—Fifty grams of the above acid was dissolved in 400 cc. of methanol and was hydrogenated in the presence of palladium black at a pressure of 0.1 atmosphere until 13 liters of hydrogen had been consumed. The catalyst was then filtered off and the filtrate was evaporated to dryness *in vacuo*. The resulting sirup was dissolved in 100 cc. of pyridine and the solution was heated to 130–140° until the vigorous evolution of carbon dioxide had stopped. The cooled mixture was then dissolved in ether. The ether solution was washed with dilute hydrochloric acid and water, and was dried over sodium sulfate. The ether was removed on the steam-bath and the residue was distilled *in vacuo*. The fraction boiling at 110–130° at 0.02 mm., solidified on cooling and represents almost pure 2-furanvaleric acid. A sample which was recrystallized from petrol ether melted at 42–43°. The yield was 20 g. (50% of the theoretical yield).

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.27; H, 7.18. Found: C, 64.02; H, 7.31.

Anilide of 2-Furanvaleric Acid.—3.3 grams of the above acid and 6 cc. of freshly distilled aniline were heated to 180° for twelve hours. The excess of aniline was removed *in vacuo*, the residue was taken up in ether and the ethereal solution was extracted with 3 *N* hydrochloric acid and water, and was dried over sodium sulfate. Sublimation

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of the reaction product at 170° and 0.02 mm. yielded a white solid which was recrystallized from a mixture of ether and petrol ether; 3.7 g. of colorless needles melting at 75–76°, was obtained.

Anal. Calcd. for $C_{15}H_{17}O_2N$: C, 74.07; H, 7.04; N, 5.75. Found: C, 73.75; H, 6.83; N, 5.81.

3,4-Dicarbethoxy-2-furanvaleric Acid (VII).—54 grams of 2-furanvaleric acid (IV) and 62 g. of diethyl-acetylenedicarboxylate were heated on the steam-bath for twelve hours. The oily addition compound (V) was then dissolved in 300 cc. of ethyl acetate and was hydrogenated in the presence of palladium black until 1 mole of hydrogen had been absorbed. The catalyst was then removed by filtration and the ethyl acetate was evaporated. The residue which consists of the partially hydrogenated compound (VI) was then heated at 16 mm. pressure to 190–200° until the evolution of ethylene had stopped. The substance was then distilled and the fraction boiling at 205–210° at 0.02 mm. was collected; 68 g. (68% of the theoretical yield) of 3,4-dicarbethoxy-2-furanvaleric acid was obtained.

3,4-Dicarboxy-2-furanvaleric Acid (VIII).—21.6 grams of the above compound was dissolved in 80 cc. of 5 *N* potassium hydroxide and the solution was heated on the steam-bath for two hours; 80 cc. of water was then added and the solution was acidified to congo red with concentrated hydrochloric acid. The crystalline acid which separated out was collected, washed with water, and dried at 100° *in vacuo*; 16.8 g. (95% of the theoretical yield) of the crude acid melting at 180–182° was obtained. The material was purified by crystallization from a mixture of methanol and ethyl acetate. Needles melting at 188–190° were obtained.

Anal. Calcd. for $C_{11}H_{12}O_7$: C, 51.56; H, 4.72. Found: C, 51.45; H, 4.90.

3,4-Dicarbethoxy-2-furanvaleric Acid Ethyl Ester (IX).—13.5 grams of the above acid, 200 cc. of absolute ethanol and 20 cc. of concentrated sulfuric acid were refluxed for twelve hours. The solution was then concentrated *in vacuo* to one-third of its volume. The residue was diluted with ice-cold water and was extracted with ether. The ether solution was washed with 2 *N* sodium carbonate and water and was dried over sodium sulfate. The ether was removed on the steam-bath and the residue was distilled *in vacuo*; 12.5 g. (70% of the theoretical yield) of the ester boiling at 165–166° at 0.02 mm. was obtained: $n^{24}D$ 1.4741; d^{24} 1.124. The same ester was obtained in 90% yield when 3,4-dicarbethoxy-2-furanvaleric acid (VII) was esterified in the manner described above.

3,4-Dicarbethoxy-2-furanvaleryl Chloride (X).—11.8 grams of 3,4-dicarbethoxy-2-furanvaleric acid (VII) was mixed with 15 cc. of thionyl chloride and the mixture was heated on the steam-bath until the vigorous reaction was over. The excess of thionyl chloride was removed *in vacuo* and the residue was distilled; 9.4 g. (74% of the theoretical yield) of the acid chloride, boiling at 177–178° at 0.02 mm., was obtained.

3,4-Dicarbethoxy-2-furanvaleric Acid Piperidide (XI).—9.4 grams of the above acid chloride (X) was dissolved in 50 cc. of dry ether and this solution slowly added to a solution of 8 g. of freshly distilled piperidine in 50 cc. of ether. The mixture was kept at room temperature for thirty minutes, then washed with 3 *N* hydrochloric acid, 2 *N* sodium carbonate and water and dried over sodium sulfate. The ether was removed and the resulting oil was distilled *in vacuo*; 9.72 g. (90% of the theoretical yield) of the piperidide boiling at 210–211° at 0.02 mm. was obtained: $n^{24}D$ 1.5006; d^{24} 1.132.

3,4-Dicarboxy-2-furanvaleric Acid Piperidide (XII).—9.5 grams of the above ester piperidide (XI) was dissolved in 20 cc. of 5 *N* potassium hydroxide and 40 cc. of methanol and the mixture refluxed for two hours. The solution was then concentrated *in vacuo* and the residue was acidified to congo red with concentrated hydrochloric acid. The resulting oil crystallized on cooling and scratching with a glass rod. The material was collected, was washed with water and was dried. Crystallization of the material from dilute alcohol yielded 6.4 g. (79% of the theoretical yield) of whetstone shaped needles melting at 132–133°.

Anal. Calcd. for $C_{16}H_{21}O_6N$: C, 59.45; H, 6.55; N, 4.33. Found: C, 59.33; H, 6.72; N, 4.31.

The author wishes to express his thanks to Mrs. Florence Baker for technical assistance, and to Mr. William Saschek, Department of Biochemistry, College of Physicians and Surgeons, Columbia University, New York, for performing the micro-analyses.

Summary

1. 3,4-Dicarboxy-2-furanvaleric acid as well as some of its derivatives have been prepared.

2. A satisfactory procedure for the preparation of 2-furanvaleric acid has been described.

3. The ultraviolet absorption curves of 3,4-dicarboxy-2-furanvaleric acid as well as 3,4-dicarboxy-furan have been given.

SUMMIT, NEW JERSEY RECEIVED AUGUST 4, 1943

[CONTRIBUTION NO. 504 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Unsaturated Synthetic Glycerides. III. Unsaturated Symmetrical Mixed Diglycerides[1]

BY B. F. DAUBERT AND H. E. LONGENECKER

Of the several reliable methods for the synthesis of diglycerides, all involve the use of a glycerol derivative with two free hydroxyls and one temporarily blocked or potential hydroxyl group. Thus, in the Fisher[2] method 1-iodohydrin (Alival) is treated with an excess of an acid chloride, producing 1-iodo-2,3-diacylglycerol. During the subsequent replacement of the iodine by an hydroxyl group, acyl migration from the 2(beta) to the 1(alpha) position of glycerol is known to occur with the resulting production of a symmetrical diglyceride. Similarly, when the 2,3-diacyl derivatives of either the 1-trityl ether of glycerol or 1-carbobenzyloxyglycerol are hydrolyzed, acyl migration occurs to yield the more stable 1,3-diglycerides.[3,4,5,6] These three independent methods have been useful

(1) The authors are indebted to Swift and Company and the Buhl Foundation for grants in support of this investigation.

(2) Fisher, *Ber.*, **53**, 1621 (1920).

(3) Jackson and King, THIS JOURNAL, **55**, 678 (1933).

(4) Daubert and King, *ibid.*, **61**, 3328 (1939).

(5) Verkade, van der Lee and Meerburg, *Rec. trav. chim.*, **51**, 850 (1932); **54**, 716 (1935).

(6) Verkade and van der Lee, *ibid.*, **55**, 267 (1936).

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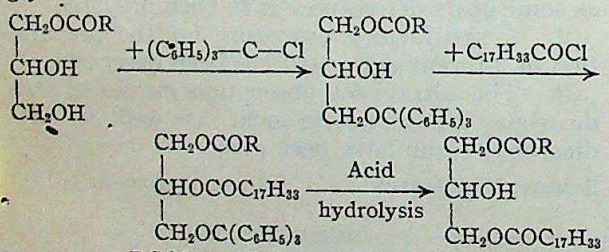
in preparing symmetrical (1,3-) diglycerides of a single fatty acid.

Verkade[6] observed that a 1-monoglyceride reacts with trityl chloride to form an easily separable 1-acyl-3-trityl glycerol with the 2-(beta) hydroxyl group unreacted. This fact makes possible the introduction of a second acyl radical differing from the one present in the original monoglyceride. Acid hydrolysis of the trityl group from the resulting 1,2-diacyl-3-tritylglycerol is again accompanied by a shift of the acyl group in the 2-(beta) position to that position formerly occupied by the trityl group. The resulting diglyceride is again symmetrical but may now contain two different acids in the 1 and 3 positions. Verkade[6] used this method to prepare several mixed symmetrical diglycerides containing two different saturated acids.

Malkin and associates[7] reported the preparation of symmetrical diglycerides containing saturated acids by the direct esterification of 1-monoglycerides (10 to 15% excess) with fatty acids in the presence of *p*-toluenesulfonic acid. This method could, likewise, be adapted to the preparation of symmetrical diglycerides containing two different fatty acids.

In the present investigation advantage was taken of acyl migration during removal, by acid hydrolysis, of the trityl group from a series of 1,2-diacyl-3-tritylglycerols to prepare symmetrical mixed diglycerides containing oleic acid and either lauric, myristic, palmitic, or stearic acid. The reactions starting with the 1-monoglycerides are as follows



$RCOO^-$ = Saturated acid radical
$C_{17}H_{33}COO^-$ = Oleyl radical

The identity and structure of the unsaturated diglycerides were verified by hydrogenation to the completely saturated symmetrical mixed diglycerides. It was necessary, however, for complete identification of the series, to prepare 1-lauryl-3-stearylglycerol by a method other than hydrogenation, since it had not previously been reported in the literature.

Experimental

1-Myristyl-3-tritylglyerol.—The method used for the preparation of this compound is essentially the same as that described by Verkade and van der Lee.[6]

Five grams of 1-monomyristin was dissolved in 10 ml. of quinoline and 5 g. of trityl (triphenylmethyl) chloride added to the solution. The mixture was refluxed on a steam-bath for two hours. On cooling the mixture to room temperature and allowing it to stand for several hours, a copious precipitate of quinoline hydrochloride separated. The semi-solid mass was dissolved in 200 ml. of ether and the solution washed successively with 0.5 *N* sulfuric acid, 5% potassium carbonate solution, and water. The solution, after drying over anhydrous sodium sulfate, was filtered and the ether distilled. The sirupy residue remaining was dissolved in 300 ml. of warm petroleum ether and the solution allowed to stand at room temperature for six hours. The small amount (0.1 g.) of unreacted monoglyceride which separated was filtered off and the petroleum ether removed from the filtrate by distillation under reduced pressure. The residue was then dissolved in 30 ml. of 95% ethyl alcohol and the solution cooled to −20°. After several crystallizations from 95% ethyl alcohol and petroleum ether the product melted at 56.0°: molecular weight, 540 ± 4 (theory, 544.74).

Anal. Calcd. for $C_{36}H_{48}O_4$: C, 79.37; H, 8.88. Found: C, 79.22, 79.19; H, 8.79, 8.82.

1-Lauryl-3-tritylglycerol.—This compound was prepared in a manner similar to that described for 1-myristyl-3-tritylglycerol; m.p. 47.0°; molecular weight, 510 ± 3 (theory, 516.69).

Anal. Calcd. for $C_{34}H_{44}O_4$: C, 79.03; H, 8.58. Found: C, 78.95, 78.99; H, 8.62, 8.65.

1-Stearyl-3-tritylglycerol, m. p. 66.0°, and **1-palmityl-3-tritylglycerol**, m. p. 62.0° (Verkade and van der Lee,[6] 67° and 62°, respectively), were prepared in an analogous manner.

1-Stearyl-2-oleyl-3-tritylglycerol.—Five grams of 1-stearyl-3-tritylglycerol was dissolved in 5 ml. of quinoline and to this solution there was added 2.5 g. of oleyl chloride dissolved in 10 ml. of dry chloroform. The mixture was shaken over a period of two hours and then allowed to stand two days at room temperature. The mixture was dissolved in 250 ml. of ether and 50 ml. of 0.5 *N* sulfuric acid, and then washed successively with small volumes of 0.5 *N* sulfuric acid, 10% potassium carbonate solution and distilled water. After drying the ether solution over anhydrous sodium sulfate, the ether was removed under reduced pressure. The liquid residue remaining was dissolved in warm petroleum ether. An equal volume of 95% alcohol was then added and the solution cooled to −20°. Repeated attempts to induce crystallization from alcohol, petroleum ether, and mixtures of these two solvents, were not successful. The liquid which separated during cooling was washed repeatedly with cold 95% alcohol. This procedure was necessary to obtain a product of satisfactory purity.

1-Palmityl-2-oleyl-3-tritylglycerol, 1-myristyl-2-oleyl-3-tritylglycerol and **1-lauryl-2-oleyl-3-tritylglycerol**, all liquids at room temperature, were prepared in a similar manner (Table I).

1-Myristyl-3-oleylglycerol.—Two grams of 1-myristyl-2-oleyl-3-tritylglycerol was dissolved in 15 to 20 ml. of petroleum ether and the solution cooled to about 5° in an ice-bath. Dry hydrogen chloride was passed into the solution for fifteen minutes. After allowing the mixture to stand at room temperature for two hours, it was dissolved in 150 ml. of ether and the ether solution washed three times with 30-ml. portions of 5% potassium carbonate solution, and water. After drying over anhydrous sodium sulfate the solution was filtered and the ether removed from the filtrate by distillation. The solid residue was dissolved in a 1:2 mixture of ether and alcohol. On cooling at 5° for four hours flaky white crystals separated. After several crystallizations from the same mixture of solvents, the vacuum-dried product melted at 41°.

Analytical constants for **1-myristyl-3-oleylglycerol** and also for **1-stearyl-3-oleylglycerol, 1-palmityl-3-oleylglycerol and 1-lauryl-3-oleylglycerol**, prepared in a similar manner, are tabulated in Table II.

1-Stearyl-2-lauryl-3-tritylglycerol.—This compound not having been reported previously was prepared by essentially the same procedure as for 1-stearyl-2-oleyl-3-tritylglycerol; m.p. 25.0°; molecular weight, 775 ± 4 (theory, 783.14).

(7) Malkin, Shurbagy and Meara, *J. Chem. Soc.*, 1409 (1937).

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TABLE I

1-ACYL-2-OLEYL-3-TRITYLGLYCEROLS

Acyl radical	Carbon, % Calcd.	Carbon, % Found		Hydrogen, % Calcd.	Hydrogen, % Found		Molecular weights[a] Calcd.	Molecular weights[a] Found	Iodine values[b] Calcd.	Iodine values[b] Found
Stearyl	80.50	80.32	80.37	10.25	10.09	10.01	865.28	857 ± 6	29.3	29.1
Palmityl	80.33	80.28	80.19	10.11	10.08	10.01	837.23	834 ± 3	30.3	30.0
Myristyl	80.15	80.12	80.06	9.97	9.87	9.96	809.18	801 ± 7	31.4	31.5
Lauryl	79.95	79.73	79.65	9.81	9.63	9.75	781.13	778 ± 5	32.5	32.1

[a] Molecular weights determined by the method of Hanson and Bowman.[8] [b] Wijs method used for all iodine values. Average of triplicates differing not more than ±0.1 iodine value unit.

TABLE II

UNSATURATED SYMMETRICAL MIXED DIGLYCERIDES (1-ACYL-3-OLEYLGLYCEROLS)

Acyl radical	Carbon, % Calcd.	Carbon, % Found		Hydrogen, % Calcd.	Hydrogen, % Found		Iodine values Calcd.	Iodine values Found	Molecular weights Calcd.	Molecular weights Found	M. p., °C.	$n^{70\text{-}0}D$[b]
Stearyl	75.19	75.22	75.09	11.97	11.87	11.91	40.7	40.5	622.98	615 ± 6	54.0[a]	1.44690
Palmityl	74.69	74.58	74.56	11.86	11.82	11.78	42.7	42.4	594.93	592 ± 4	46.0	1.44574
Myristyl	74.15	74.20	74.12	11.74	11.70	11.72	44.8	44.5	566.88	561 ± 2	41.0	1.44455
Lauryl	73.55	73.32	73.41	11.60	11.51	11.56	47.1	47.2	538.83	531 ± 4	32.0	1.44335

[a] This compound is identical with that prepared by direct esterification of 1-monostearin with oleyl chloride, reported in a previous paper.[9] [b] Refractive indices were derived from graphs plotted from index readings over a range of about 10 to 15°; dn/dt for each compound of the series was 0.00039.

Anal. Calcd. for $C_{51}H_{78}O_5$: C, 79.75; H, 10.04. Found: C, 79.69, 79.71; H, 10.02, 9.99.

Hydrolysis in petroleum ether solution with dry hydrogen chloride yielded 1-stearyl-3-laurylglycerol; m. p. 62.0°; molecular weight, 534 ± 4 (theory, 540.84).

Anal. Calcd. for $C_{33}H_{64}O_5$: C, 73.28; H, 11.93. Found: C, 73.21, 73.16; H, 11.89, 11.88.

Proof of Structure.—The structure and identity of each of the new unsaturated symmetrical mixed diglycerides was proved by hydrogenation to the corresponding saturated analogs and by conversion to 1,2-diacyl-3-oleylglycerols. The latter compounds were identical with those prepared by an independent method and reported in a previous paper[10] (Table III).

TABLE III

HYDROGENATION OF 1-ACYL-3-OLEYLGLYCEROLS

Acyl radical in 1-acyl-3-stearylglycerol	Melting point, °C. Reported	Melting point, °C. Found
Stearyl	79.1[a]	79.0
Palmityl	71.0 to 71.5[b]	71.0
Myristyl	65.5 to 66.5[c]	66.0
Lauryl	62.0[d]	62.0

[a] Averill, Roche and King, THIS JOURNAL, 51, 870, (1929). [b] Verkade and van der Lee.[6] [c] Verkade, van der Lee and Meerburg.[5] [d] Melting point of 1-stearyl-3-laurylglycerol prepared by an independent method as reported in this paper. Mixed with the hydrogenation product of 1-lauryl-3-oleylglycerol there was no depression of the melting point.

(8) Hanson and Bowman, *Ind. Eng. Chem., Anal. Ed.*, 11, 440 (1939).

(9) Daubert, Spiegl and Longenecker, THIS JOURNAL, 65, 2144 (1943).

Summary

Physical and chemical data are reported for seven new tritylglycerol intermediates: 1-myristyl-3-tritylglycerol, 1-lauryl-3-tritylglycerol, 1-stearyl-2-oleyl-3-tritylglycerol, 1-palmityl-2-oleyl-3-tritylglycerol, 1-myristyl-2-oleyl-3-tritylglycerol, 1-lauryl-2-oleyl-3-tritylglycerol, and 1-stearyl-2-lauryl-3-tritylglycerol.

Physical and chemical data are also reported for four new unsaturated symmetrical mixed diglycerides: 1-stearyl-3-oleylglycerol, 1-palmityl-3-oleylglycerol, 1-myristyl-3-oleylglycerol, 1-lauryl-3-oleylglycerol, and a new saturated symmetrical mixed diglyceride, 1-stearyl-3-laurylglycerol.

The refractive index and melting point of the unsaturated symmetrical mixed diglycerides increases with increase in the length of the carbon chain of the saturated fatty acid. The change in refractive index with change in temperature agrees in value with that previously reported for other series of synthetic glycerides.

PITTSBURGH, PA. RECEIVED SEPTEMBER 23, 1943

(10) Daubert, Fricke and Longenecker, THIS JOURNAL, 65, 2142 (1943).

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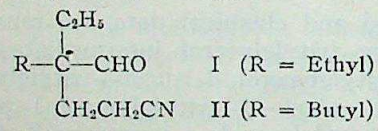
[CONTRIBUTION FROM ROHM AND HAAS COMPANY AND RESINOUS PRODUCTS AND CHEMICAL CO.]

The Chemistry of Acrylonitrile. V. Cyanoethylation of Aldehydes

BY HERMAN ALEXANDER BRUSON AND THOMAS W. RIENER

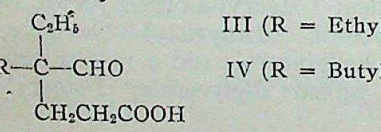
Acrylonitrile reacts with aldehydes in the presence of alkaline catalysts to yield condensation products which in general are more complex than those obtained by the action of acrylonitrile upon ketones.[1]

The direct cyanoethylation reaction so characteristic of ketones, is shown most clearly by those aldehydes which do not readily aldolize, oxidize, or resinify under the influence of the alkaline catalyst used. Typical of such amenable aldehydes are the dialkyl acetaldehydes, particularly those which are higher in the series than isobutyraldehyde. Of these, the commercially available diethylacetaldehyde and 2-ethylhexanal are eminently suitable. These aldehydes react smoothly with acrylonitrile in the presence of a little concentrated aqueous potassium hydroxide solution as a catalyst to form the corresponding cyanoethylation products (I) and (II) in good yields (75–80%).



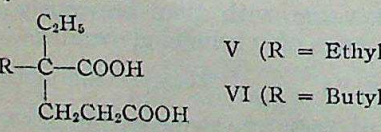
I (R = Ethyl)
II (R = Butyl)

From these aldehydo-nitriles, the corresponding aldehydo-acids (III) and (IV) were obtained by hydrolysis with aqueous sodium hydroxide solution; the tertiary aldehyde groups being hardly affected by the alkali.



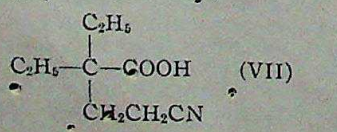
III (R = Ethyl)
IV (R = Butyl)

Upon oxidation with air, hydrogen peroxide, or potassium permanganate, the aldehydo-acids (III) and (IV) yielded the corresponding α,α-dialkylglutaric acids (V) and (VI), respectively, in crystalline form.



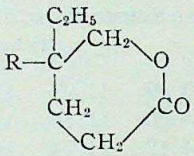
V (R = Ethyl)
VI (R = Butyl)

Although the aldehydo-nitriles (I) and (II) are not readily affected by dilute alkalies, they do rapidly autoxidize in the air to the corresponding cyano-acids. From (I), the cyano-acid (VII) separates in crystalline form upon exposure of a thin layer of the cyano-aldehyde to the air, whereas (II) remains oily.



(VII)

Upon catalytic hydrogenation of the sodium salts of the aldehydo-acids (III) and (IV) in water by means of nickel, the sodium salts of the respective δ-hydroxy acids are formed, which upon acidification yield the corresponding δ-lactones (VIII) and (IX).

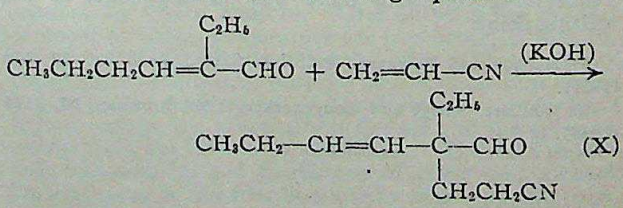


VIII (R = Ethyl)
IX (R = Butyl)

On the other hand, isobutyraldehyde and acetaldehyde are so strongly aldolized that they condense with acrylonitrile in the presence of potassium hydroxide to form a complex mixture of higher cyanoethylation products. The same holds true for propionaldehyde, *n*-butyraldehyde and heptaldehyde. Crotonaldehyde as well as acetaldol likewise form more complex nitrogeneous condensation products with acrylonitrile.

Since it appeared probable that dehydration products of the aldols involved in these reactions, also took part in the condensation with acrylonitrile, it was thought that α-ethyl-β-propylacrolein which is easily formed by the action of alkali on *n*-butyraldehyde through dehydration of the butyraldol[2] might yield a clue concerning the nature of some of the more complex cyanoethylation products encountered.

When equimolecular proportions of α-ethyl-β-propylacrolein and acrylonitrile were mixed in the presence of concentrated aqueous or methanolic potassium hydroxide solution as a catalyst, reaction occurred to form a 50% yield of a *mono*-cyanoethylation product *even though an α-hydrogen atom is lacking in the aldehyde used.* This *mono*-cyanoethylation product (X) is formed in accordance with the following equation



(X)

Under the influence of the alkali, the α-ethyl-β-propylacrolein apparently undergoes a hydrogen shift and the migrating hydrogen atom becomes stabilized by the powerful acceptor action of the acrylonitrile to yield compound (X). In this respect, the reaction is quite analogous to the behavior of other α,β-unsaturated compounds such as mesityl oxide, crotonamide and

(1) Bruson and Riener, THIS JOURNAL, 64, 2850 (1942).

(2) Weizmann and Garrand, *J. Chem. Soc.*, 329 (1920).

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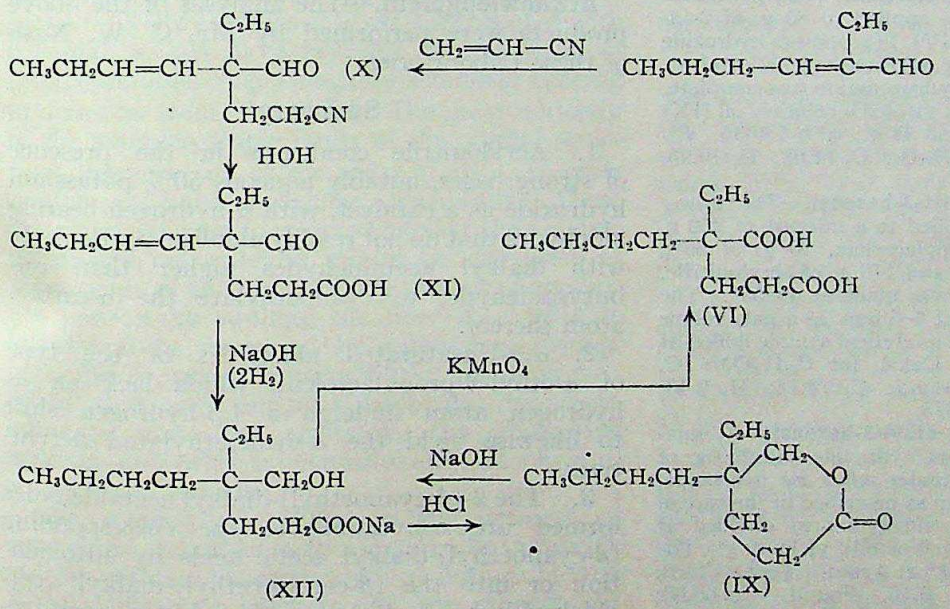
crotononitrile toward acrylonitrile as described previously.[3]

That the cyanoethyl group is in fact *alpha* to the aldehydo group in (X) was shown by hydrolyzing (X) to the unsaturated aldehydo-acid (XI) by means of aqueous sodium hydroxide solution. The pure aldehydo-acid was isolated, converted to its sodium salt and the aqueous solution of the latter was subjected to catalytic hydrogenation in the presence of Raney nickel. The sodium salt of the saturated hydroxy acid formed (XII) was acidified to yield a liquid lactone (IX) which was found to be identical with γ-ethyl-γ-butyl-δ-valero-lactone obtained previously from 2-ethylhexanal through compounds II and IV. Furthermore a portion of this lactone was oxidized in alkaline solution by means of potassium permanganate to α-ethyl-α-butylglutaric acid identical with (VI) derived from 2-ethylhexanal.

The sequence of reactions described above is shown more clearly in the appended equations.



Experimental

(I) **2-(β-Cyanoethyl)-2-ethylbutyraldehyde.**—To a stirred solution of 700 g. of freshly distilled 2-ethylbutyraldehyde (7 moles) and 20 g. of aqueous 50% potassium hydroxide solution, there was added dropwise 408 g. of acrylonitrile (7.7 moles) during the course of two hours while maintaining the reaction temperature at 55–58° by occasional cooling. After all had been added, the mixture was stirred for an additional ninety minutes until the exothermal reaction had ceased, and finally heated for one hour at 55° to complete the reaction. The product was acidified to congo red with dilute hydrochloric acid, washed twice with water, dried under reduced pressure and the residual oil (1018 g.) distilled in vacuum while nitrogen was admitted through the capillary tube to prevent oxidation. The crude product distilled at 115 to 125° at 4–6 mm. as a colorless oil; yield 821 g. or 76.6%. Upon redistillation in nitrogen under vacuum the analytical sample boiled at 128° at 4 mm. *Anal.* Calcd. for $C_9H_{15}ON$: C, 70.53; H, 9.87; N, 9.14. Found: C, 69.98; H, 9.91; N, 9.24; $n^{25}D$ 1.4500; d^{25}_4 0.9528.

(II) **2-(β-Cyanoethyl)-2-ethylhexanal.**—The procedure above was applied to a mixture of 384 g. 2-ethylhexanal, 10 g. 50% potassium hydroxide solution and 175 g. of acrylonitrile. The product distilled at 130–138° at 4 mm. as a colorless oil; yield 432 g. or 79.5%. Upon redistillation in nitrogen the analytical sample boiled at 140–142° (5 mm.). *Anal.* Calcd. for $C_{11}H_{19}ON$: C, 72.87; H 10.57; N, 7.73. Found: C, 73.00; H, 10.61; N, 7.82; $n^{25}D$ 1.4515; d^{25}_4 0.9269.

(III) **2-(β-Carboxyethyl)-2-ethylbutyraldehyde.**—A mixture of 153 g. of compound (I), 50 g. of sodium hydroxide and 500 cc. of water was stirred and boiled under reflux for one and one-half hours until the oil had disappeared. The solution was cooled, acidified with hydrochloric acid, and the precipitated oil separated, washed with water and dried in vacuum. The residual oil (152 g.) was distilled *in vacuo* in a stream of nitrogen. The product (122 g.) came over at 145–150° (5 mm.) as a colorless oil; acid no. 335 (calcd., 326). The analytical sample obtained by redistillation in vacuum in an atmosphere of nitrogen, boiled at 142° (3 mm.). *Anal.* Calcd. for $C_9H_{16}O_3$: C, 62.74; H, 9.37. Found: C, 62.40; H, 9.46; $n^{25}D$ 1.4550; d^{25}_4 1.0338.

(IV) **2-(β-Carboxyethyl)-2-ethylhexanal.**—The procedure described above was applied to a mixture of 30 g. of compound (II), 10 g. of sodium hydroxide and 100 g. of water except that the boiling was continued for five hours. The crude yield of aldehydo-acid boiling at 160–165° (4 mm.) was 24.5 g. The analytical sample obtained by redistillation *in vacuo* was a colorless oil boiling at 157° (4 mm.). *Anal.* Calcd. for $C_{11}H_{20}O_3$: C, 65.94; H, 10.07. Found: C, 65.90; H, 10.12; $n^{25}D$ 1.4564; d^{25}_4 1.0325.

(V) **α,α-Diethylglutaric Acid.**—To a stirred solution of 41.6 g. of compound (III), 25 g. of potassium hydroxide and 250 g. of water, a suspension of 57 g. of potassium permanganate in 500 g. of warm water was added gradually during the course of fifteen minutes while maintaining the reaction temperature at 30–40° by occasional cooling. The mixture was stirred for three hours and allowed to stand eighteen hours. The product was filtered, the precipitate washed, and the combined washings and filtrate acidified with hydrochloric acid. The turbid solution obtained was evaporated to dryness *in vacuo* on a steam-bath and the crystalline residue extracted several times with acetone. The acetone extract upon evaporation of the acetone deposited 26 g. of colorless crystals which after recrystallization from nitromethane formed colorless needles, m. p. 84° (uncor.). *Anal.* Calcd. for $C_9H_{16}O_4$: C, 57.40; H, 8.57. Found: C, 57.20; H, 8.70.

(VI) **α-Ethyl-α-butylglutaric Acid.**—A suspension of 57 g. of potassium permanganate in 500 cc. of water was added gradually to a solution of 60 g. of compound (IV), 250 cc. of water and 25 g. of potassium hydroxide at 45–50°. The mixture was stirred thereafter at room temperature for eighteen hours, filtered, and the filtrate acidified with concentrated hydrochloric acid. The product precipitated as a viscous oil. It was taken up in toluene, washed once with water and dried to yield 53 g. of crude acid. This was dissolved in hot nitromethane from which it separated on cooling in colorless crystals; yield 39 g. After several recrystallizations from nitromethane the melting point remained constant at 81–82°. *Anal.* Calcd. for $C_{11}H_{20}O_4$: C, 61.07; H, 9.28. Found: C, 60.70; H, 9.25.

(3) Bruson and Riener, THIS JOURNAL, 65, 18 (1943).

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(VII) 2-(β-Cyanoethyl)-2-ethylbutyric Acid.—A small quantity of 2-(β-cyanoethyl)-2-ethylbutyraldehyde (I) was spread out on a watch glass and exposed to the air for about a week. The crystalline crust which formed was separated and recrystallized from diisobutylene or petroleum ether (90–100°). The product separated in colorless needles, m.p. 88° (uncor.). *Anal.* Calcd. for $C_9H_{15}O_2N$: C, 63.86; H, 8.94; N, 8.28. Found: C, 63.80; H, 8.88; N, 8.29.

(VIII) γ,γ-Diethyl-δ-valerolactone.—Eighty-six grams of 2-(β-carboxyethyl)-2-ethylbutyraldehyde (III) was made faintly alkaline with a solution of about 20 g. of sodium hydroxide in 115 g. of water. This solution was shaken in an autoclave with 10 g. of Raney nickel catalyst and hydrogen under an initial pressure of 100 atmospheres, for seven hours at 120–140°. At the end of this time the pressure had fallen to about 40 atmospheres. The mixture was filtered free from catalyst and the clear filtrate acidified with concentrated hydrochloric acid. The thick oil which separated was dissolved in toluene, washed with water and evaporated to dryness *in vacuo* on a steam-bath. The residual oil was distilled under reduced pressure. The lactone came over between 112 and 118° at 4–5 mm. as a colorless oil; yield 63 g. The analytical sample obtained by redistillation boiled at 101° (2.5 mm.); $n^{25}D$ 1.4634; d^{25}_4 1.0064. *Anal.* Calcd. for $C_9H_{16}O_2$: C, 69.17; H, 10.33. Found: C, 68.78; H, 10.40.

(IX) γ-Ethyl-γ-butyl-δ-valerolactone.—The procedure described in (VIII) above was applied to 80 g. of 2-(β-carboxyethyl)-2-ethylhexanal (IV), 16 g. sodium hydroxide and 100 g. of water, using 10 g. of Raney nickel catalyst. After three hours at 125° the hydrogenation was complete. The acidification of the product yielded a colorless oil (IX) boiling at 124° (3.5 mm.); yield 44 g.; $n^{25}D$ 1.4635; d^{25}_4 0.9747. *Anal.* Calcd. for $C_{11}H_{20}O_2$: C, 71.68; H, 10.95. Found: C, 71.30; H, 11.19.

(X) 2-(β-Cyanoethyl)-2-ethyl-3-hexenal.—The procedure described for (I) was applied to a mixture of 252 g. freshly distilled α-ethyl-β-propylacrolein, 10 g. of 50% potassium hydroxide solution, and 110 g. of acrylonitrile, except that the condensation was made at 45–55°. The product distilled at 126–135° at 4–5 mm. as a pale yellow oil; yield 175 g. or 49%. The analytical sample boiled at 138–140° at 6 mm. *Anal.* Calcd. for $C_{11}H_{17}ON$: C, 73.68; H, 9.57; N, 7.82. Found: C, 73.14; H, 9.43; N, 7.63; $n^{25}D$ 1.4640; d^{25}_4 0.9375.

(XI) 2-(β-Carboxyethyl)-2-ethyl-3-hexenal.—A mixture of 55 g. (X), 20 g. sodium hydroxide and 200 g. of water was stirred and boiled under reflux for five hours, cooled, acidified, and worked up as described in the case of compound (III). The crude aldehydo-acid distilled at 160–170° at 5 mm. as a pale yellow oil; yield 40 g. The analytical sample boiled at 154° at 4 mm. *Anal.* Calcd. for $C_{11}H_{18}O_3$: C, 66.62; H, 9.15. Found: C, 66.60; H, 9.35; $n^{25}D$ 1.4695; d^{25}_4 1.0112.

Hydrogenation of (XI).—Sixty-three grams of 2-(β-carboxyethyl)-2-ethyl-3-hexenal (XI) was made faintly alkaline with an aqueous 20% sodium hydroxide solution and shaken in an autoclave with 10 g. of Raney nickel catalyst for five hours at 130–135° with hydrogen at an initial pressure of 110 atmospheres. The filtered product (XII) was acidified with concentrated hydrochloric acid and the heavy oil taken up in toluene, washed, and evaporated to dryness *in vacuo* on a steam-bath. The residual oil was distilled under reduced pressure. The product (45 g.) came over at 121–123° at 3 mm. as a colorless oil. The redistilled analytical sample boiled at 120° (3 mm.) and possessed the following constants: $n^{25}D$ 1.4632; d^{25}_4 0.9736. *Anal.* Calcd. for $C_{11}H_{20}O_2$: C, 71.68; H, 10.95 Found: C, 71.24; H, 10.96. Its constants and analysis show it to be identical with γ-ethyl-γ-butyl-δ-valerolactone (IX).

Oxidation of γ-Ethyl-γ-butyl-δ-valerolactone.—Part of the above lactone (18.4 g.) obtained from the hydrogenation of the unsaturated aldehydo-acid (XI) was oxidized by dissolving it in a solution of 11.2 g. of potassium hydroxide and 200 g. of water. To this solution there was added while stirring, a suspension of 47.4 g. of potassium permanganate in 400 g. of water at 35–40°. The mixture was then heated for eight and one-half hours at 55–60°, filtered and the filtrate acidified with concentrated hydrochloric acid. The oil which separated solidified after several hours at 5°; yield 17 g. After recrystallization from nitromethane it formed colorless needles, m. p. 81° (uncor.). A mixed melting point with (VI) showed no depression. The product was therefore α-ethyl-α-butylglutaric acid.

Acknowledgment.—The analyses of the above products were performed by Mr. C. W. Nash of these Laboratories.

Summary

1. Acrylonitrile condenses in the presence of strong bases, notably aqueous 50% potassium hydroxide as a catalyst, with α-hydrogen-bearing aldehydes that do not readily aldolize, particularly with dialkyl acetaldehydes higher than isobutyraldehyde, to cyanoethylate the α-carbon atom thereof.

2. α,β-Unsaturated aldehydes of the type of α-ethyl-β-propylacrolein, which lack an α-hydrogen atom undergo a 1,3-hydrogen shift to likewise yield the α-cyanoethylated derivatives.

3. The 2-(β-cyanoethyl)-dialkyl acetaldehydes formed are convertible to the corresponding (β-cyanoethyl)-dialkyl acetic acids by autoxidation or into the (β-carboxyethyl)-dialkyl acetaldehydes by hydrolysis. The latter upon reduction yielded γ,γ-dialkyl-δ-valerolactones, and upon oxidation α,α-dialkyl glutaric acids.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 288]

A Study of the Amorphous Portion of Dry, Swollen Cellulose by an Improved Thallous Ethylate Method[1,2]

BY A. G. ASSAF, R. H. HAAS AND C. B. PURVES

Several recent reviews[3] summarize in detail the modern concept of the structure of fibrous cellulose. It is only necessary to remark here that the linear macromolecules are crystallized together along intermittent portions of their length to form elongated, dense crystallites, or micelles, that are of submicroscopic dimensions and produce a well-defined X-ray diffraction pattern. Other portions of the macromolecules have a more confused relationship in space to one another, give rise to a diffuse or "amorphous" X-ray background and form a less dense, highly porous system of great absorptive capacity. The coarsest flaws and discontinuities in the fiber are visible in the microscope and electron microscope.[4] X-Ray studies of fibers impregnated with colloidal metals have revealed the presence of intercommunicating, elongated channels ranging in diameter from 50–120 Å.[5] The great majority of the submicroscopic faults in the crystal structure, however, are of the order of 10 Å. in cross section, or have molecular dimensions. These ideas make it easy to understand that the amount of amorphous cellulose might be increased at the expense of the less perfectly organized crystallite portion by swelling the fiber in a suitable liquid and be decreased by subsequent drying, particularly under tension.[6a,6b,7] There is evidence that such changes have an important influence upon the elasticity, the absorptive capacity and other industrially valuable physical properties of the fiber.[6b]

One method of estimating the amount of amorphous cellulose is to measure the intensity of the diffuse "background" radiation in the X-ray diffraction pattern of the fiber.[6b] In other methods, the solid cellulose is submitted to a suitable chemical change and the percentage of the more accessible, amorphous portion is calculated from the extent of the initial, more rapid reaction. The rate plots of various heterogeneous reactions[8,9] have been interpreted in this way. These chemical procedures suffer from the disadvantage that the reagents either do, or possibly may, penetrate the cellulose crystallites and may also cause swelling during the estimation. Both eventualities would tend to make the results high by an undetermined amount. In an endeavor to avoid this difficulty, Harris and Purves studied the thallation produced in ramie fiber by thallous ethylate dissolved in ether or benzene, which are non-hydroxylic, non-swelling liquids.[10] Since thallous ethylate is a strong base like its sodium analog, cellulose hydroxyl groups that came into contact with the reagent were changed to thallium alcoholates

$$\text{Cellulose OH} + \text{TlOEt} \longrightarrow \text{Cellulose OTl} + \text{EtOH}$$

The reaction was considered to be restricted to the amorphous cellulose because the thallation of finely powdered sucrose crystals, or unswollen ramie fiber, was very small and because the X-ray diffraction pattern of thallium cellulosate had no signs of a regularly oriented thallium crystal lattice. The thallium cellulosate was heated with excess methyl iodide,[11] or dimethyl sulfate, in benzene and, after purification, the methoxyl content

$$\text{Cellulose OTl} + \text{MeI} \longrightarrow \text{Cellulose OMe} + \text{TlI}$$

of the resulting partly methylated cellulose was determined. Since the thallation and methylation of some fructosides proceeded almost quantitatively with sufficient excess of the reagents,[12] the methoxyl substitution of the partly methylated cellulose was accepted as proportional to the number of hydroxyl groups that had come into contact with the thallous ethylate reagent. The present article describes substantial improvements in the technique of the estimation, together with the behavior of dry, highly swollen cotton linters toward thallous ethylate dissolved in several organic liquids. A new definition of amorphous cellulose is suggested and the measurements show that its absolute amount varies greatly.

Experimental

The methods are described in detail. Although straightforward enough in principle, they can be used successfully only by avoiding many manipulative errors that are not so unimportant as they may seem.

(1) Presented at the February, 1943, meeting in Cumberland, Maryland, of the Western Maryland Section of the American Chemical Society.

(2) Abstracted from Theses submitted to the faculty of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degrees of Doctor of Philosophy (A. G. A., May 1942) and of Bachelor of Science (R. H. H., December 1942).

(3) See, for example, Marsh and Wood "An Introduction to the Chemistry of Cellulose," 2nd ed., Chapman and Hall, London, 1942, pp. 380–405.

(4) Barnes and Burton, *Ind. Eng. Chem.*, **35**, 120 (1943). Earlier references are cited.

(5) Frey-Wyssling, *Protoplasma*, **25**, 261 (1936); **27**, 372 (1937). The fine structure of fibrous cellulose is discussed.

(6) (a) See, for example, the reviews by Mark, *Ind. Eng. Chem.*, **34**, 449 (1942); (b) *J. Phys. Chem.*, **44**, 764 (1940).

(7) Kratky, *Angew. Chem.*, **53**, 153 (1940), a review.

(8) Hess and Trogus, *Z. physik. Chem.*, **B15**, 157 (1931–1932); *Kolloid-Z.*, **68**, 168 (1934).

(9) Nickerson, *Ind. Eng. Chem.*, **33**, 1022 (1941); **34**, 85, 1480 (1942).

(10) Harris and Purves, *Paper Trade J.*, **110**, 29 (Feb. 8, 1940).

(11) Fear and Menzies, *J. Chem. Soc.*, 937 (1926).

(12) Purves and Hudson, THIS JOURNAL, **59**, 49 (1937).

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Preparation of Cellulose Samples.—Thoroughly dewaxed, air-dried, high grade cotton linters,[13] 15 g., were immersed in 540 cc. of 10% caustic soda kept at 5°,[14] and after three hours the loose, swollen mass was diluted with 540 cc. of 2% caustic soda. Thirty minutes later the cotton was recovered by filtration and was washed thoroughly and in succession with water, with 1% acetic acid and with distilled water. Slight squeezing quickly removed most of the excess moisture before the wet mass was dispersed in a liter of 99+ % methanol. The methanol was removed and replaced by a fresh amount after fifteen minutes. A third immersion, this time in magnesium-dried methanol, was followed by two more, each of thirty minutes duration, in one-liter volumes of sodium-dried, thiophene-free benzene. The supernatant liquors were easily reclaimed and purified. Great care was taken to avoid letting the cellulose dry out even superficially, by keeping it completely covered by the methanol or benzene, and by quick manipulation during the transfers. Neglect of this precaution resulted in non-uniform preparations.

The swollen linters, now moist with benzene, were dried for several days in a desiccator containing solid paraffin wax. The desiccator was evacuated at intervals to 25 mm. pressure, but the use of a higher vacuum was avoided because a too rapid, irregular evaporation of the benzene produced a non-uniform product. This mishap was signalized by the appearance of white patches on the surface of the rather translucent mass. Although up to 15 g. of linters could be swollen and dried in a uniform way with available laboratory equipment, the degree of swelling could not be exactly duplicated in successive preparations. The dried, swollen linters were stored for ten days or more over concentrated sulfuric acid in a desiccator that was *not* evacuated and were then ready for thallation. Solid caustic potash *in vacuo* was a less efficient desiccating agent. The effect of this final drying on moisture-containing preparations is discussed in another article.[15]

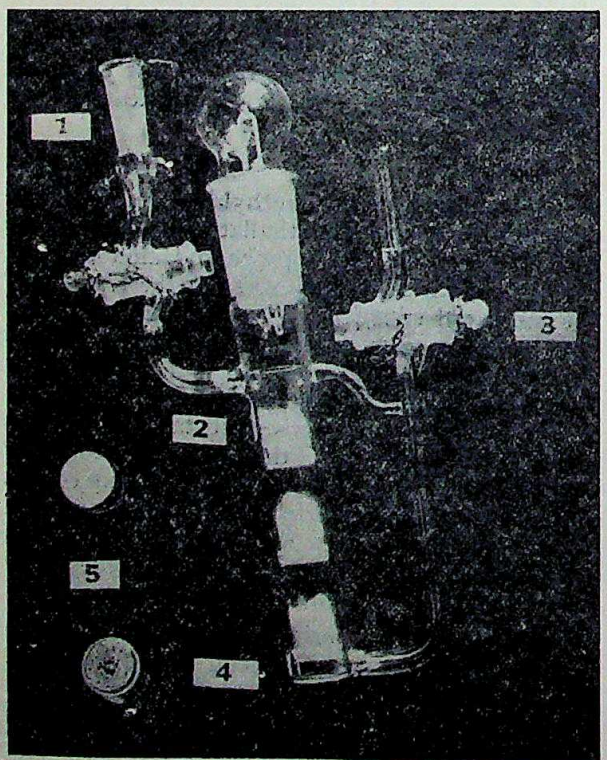

Fig. 1.—Apparatus used for thallation of cellulose.

Solvents.—The ready decomposition of thallous ethylate by moisture, by peroxides and other catalysts made it essential to purify all solvents carefully. Standard methods were used.[16]

Commercial 1,4-dioxane was freed from any acetals by refluxing with dilute hydrochloric acid in the presence of a stream of air. Thiophene was removed from benzene by bubbling the vapors, at 80°, through concentrated sulfuric acid. Other solvents were given suitable preliminary purifications when necessary. All hydrocarbons and ethers were dried with sodium before fractional distillation and were stored over sodium wire in brown glass bottles to avoid the formation of peroxides. These solvents were decanted from the sodium when required. All alcohols were dried either by adding small pieces of sodium or by refluxing with clean magnesium ribbon, and were recovered by distillation just before use. Methyl iodide was redistilled from phosphorus pentoxide.

Preparation of Thallous Ethylate Solutions.—Thin slices of clean, silvery thallium metal, 2 g., contained in a 125 cc. glass-stoppered, thick-walled Erlenmeyer flask, were covered with 50 cc. of absolute ethanol, and a stream of dry oxygen gas was played over the surface of the liquid for one or two minutes.[17] The flask was then stoppered, shielded from light and shaken mechanically. Solution of the metal was complete within two hours if the oxygen atmosphere was renewed at fifteen minute intervals. It was inadvisable to use thallium pellets in the preparation unless their surface was quite free from the insoluble brown crust formed by prolonged exposure to the air. The use of a trace of iodine to hasten the solution of the metal[10] was abandoned because iodine also catalyzed the decomposition of the thallous ethylate.

A small piece of porous porcelain was added to the solution to promote uniform boiling during the removal of ethanol in the vacuum of a water pump. The latter part of the distillation was from a warm water-bath but an excessive use of the pump was avoided lest moisture reach the ethylate when the vapor pressure of the residual alcohol became low. When the flask was shielded from light and the technique of distillation was satisfactory, the residual thallous ethylate formed about 1 cc. of a heavy, pale yellow oil. The oil was kept at room temperature for ten minutes in a high vacuum to remove any traces of ethanol and was dissolved in 50 cc. of the pure, anhydrous solvent to be used. Glass-stoppered graduates of 100-cc. capacity were convenient receptacles for these solutions.

The normality of the thallous ethylate was determined by pipeting 5 cc.[18] into a mixture of 20 cc. of methanol and 10 cc. of 0.1 *N* hydrochloric acid, the excess of which was then titrated with standard caustic soda. Dilution of the thallous ethylate solution to 0.1 *N* was made with the appropriate volume of the pure solvent. These solutions did not change their normality during several weeks if kept near 0° in the dark, but exposure to light caused a rather rapid formation of a spongy, brown decomposition product. Thallous ethylate oil was also fairly stable when properly stored.

Apparatus.—The all-glass Pyrex apparatus (Fig. 1) was designed for triplicate cellulose samples and was made from 20-mm. tubing about five inches long. The top carried a no. 20 female joint and could be closed with a well-fitting, lightly greased, ground stopper. Liquids introduced through the no. 7 female joint (1) from a 30-cc. separatory funnel passed through a stopcock and a sintered glass filter (2) before entering the tube a short distance below the stopper. Solutions were withdrawn through the stopcock (3) which was attached to the side of

(13) The authors wish to thank Dr. H. M. Spurlin and the Hercules Powder Company, Hopewell, Virginia, for the gift of this material.

(14) Richter and Glidden, *Ind. Eng. Chem.*, **32**, 480 (1940).

(15) Assaf, Haas and Purves, THIS JOURNAL, **66**, 64 (1944).

(16) Weissberger and Proskauer, "Organic Solvents," The Clarendon Press, Oxford, 1935.

(17) Lamy, *Ann. chim. phys.*, [4] **3**, 373 (1864).

(18) Although thallous ethylate is practically non-volatile and produced no ill effect on health during the research, the reader is reminded that many thallium compounds are cumulative poisons.

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the tube by a solid glass support and to the flat bottom (4) by capillary tubing. Both stopcocks were of the 2-mm. slant-bore type.

The cellulose samples were contained in three glass cups, one inch in height, that fitted rather closely, one above the other, into the 20-mm. tube. These cups, shown separately at (5), had sintered glass bottoms for finely divided samples and perforated bottoms for fibrous ones. An annular segment of glass rod raised the lowest cup from the bottom of (4) so that liquid passed without obstruction into the capillary exit tube.

Procedure for Thallation and Methylation.—The cotton samples, 0.1 to 0.3 g., were transferred from a desiccator into the tared cups and were quickly weighed on a magnetically damped balance prior to insertion into the apparatus (Fig. 1). The stopper was replaced promptly to prevent access of moisture and the apparatus was at once evacuated with an oil pump attached to (3). A low result was obtained when this evacuation was neglected. Stopcock (3) was then closed and (1) was opened to permit 0.1 *N* thallous ethylate solution to be sucked into the apparatus from the separatory funnel. About 20 cc. of solution was sufficient to fill all three cups and immerse them completely. After standing in the dark at room temperature for one hour, the partly exhausted solution was sucked out through stopcock (3), with a minimum use of a water pump, and the thallation was repeated with fresh solution drawn in through (1). Samples thallated in ethers or hydrocarbons were colored yellow and, the deeper the color, the greater the thallation. When the thallous ethylate was dissolved in an alcohol, no color developed, although thallation occurred. The thallous ethylate solution was withdrawn at the end of the second hour in the dark and residual amounts were washed from the samples by filling the apparatus with pure, dry benzene. Four or five benzene extractions, the first of fifteen and the others each of five minutes duration, were sufficient. The wet samples were then prepared for methylation by filling the apparatus with benzene containing a large excess, 2 cc., of methyl iodide. The no. 20 ground-glass stopper (Fig. 1) was replaced with a glass-jointed reflux condenser whose upper end was equipped with a calcium chloride tube, stopcocks (1) and (3) were closed and the entire apparatus was immersed up to the level of the upper sample cup in a water-bath kept at 80°. No exclusion of light was necessary during the methylation, which was complete within three and one-half hours. Since thallous iodide was a by-product of the reaction, the methylation was attended by a color change in the samples from yellow or white to orange, the final depth of which was a rough measure of the amorphous cellulose. An experienced operator could complete the thallation and methylation of twenty-one cellulose samples, contained in seven sets of equipment, during one long working day. The condenser was then exchanged for the glass stopper, the excess methyl iodide–benzene mixture in the cell was sucked out by the water pump and pure benzene was sucked in. The first two benzene extractions, each of fifteen minutes' duration, were followed by six more each lasting for five to ten minutes. Thoroughness was essential in this extraction lest traces of residual methyl iodide invalidate the final methoxyl estimation. The apparatus was then connected to a vacuum pump but in the beginning stopcock (3) was kept open only momentarily in order to avoid scattering of the samples by a too sudden evaporation of the residual benzene. After a final drying in high vacuum at 80° for two hours, the whole of each sample, with its occluded thallous iodide, was analyzed at leisure for its methoxyl content. Clark's procedure[19] was followed except that 5 g. rather than 2 g. of phenol was added to the hydriodic acid to promote more regular ebullition, and the sample was dissolved in the reagent by a preliminary heating for a few minutes in a boiling water-bath.[20] The methoxyl content was expressed as a percentage of the original, *unsubstituted* cellulose, and multiplication by the factor 100/57.4 gave the percentage of the cellulose hydroxyl groups that had been methylated.[21] This value was assumed to be equal to the percentage of the cellulose wetted by the solvent for the thallous ethylate.

(19) Clark, *J. Assoc. Official Agr. Chem.*, **15**, 136 (1932).

(20) Arndt and Neumann, *Ber.*, **70B**, 1835 (1937).

TABLE I

THALLOUS ETHYLATE METHYLATIONS OF DIFFERENT SAMPLES OF DRY, SWOLLEN LINTERS

Solvent for $TlOC_2H_5$	Methoxyl introduced[a] % Cup 1	Cup 2	Cup 3	Mean %	Hydroxyl groups %[b]	Error, ± %
Benzene	6.1	5.7	5.7	5.8	10.1	5
Decalin	3.4	2.2	2.9	..	..	25
Decalin	4.1	4.1	...	..	..	0
Decane	5.7	5.7	...	5.7	9.9	0
Ethyl ether	11.5	10.0	9.7	10.4	18.1	10
Ethyl ether	7.4	6.6	7.7	7.2	12.5	8
Isoamyl ether	5.0	4.2	3.9	..	..	14
Methanol[c]	4.8	4.7	4.9	4.8	8.4	2
Ethanol[c]	6.5	6.5	6.4	6.5	11.3	1.5
Propanol[c]	4.8	5.3	5.2	5.1	8.9	4
n-Amyl ether[c]	7.5	7.5	7.5	7.5	13.0	0

[a] Based on weight of original cellulose sample. [b] Mean methoxyl percentage × 100/57.4 = percentage of cellulose hydroxyl groups methylated. [c] Extraction of last traces of methyl iodide as described in experimental portion.

Reproducibility of the Estimation.—Table I contains a representative portion of the data, which included more than two hundred and fifty individual estimations. Cups 1, 2 and 3 refer to triplicate analyses carried out simultaneously in the top, middle and bottom cups of a single piece of apparatus. If the observed methoxyl content decreased markedly and steadily from the top to the bottom cup, as in the case quoted for thallous ethylate in isoamyl ether, incomplete thallation was at once suspected and the analyses were repeated. The other serious cause of divergence between triplicates was failure to extract the last traces of methyl iodide from the methylated samples prior to the methoxyl estimation. Most of the present data were obtained before this fact was fully appreciated and the divergence from the averages quoted below was sometimes as much as ± 10%. When the method of extraction already described was rigidly followed, the agreement between triplicates was usually better than ± 5%. The third analysis on samples known to be uniform was sometimes omitted when the first two gave the same result. Wide fluctuations that persisted in a second series of analyses were characteristic of samples that were not uniform and were usually connected with poor technique during the drying of the swollen cellulose.

Estimation of Cellulose Hydroxyl Groups by Means of Methylmagnesium Iodide.—Use was made of a modified Zerewitinoff apparatus that had been extensively tested during the determination of active hydrogen in insulating and other oils.[22,23] A thoroughly dried specimen of highly swollen linters, 0.117 g., was brought into contact with excess of an approximately 0.4 *M* solution of methylmagnesium iodide in isoamyl ether[24] and 4.96 cc. of methane (cor. to N.T.P.) was collected. This amount corresponded to the active hydrogen in 10.2% of the hydroxyl groups in the sample. A preliminary result of 5.7% was rejected as erroneous. Parallel estimations by the thallation-methylation method, giving 6.8, 6.5 and 6.5% methoxyl with thallous ethylate dissolved in the same

(21) Trimethyl cellulose has a methoxyl content of (3 × 31 × 100)/162, or 57.4% on this basis, and the figure for lower methylated derivatives is directly proportional to their substitution.

(22) Assaf and Gladding, *Ind. Eng. Chem., Anal. Ed.*, **11**, 164 (1939).

(23) Larsen, *ibid.*, **10**, 195 (1938).

(24) Kohler and Richtmyer, THIS JOURNAL, **52**, 3736 (1930).

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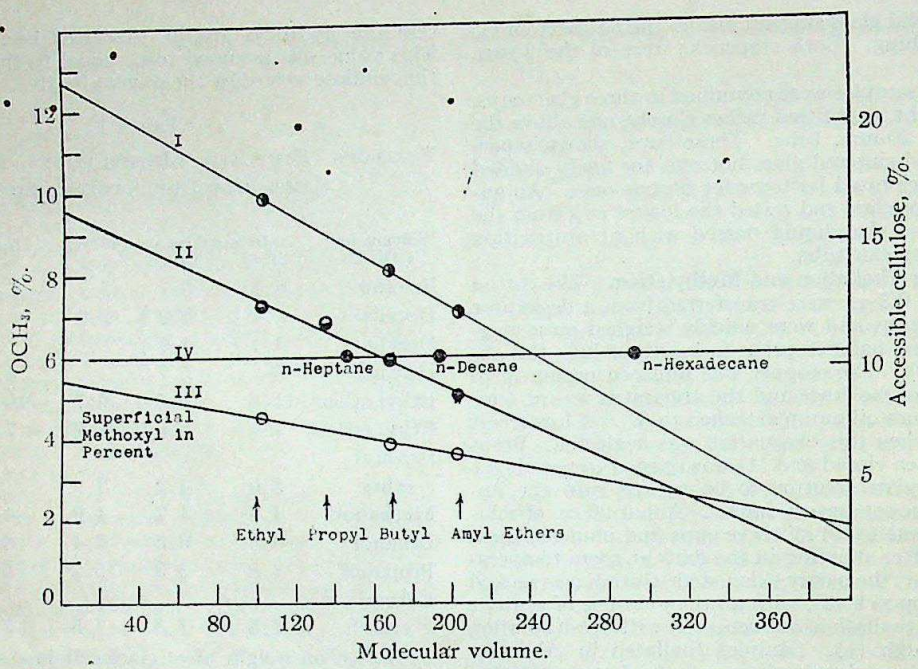

Fig. 2.—Superficial methylation and accessible cellulose plotted against molecular volume of thallous ethylate solvent: ethers, ○, ◑ and ◒; hydrocarbons, ●.

solvent, indicated that 11.5% of the hydroxyl groups had been methylated. The latter figure was 20% with thallous ethylate in diethyl ether. Although the Zerewitinoff method checked the thallous ethylate technique, the utility of the former for present purposes was limited by its sensitivity to traces of moisture in the sample and by the necessity of employing a solvent with a low vapor pressure.

Results and Discussion

In Fig. 2, the percentage of methoxyl introduced into three different samples of uniformly swollen, dried linters by the thallation-methylation technique is plotted against the molecular volume of the liquid in which the thallous ethylate was dissolved. Each point is the average of duplicate or triplicate estimations that agreed with the mean to within ±10% and all thallations of each cellulose sample were made simultaneously in order to avoid the effects of possible change in the specimen.[15] These precautions were taken throughout the work. The points for ethyl, *n*-propyl (Fig. 2, plot II), *n*-butyl and *n*-amyl ethers fall on three straight lines whose slope and position are characteristic of the cellulose sample. Although the decrease in the degree of methylation with increasing molecular volume could have been predicted from the work of others,[25,26,27] the closely linear nature of the relationship suggests that the cross-section of the capillaries in the amorphous portion of the linters diminishes in a regular way as a crystalline region is approached. Plot IV, obtained with the same cellulose and at the same time as the other plot II, demonstrates that the extent of thallation with the normal hydrocarbons is entirely independent of their molecular volume. Attempts were made to reconcile the data in the two series by plotting the per cent. of methylation against some other physical property, such as the viscosities or the molecular weights, of the liquids in question. These attempts revealed no regular relationship and the results with normal hydrocarbons require amplification. Their curious behavior may be connected with the fact that they differ from ethers in having no dipole moment and no residual affinity for hydroxyl groups. Since branched chain and cyclic molecules are more limited in shape configurations than their normal analogs, it is to be expected that they would have greater difficulty in entering the finest capillaries and would permeate the amorphous portion of cellulose less efficiently. Figure 3 shows that the methoxyl contents produced with thallous ethylate in isoamyl ether, 1,4-dioxane and decalin were lower than those obtained with *n*-amyl ether, diethyl ether and *n*-decane, respectively, although each pair had approximately the same molecular volume. The figure for dioxane is interpolated from similar experiments.

The data summarized in Fig. 4 are strictly comparable with the exception of those for methanol, which were obtained with an 0.056 *N*, instead of the usual 0.1 *N*, thallous ethylate solution.[28] Individual estimations are recorded because those for the ethers were unusually discordant. Although the results with the normal alcohols from ethyl to heptyl are regular and reproducible, the molecular volume plot is not linear and lies below that of the ethers. Since

(25) Sheppard and Newsome, *J. Phys. Chem.*, **36**, 2306 (1932).

(26) Russell, Maass and Campbell, *Can. J. Research*, **15B**, 13 (1937).

(27) Kanamaru and Chao, *Kolloid-Z.*, **84**, 85 (1938).

(28) The addition of methanol to liquid thallous ethylate caused the prompt deposition of the sparingly soluble, crystalline methylate.

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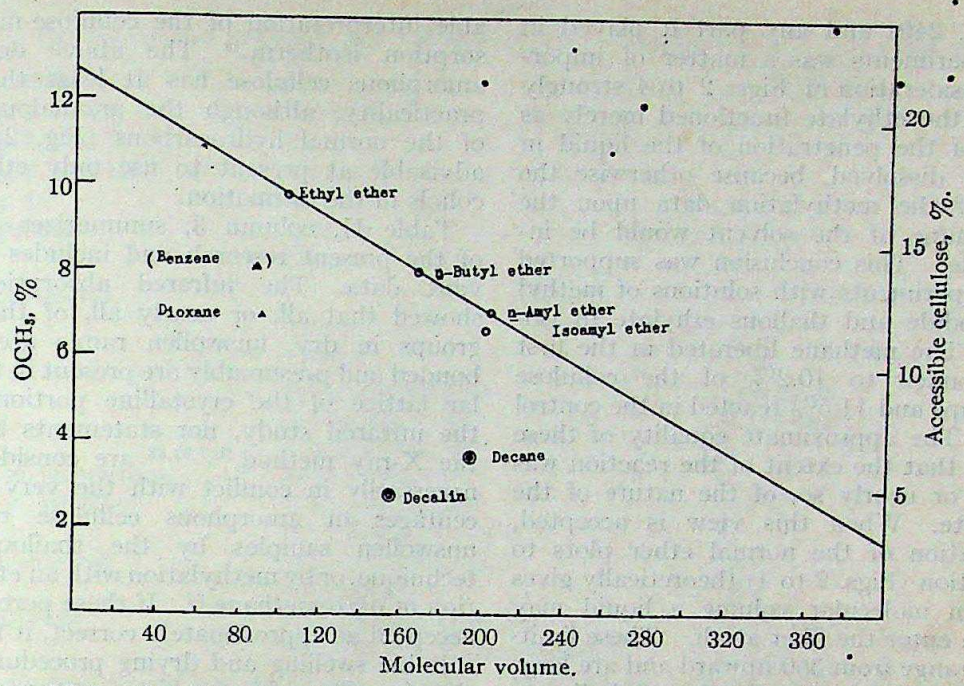

Fig. 3.—The superficial methylation of a uniform, swollen cellulose by thallous ethylate dissolved in various liquids.

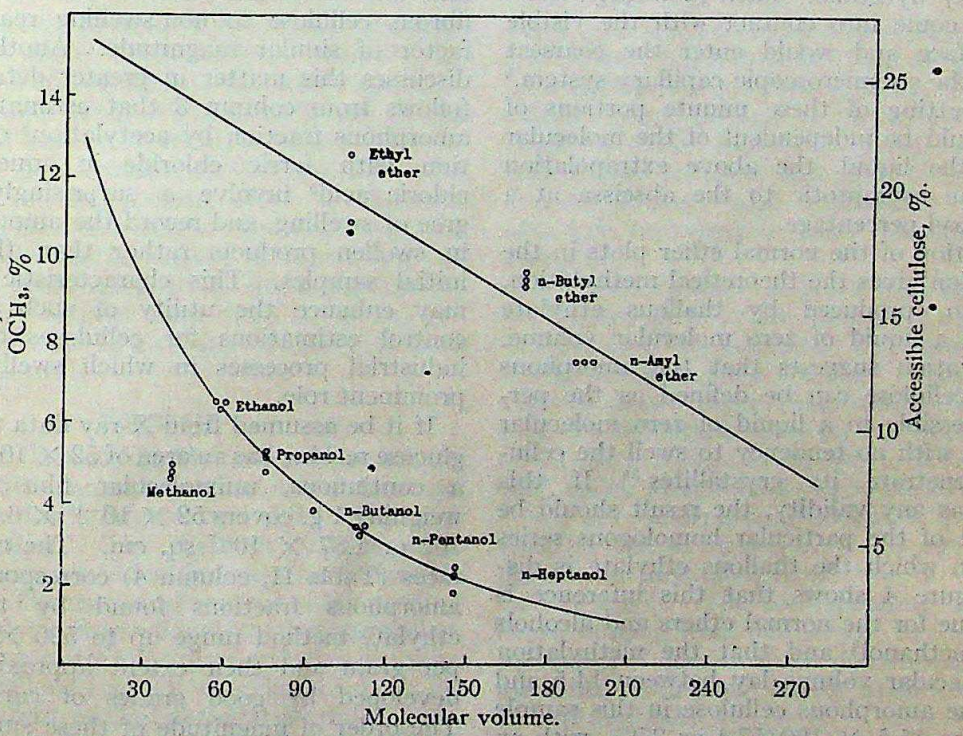

Fig. 4.—The superficial methylation of a uniform, swollen cellulose by thallous ethylate dissolved in various normal alcohols and ethers: triplicate estimations shown.

alcohols swell cellulose somewhat, they should penetrate the amorphous portion more readily than ethers of comparable molecular volume and lead to more, rather than less, thallation and methylation. This discrepancy strongly suggests that thallation in alcohols was incomplete, probably because the large number of hydroxyl groups they contain competed effectively with those in the cellulose for the thallium. There is also a possibility that molecular association rendered the effective volumes of the alcohols three to seven times larger than those calculated.[29]

The thallous ethylate molecule has a calculated molecular volume of about 69 (density about

(29) Fox and Martin, *Trans. Faraday Soc.*, **36**, 897 (1940), express the opinion that up to four benzyl alcohol molecules may form hydrogen bonds with each other. The resulting, unstable, cyclic structure may have the hydrocarbon groups on the outside.

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3.6,[17] mol. wt. 249) and any part it played in the above experiments was a matter of importance. A consideration of Figs. 2 to 4 strongly suggests that the ethylate functioned merely as a delineator of the penetration of the liquid in which it was dissolved, because otherwise the dependence of the methylation data upon the molecular volume of the solvent would be incomprehensible. This conclusion was supported by parallel experiments with solutions of methyl magnesium iodide and thallous ethylate in isoamyl ether. The methane liberated in the first case corresponded to 10.2% of the cellulose hydroxyl groups and 11.5% reacted in the control experiment. The approximate equality of these figures shows that the extent of the reaction was independent, or nearly so, of the nature of the reactive solute. When this view is accepted, the extrapolation of the normal ether plots to zero methylation (Figs. 2 to 4) theoretically gives the maximum molecular volume a liquid may have if it can enter the fiber at all. These limiting volumes range from 360 upward and are large enough to accommodate molecules as bulky as those of many dyestuffs. Such molecules, however, would come into contact with the visible external surface and would enter the coarsest channels of the submicroscopic capillary system.[5] Since the wetting of these minute portions of the fiber would be independent of the molecular volume of the liquid, the above extrapolation must become asymptotic to the abscissa at a small methoxyl percentage.

Extrapolation of the normal ether plots in the other direction gives the theoretical methylation, or thallation, produced by thallous ethylate dissolved in a liquid of zero molecular volume. This observation suggests that the amorphous portion of cellulose can be defined as the percentage accessible to a liquid of zero molecular volume and with no tendency to swell the cellulose or penetrate its crystallites.[30] If this definition has any validity, the result should be independent of the particular homologous series of liquids in which the thallous ethylate is dissolved. Figure 4 shows that this inference is probably true for the normal ethers and alcohols (omitting methanol) and that the methylation at zero molecular volume lay between 14.5 and 16.5%. The amorphous cellulose in this sample was therefore 15.5 × 100/57.4 or 27%, with an absolute error of the order of ±2%. Since the extrapolation was a large one, an attempt was made to determine the data for dimethyl ether (mol. vol. 40) which falls at an intermediate point on the plot. The estimation was tried at atmospheric pressure and −30° but was not completed because the thallous ethylate crystallized rapidly from solution at this low temperature. Another attempt with water (mol. vol. 18) was more successful and led to a new and reasonable interpretation of the cellulose-moisture adsorption isotherm.[15] The above definition of amorphous cellulose has at least the merit of practicality, although the anomalous behavior of the normal hydrocarbons (Fig. 2) makes it advisable at present to use only ethers or alcohols in the estimation.

Table II, column 3, summarizes the results of the present research and includes other relevant data. The infrared absorption study[31] showed that all, or nearly all, of the hydroxyl groups in dry, unswollen ramie are hydrogen bonded and presumably are present in the molecular lattice of the crystalline portion. Neither the infrared study, nor statements based upon the X-ray method,[6b,7,32,33] are considered to be necessarily in conflict with the very small percentages of amorphous cellulose revealed in unswollen samples by the thallous ethylate technique, or by methylation with an ethereal solution of diazomethane.[34] If these percentages are accepted as approximately correct, it follows that suitable swelling and drying procedures increase the amorphous fraction fifty or even an hundredfold and therefore increase the accessibility of fibrous cellulose to non-swelling reagents by a factor of similar magnitude. Another article[15] discusses this matter in greater detail. It also follows from column 3 that estimations of the amorphous fraction by acetylation[8] or by oxidation with ferric chloride in aqueous hydrochloric acid[9] involve a surprisingly large degree of swelling, and record the amounts present in swollen products rather than those in the initial samples. This characteristic, of course, may enhance the utility of such methods as control estimations for celluloses destined for industrial processes in which swelling plays a prominent role.

If it be assumed from X-ray data that a single glucose residue has an area of 52×10^{-16} sq. cm.,[35] a continuous, unimolecular film of cellulose weighing 1 g. covers $52 \times 10^{-16} \times 6.02 \times 10^{+23}/162$ or $1.87 \times 10^{+7}$ sq. cm. The colloidal surfaces (Table II, column 4) corresponding to the amorphous fractions found by the thallous ethylate method range up to 520×10^{4} sq. cm. per gram and their extent approximates those developed by good grades of carbon black.[36] The order of magnitude of these surfaces is also in agreement with the general value of 300×10^{4} sq. cm. per gram derived for swollen celluloses

(30) We are indebted to Dr. R. F. Conaway, of E. I. du Pont de Nemours and Company, for suggesting this definition.

(31) Ellis and Bath, THIS JOURNAL, **62**, 2859 (1940).

(32) Meyer, *Ber.*, **70**, 266 (1937).

(33) Kratky, *Silk and Rayon*, **13**, 480, 571, 634, 638 (1939); *C. A.*, **33**, 6041 (1939); **34**, 259 (1940), a review.

(34) Reeves and Thompson, *Contrib. Boyce Thompson Inst.*, **11**, 55 (1939); *C. A.*, **34**, 3923 (1940). The degree of methylation increased with the moisture content.

(35) Adam, *Trans. Faraday Soc.*, **29**, 90 (1933), found 52 sq. Å. from a model built to scale and 55 to 60 sq. Å. from measurements of unimolecular films. A value of 42 sq. Å. was assumed by one of the present authors in the earlier article.[10]

(36) Brown and Smith, *Ind. Eng. Chem.*, **34**, 352 (1942).

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TABLE II

THE AMORPHOUS FRACTION AND COLLOIDAL SURFACE OF VARIOUS CELLULOSE SAMPLES

Swollen samples[a]	Method	Amorphous cellulose, %	Colloidal surface sq. cm./g. $\times 10^{-4}$
Linters, Fig. 2, Plot I	TlOEt	22	420
Linters, Fig. 2, Plot II	TlOEt	17	330
Linters, Fig. 2, Plot III	TlOEt	9	170
Linters, Fig. 4	TlOEt	27	520
Linters, regenerated	TlOEt[10]	3.3	60
Ramie	TlOEt[10]	18	360
Unswollen samples[b]			
Linters	TlOEt	0.4	8
Ramie	TlOEt[10]	0.25	5
Ramie	Infrared absorption[31]	Very small	
Linters	X-Ray diffraction[33]	Practically none	
"Cellulose"	X-Ray diffraction[32]	10	190
Viscose rayon, unstretched	X-Ray diffraction[6b]	60	1150
Viscose rayon, stretched	X-Ray diffraction[6b]	30	580
Viscose rayon	$FeCl_3$ in aqueous HCl[9]	21	400
Linters, unmercerized	$FeCl_3$ in aqueous HCl[9]	5	100
Cellulose	Diazomethane[34]	0.4	8
Linters, mercerized	$FeCl_3$ in aqueous HCl[9]	11	210
Ramie	Esterification, X-ray diffraction[8]	30–50	580–960

[a] Swollen in caustic soda and dried by solvent exchange. [b] Dried directly, at 25° or 105°, whether previously swollen or not.

from the areas covered by various adsorbed films.[37] The latter investigations, however, assign a cross-sectional area to the adsorbed molecule, rather than to the cellulose itself, and assume the adsorbed film to be monomolecular and continuous. A close comparison of these data with the results of the present work is therefore hardly possible. As might be expected, the microscopically visible surface of about 2×10^3 sq. cm. per gram assigned to unswollen fibers[37] is considerably smaller than the 5×10^4 sq. cm. per gram available to an ether of zero molecular volume (Table II).

Summary

1. Cotton linters, highly swollen in caustic soda and dried through methanol and benzene, were immersed in a large excess of 0.1 *N* thallous ethylate solution. The thallium cellulosate so formed was methylated with excess methyl iodide in benzene. The methoxyl content of the product was accepted as proportional to the percentage of the cellulose wetted by the particular liquid in which the thallous ethylate was dissolved.

2. The extent of the methylation did not depend upon the molecular volume of normal hydrocarbon solvents for the thallous ethylate, but the relationship was inverse and linear for the normal ethers from diethyl to di-*n*-amyl. Branched chain or cyclic ethers and hydrocarbons penetrated the cellulose less efficiently than their normal analogs and thallations in alcohols, although reproducible, were thought to be incomplete.

3. "Amorphous" cellulose was defined to be the percentage wetted by an ether of zero molecular volume and was estimated by extrapolating the linear methylation-molecular volume plots of three or more straight chain ethers. An extrapolation of the similar plot for the normal alcohols from ethyl to hexyl tended to confirm the result, which was probably accurate to ±10%.

4. The amorphous fractions of swollen linter samples were as high as 27 ± 2% but the amount present in unswollen fibers was of the order of 0.25 to 0.5%. The corresponding colloidal surfaces, ranging from 520×10^4 to 5 or 10×10^4 sq. cm. per gram, were not inconsistent with published estimates based upon other experimental methods.

(37) Stamm and Millett, *J. Phys. Chem.*, **45**, 43 (1941). Includes a review of the literature.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY No. 289]

A New Interpretation of the Cellulose–Water Adsorption Isotherm and Data Concerning the Effect of Swelling and Drying on the Colloidal Surface of Cellulose[1,2]

BY A. G. ASSAF, R. H. HAAS AND C. B. PURVES

The great affinity of dry cellulose for water is today attributed to the hydrogen bonding capacity[3] of the alcoholic groups because progressive masking of the latter by esterification progressively reduces the amount of moisture absorbed from standard, humid surroundings.[4,5,6a] Although immersion in heavy water replaces the hydrogen in all alcoholic groups throughout the mass of cellulose by deuterium,[7] X-ray[8] and optical data[9] strongly suggest that the water molecule as a whole fails to penetrate the crystallites and that the absorption is a function of the amorphous portion. It is well known[10] that cellulose acquires an equilibrium moisture content when kept for a sufficiently long time in a humid atmosphere and that the adsorption isotherm is of the sigmoid type illustrated in Fig. 1, plots I and II. Flexed curves are also obtained by plotting the absorbed moisture, or the relative humidity, against other physical properties such as the rigidity,[11a] the electrical conductivity,[6,12] capacitance and power factor.[13] Moreover, similar relationships exist between the amount absorbed and the specific heat[14] and apparent specific volume[15] of the absorbed water, the heats of wetting by water, aqueous alkali and methanol,[12,16] the selective absorption of water, or of solute, from various solutions[17] and the absorption of gases[18,19] and alcohols.[5b,20,21] All the results are consistent with the view that the first avid adsorption of moisture (to region B, Fig. 1) is caused by the strong hydrogen bonding of single molecules to each of all the alcoholic groups accessible to water in the amorphous portion of the cellulose. The intermediate, nearly linear portions of plots I and II (region B to region D) correspond either to the formation of multilayers that are held with diminishing tenacity[3] or to the filling up of the finer capillaries.[19,22] There is agreement to the effect that the steep, final portion of the adsorption isotherm (from region D) at high humidities owes its shape to the swelling of the cellulose and to the condensation of "free" or "unbound" water in the coarser capillaries.[23] On this interpretation, the moisture content at B provides a measure of the amount of cellulose, or of the extent of its col-

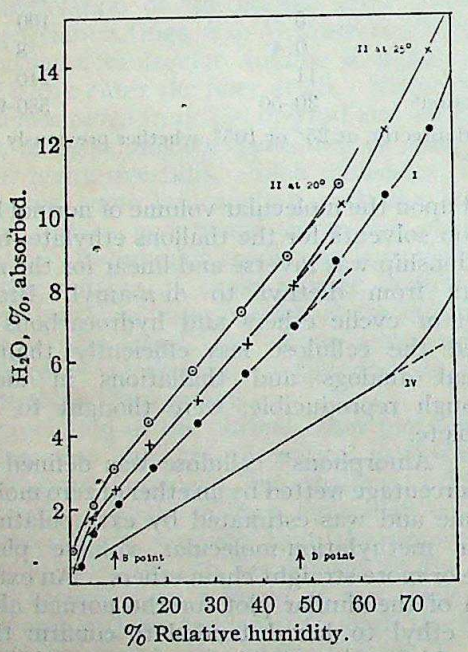

Fig. 1.—Moisture adsorption isotherms: Cellulose I at 25°, ●; Cellulose II at 20°, ○; Cellulose II at 25°, ×; Plot IV is Urquhart and Williams'[10] data for unswollen cotton at 80°.

(1) Presented in part at the February, 1943, meeting in Cumberland, Maryland, of the Western Maryland Section of the American Chemical Society.

(2) Abstracted from Theses submitted to the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degrees of Doctor of Philosophy (A. G. A., May, 1942) and of Bachelor of Science (R. H. H., December, 1942).

(3) Babbitt, *Can. J. Research*, **20A**, 143 (1942), gave several literature references. See also the review by Barrer, *J. Soc. Dyers and Colourists*, **57**, 264 (1941).

(4) Urquhart, *J. Text. Inst.*, **20**, T125 (1929).

(5) Sheppard and Newsome (a) *Ind. Eng. Chem.*, **26**, 285 (1934); (b) *J. Phys. Chem.*, **36**, 2306 (1932).

(6) Walker, (a) *Textile Research*, **7**, 229, 289 (1937); (b) *J. Text. Inst.*, **24**, T145 (1933); (c) *J. Applied Phys.*, **8**, 261 (1937).

(7) Champetier and Viallard, *Compt. rend.*, **205**, 1387 (1937).

(8) Katz, *Physik. Z.*, **25**, 321 (1924); *Trans. Faraday Soc.*, **29**, 279 (1933).

(9) The researches of Nägeli and of Ambronn were reviewed by Steinbrinck, *Kolloid-Beihefte*, **23**, 6 (1926–1927).

(10) Urquhart and Williams, *J. Text. Inst.*, **15**, T559 (1924).

(11) Peirce, *ibid.*, (a) **15**, T501 (1924); (b) **20**, T133 (1929).

(12) Argue and Maass, *Can. J. Research*, **13B**, 156 (1935).

(13) Whitehead, "Impregnated Paper Insulation," Wiley and Sons, New York, N. Y., 1935, pp. 13–35.

(14) Shipley, Campbell and Maass, *Can. J. Research*, **17B**, 40 (1939).

(15) Maass and Campbell, *Pulp Paper Mag. Canada*, **40**, 108 (1939).

(16) Morrison, Campbell and Maass, *Can. J. Research*, **18B**, 168 (1940).

(17) Stamm and Hansen, *J. Phys. Chem.*, **42**, 209 (1938).

(18) Grace and Maass, *ibid.*, **36**, 3046 (1932).

(19) Stamm and Millett, *ibid.*, **45**, 43 (1941). A literature review is included.

(20) Russell, Maass and Campbell, *Can. J. Research*, **15B**, 13 (1937).

(21) Kanamaru and Chao, *Kolloid-Z.*, **84**, 85 (1938).

(22) Stamm, "Colloid Chemistry of Cellulosic Materials," U. S. Dept. Agric. Misc. Publ., No. 240 (1936).

(23) Marsh and Wood, "An Introduction to the Chemistry of Cellulose," Chapman and Hall, London, 2nd Ed., 1941, pp. 29–48. See also Bancroft and Calkin, *Textile Research*, **4**, 371 (1933–1934).

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loidal surface, that is accessible to water, and similar information can be obtained by studying the adsorption of other vapors.[19] These views have the great merits of being intrinsically reasonable, of correlating a very large mass of information and of being not inconsistent with the work of Emmett and his collaborators on the adsorption of gases by inorganic catalysts.[24] Nevertheless, the validity of applying this interpretation to adsorption by cellulose does not appear to be supported by direct, experimental proof. The present research originated in an attempt to remedy this deficiency. As explained in the preceding article,[25] the fraction of the cellulose alcoholic groups wetted by a normal ether can be determined by using a thallous ethylate solution and by subsequently methylating the thallium cellulosate produced. The relationship between the percentage wetted and the molecular volume of the normal ether is linear and extrapolation to molecular volumes of 18 and 35[26] gives the percentages theoretically available for adsorption of vapors of water and nitrogen molecules, respectively. The weights of adsorbed layers were calculated from these amounts by assuming that each available alcoholic group bonded one molecule and the data were compared with those corresponding to the B and D points on the adsorption isotherms of the same cellulose samples. Although alteration in the colloidal surface of the samples during the adsorption of nitrogen and ethers could be assumed to be negligible, many quantitative results confirmed the fact that the sorption of water produced changes of great magnitude in unswollen cellulose. This effect was minimized, but not eliminated, in the comparative experiments by employing samples that were already highly swollen.

Experimental

Cellulose Samples.—The high grade cotton linters[27] were dewaxed, swollen in caustic soda and dried through methanol and benzene with all the precautions previously described.[25] Sample I contained 1.47% of moisture when examined, but samples II and III were thoroughly dried over concentrated sulfuric acid at room temperature and atmospheric pressure.

Estimation of Accessible Cellulose.—The thallations of approximately 0.3-g. samples of celluloses I, II and III were carried out with excess thallous ethylate dissolved in normal ethers exactly as already described, and the methylation of the thallium cellulosates was completed in the same way.[25] The methoxyl contents in duplicate or triplicate estimations of cellulose I were 11.5, 10.0 and 9.7% in diethyl, 8.1, 8.1% in dibutyl and 5.5, 7.4 and 6.7% in diamyl ether. Cellulose III gave values of 10.7, 12.6, 10.9; 9.7, 9.3, 9.5; and 7.5, 7.5, 7.5% methoxyl, respectively, with thallous ethylate dissolved in the same three ethers. The average methylation corresponding to each ether is plotted in Fig. 2 against the molecular volume of the ether and extrapolation to volumes of 18 and 35, respectively, gave the methylation theoretically corresponding to the penetration of the celluloses by water vapor and nitrogen gas. Ethyl ether values of 10.7, 11.6 and 11.1% methoxyl were the only ones available for cellulose II, but the line drawn through this point is approximately correct, since the slopes of the plots for highly swollen celluloses do not vary greatly. The difference between samples II and III, although obvious in Fig. 2, was in fact well within the experimental error. As previously explained,[25] multiplication of the methoxyl percentage by the factor 100/57.4 gave the percentage of cellulose, or of cellulose alcoholic groups, accessible to the penetrant (Fig. 2, Tables I and II). The product of the latter percentages and the factor 1.87×10^7 expressed the data as accessible colloidal surface in sq. cm. per g. of cellulose.

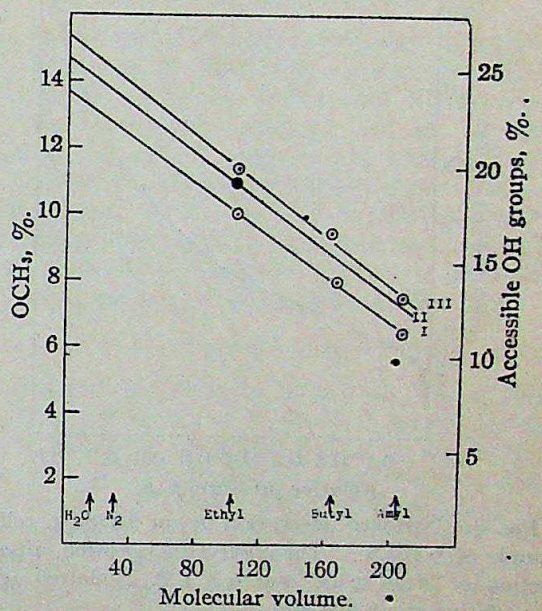

Fig. 2.—Superficial thallation–methylation of celluloses I, II and III, with thallous ethylate in normal ethers. Molecular volume of ether plotted against %OCH_3 and % accessible hydroxyl groups in the celluloses.

Sorption of Water Vapor at 20 and 25°.—The lower portions of twelve small desiccators, kept in a room whose temperature was constant at 20, or 25°, to within 1°, were filled with aqueous sulfuric acid of various definitely known concentrations. Published tables[28] gave the relative humidity within each desiccator at either temperature.

The cellulose sample, 1.5 to 1.7 g., held in an open weighing bottle, was kept in the desiccator containing concentrated sulfuric acid until the weight became constant, when the sample was assumed to be quite dry. It was then transferred to desiccators of increasing humidity, and daily weighings, quickly made on a magnetically damped balance, determined the moisture absorbed. The sample remained in each desiccator until weighings made on successive days did not differ by more than 1 mg. Three days at the lower humidities and five to seven days at the higher ones were required for equilibrium to be established within this weight limit. The best straight line was drawn through the observed points in the linear, intermediate portion of each adsorption isotherm (Figs. 1 and 4) and the moisture contents at the humidities where the plots commenced to diverge perceptibly from the extrapolation of this line were observed (Table I).[24] At ordinary temperatures, these humidities were 7 to 10% for the B, and 45 to 50% for the D point.

(24) Emmett and Brunauer, THIS JOURNAL, **59**, 1553 (1937).

(25) Assaf, Haas and Purves, *ibid.*, **66**, 59 (1944).

(26) "International Critical Tables," McGraw-Hill Book Co., Inc., New York, N. Y., 1926, give 0.808 g./cm.³ as the density of liquid nitrogen at −195.8°. This value was used in the calculation of the molecular volume.

(27) The authors wish to thank Dr. H. M. Spurlin and the Hercules Powder Company, Hopewell, Virginia, for the gift of this material.

(28) Wilson, *Ind. Eng. Chem.*, **13**, 326 (1921).

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The desorption isotherms were obtained by transferring the cellulose samples through the desiccators in reverse order, but the data are omitted from Fig. 1. Sample I had 26.7% moisture at 100% relative humidity, when desorption was commenced, and the corresponding figure for sample II was 40.4% at 20°. The desorption of III and of II at 25° was from equilibrium at 56% relative humidity, or from just beyond the D point, when the moisture contents were 7.35 and 10.7%, respectively (Figs. 1 and 4). After desorption had been completed by standing over concentrated sulfuric acid, the standard estimation with thallous ethylate in ethyl ether gave methoxyl contents of 0.2, 0.2, 1.4 and 2.5% (latter in ethanol) for samples I, II at 20°, II at 25° and III, respectively. A value of 0.5% methoxyl (ethyl ether) was obtained when 2.06% moisture still remained in cellulose I.

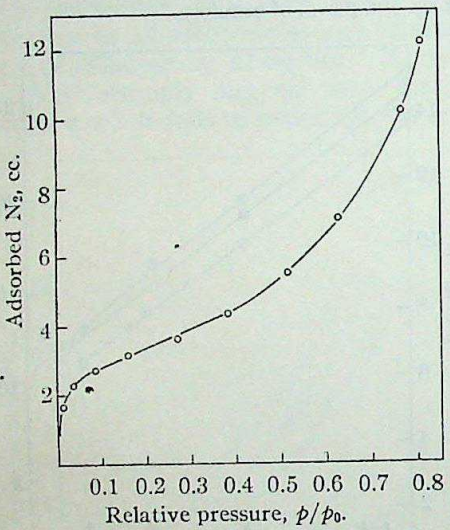

Fig. 3.—Nitrogen adsorption by an 0.3284 g. cellulose sample at −195.8°. The observed adsorption, after correction for "dead space" and to N.T.P., is plotted against the relative vapor pressure.

Adsorption of Nitrogen at −195.8°.—The isotherms for celluloses I and II were determined by the method of Brunauer, Emmett and Teller[29,30] with 0.2-g. samples. Helium was used to estimate the "dead space" in the apparatus and the data for the adsorption of nitrogen were corrected accordingly. The preliminary evacuation was at 80°. If v is the volume adsorbed at pressure p, and p_0 is the saturation pressure at the same temperature, v_m, the volume adsorbed at the first inflection of the isotherm (the B point) is given by the relationship

$$\frac{p}{v(p_0 - p)} = \frac{1}{v_m C} + \frac{C - 1}{v_m C}\frac{p}{p_0}$$

where C is a constant.

Samples I and II had v_m values of 2.34 cc. and 2.83 cc., corrected to N.T.P. These results correspond to adsorptions of 11.6 cc. and 14.0 cc. per gram of cellulose, or to unimolecular layer surfaces of 53.0×10^4 sq. cm./g. and 64.6×10^4 sq. cm./g., respectively, if 17 sq. Å. is assumed for the area covered by a nitrogen molecule in the liquid condition. A complete isotherm for a different sample is reproduced (Fig. 3) to show that the shape is sigmoid and that the above method of calculating area was probably legitimate when applied to cellulose. The area computed for this sample was 34.8×10^4 sq. cm./g.

(29) Brunauer, Emmett and Teller, THIS JOURNAL, 60, 309 (1938).

(30) We wish to thank Dr. W. R. Smith and Mr. F. S. Thornhill, of the Godfrey Cabot Laboratories, Boston, Massachusetts, for their great kindness in determining all of the nitrogen isotherms and in calculating the results.

Results and Discussion

Suggested Interpretation of the Cellulose-Moisture Adsorption Isotherm.—When swelling is neglected, the percentages of the cellulose samples I, II and III theoretically accessible to water vapor can be read from Fig. 2 and are recorded in Table I, column 2, as percentages of accessible alcoholic groups. If each of the latter is assumed to become hydrogen bonded to one water molecule, the calculated moisture content of the entire mass of cellulose is one-third of this percentage because fully hydrated cellulose, $C_6H_{10}O_5 \cdot 3H_2O$, has 33.3% water (column 3). The B and D points of inflection in the moisture adsorption–relative humidity plots at 20 or 25° (Figs. 1 and 4), are given in columns 5 and 6 of Table I. Comparison between columns 3 and 5 shows at once that the water adsorption calculated from the thallous ethylate-methylation data is far higher than that at the B point. Since the accuracy of the calculated values is thought to be well within ±15% and lines

TABLE I

CORRELATION OF ACCESSIBLE ALCOHOLIC GROUPS WITH THE MOISTURE ADSORPTION ISOTHERM OF CELLULOSE

	Accessible[a] OH groups, %	H_2O[b] calcd., %	Water adsorbed Temp.	B[c] point, %	D[c] point, %	Ratio B point / D point
Cellulose I	22.8	7.6	25°	2.1	6.9	0.30
Cellulose II	24.4	8.1	25°	2.4	7.9	0.30
			20°	3.1	9.0	0.34
Cellulose III	25.6	8.5	20°	2.3	7.4	0.31
Unswollen			20°	2.0	6.0	0.33
cotton[d]	..	...	25°	1.9	5.8	0.33

[a] Data in Fig. 2 extrapolated to molecular volume 18. [b] Calcd. by assuming that one water molecule was adsorbed by each accessible alcoholic group. [c] From Figs. 1 and 3. [d] From Urquhart and Williams' data.[10]

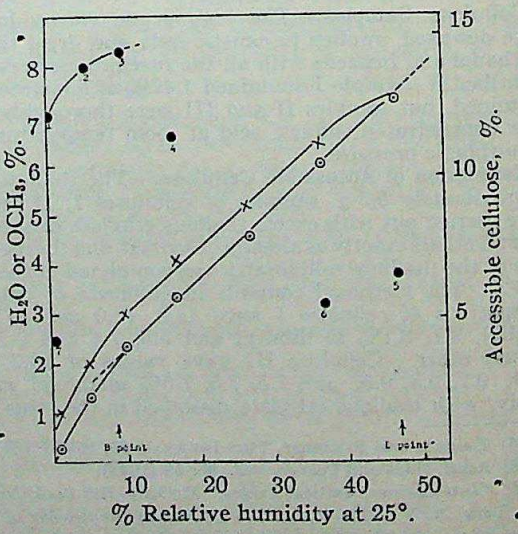

Fig. 4.—Water sorption isotherm of Cellulose III at 25°: adsorption, ⊙; desorption, ×; concurrent estimations of cellulose accessible to thallous ethylate in ethanol,

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drawn through the isotherms to produce a similar variation are obviously misplaced, the total experimental error of perhaps ±30% is quite insufficient to reconcile the two sets of values. The same remark is true of the effect of any swelling during moisture adsorption because the observed B point would have already been increased, rather than decreased, by this contingency. On the other hand, the agreement between columns 3 and 6 of Table I is good, especially since the exact position of the D point cannot be read from the plots with accuracy and is probably sensitive to swelling. The conclusion reached is that a complete coverage of the accessible cellulose hydroxyl groups by water corresponds to the second region of inflection in the adsorption isotherms for ordinary temperatures, and not to the first, as has hitherto been supposed.

If this conclusion is entertained, it becomes desirable to find a new interpretation for the B point. Each glucose residue in cellulose contains three hydroxyl groups that differ markedly in chemical reactivity. Those in the primary or sixth positions of the glucose units are known to react more rapidly in esterification and de-esterification,[31,32] etherification[33] and possibly nitration[34] than those in the two secondary alcoholic positions. Those in some sugar derivatives behave similarly.[35] Simple primary alcohols are considered to be more highly associated in benzene solution than their secondary isomers,[36,37,38,39] and their boiling points at atmospheric pressure are about 20° higher.[40] All these observations make it plausible to argue that primary alcohols form intermolecular hydrogen bonds, and, presumably, hydrogen bonds with water molecules, that are stronger than those pertaining to secondary alcohols. The initial strong adsorption of water by cellulose (up to the B region, Fig. 1) accordingly may be attributed for the most part to the primary alcoholic groups, and is identifiable with the powerful "*a*" absorption assumed by Peirce.[11b] The intermediate portion of the isotherm represents the weaker adsorption of the secondary alcoholic groups but is progressively distorted from the region of the D point onward by enlargement of surface through swelling and by the filling up of the capillaries. Since there is on the average one primary for every two secondary alcoholic groups accessible in the cellulose, the above interpretation requires that the moisture content at the B point should be approximately one-third of that at the D point. This deduction is supported by the most probable ratios observed both in our own experiments and in those of others[10] (Table I, column 7), although it is true that graphical manipulation of the data in Figs. 1 and 4 may give values ranging from 0.25 to 0.4.

Another deduction from the new interpretation is that the shape of the adsorption isotherm must be determined by the three equilibria

$$R_2OH + H_2O \rightleftharpoons R_2OH\cdot H_2O$$
$$R_3OH + H_2O \rightleftharpoons R_3OH\cdot H_2O$$
$$R_6OH + H_2O \rightleftharpoons R_6OH\cdot H_2O$$

when both swelling and the slight affinity of water for acetal oxygens and hydrocarbon chains are neglected. R_2OH, R_3OH and R_6OH represent the equimolar amounts, m, of alcoholic groups in the second, third and sixth positions of the glucose residues accessible to moisture in the cellulose. If x_2, x_3 and x_6 moles are the equilibrium amounts of moisture adsorbed by the three kinds of alcoholic group at the vapor pressure p, the law of mass action states that

$$x_2/p(m - x_2) = \text{a constant } K_2, \text{ or } x_2 = K_2mp/(1 + K_2p)$$

with similar equations for x_3 and x_6. Since these equations are identical in form to those devised by Langmuir for unimolecular layer adsorption, cellulose may be regarded as a surface containing equal amounts of three kinds of elementary space, each adsorbing with different intensity.[41] The constant K_6 is so large that the primary alcoholic groups are extensively hydrated at a relative humidity of 7 to 10% (Fig. 1), but K_2 and K_3 are such that the hydration of the secondary alcoholic groups is very much less in the same conditions. It follows that the selective hydration of R_6OH is responsible for the 15.7 kcal. of heat evolved when one mole of water vapor at ordinary temperature is adsorbed by a very large mass of perfectly dry cellulose.[3,42] Since the latent heat of condensation of water vapor is 10.5 kcal., the difference of 5.2 kcal. may be attributed to the heat of formation of the $R_6OH\cdot H_2O$ hydrogen bond. This value is approximately half-way between those of 4.5 and 6.0 kcal. reported for the hydrogen bond strength in ice and aliphatic alcohols, respectively.[43,44] It is to be expected that the $R_2OH\cdot H_2O$ and $R_3OH\cdot H_2O$ bonds have a heat of formation smaller than 5.2 kcal. and this supposition, plus the utilization of energy to cleave pre-existing cellulose–cellulose hydrogen bonds during swelling, would explain

(31) Cramer and Purves, THIS JOURNAL, **61**, 3458 (1939).
(32) Gardner and Purves, *ibid.*, **64**, 1539 (1942).
(33) Mahoney and Purves, *ibid.*, **64**, 9 (1942).
(34) Murray and Purves, *ibid.*, **62**, 3194 (1940).
(35) Hockett and Downing, *ibid.*, **64**, 2463 (1942).
(36) Biltz, *Z. physik. Chem.*, **29**, 249 (1899).
(37) Peterson and Rodebush, *J. Phys. Chem.*, **32**, 709 (1928).
(38) Lassettre, *Chem. Rev.*, **20**, 259 (1937).
(39) Huggins, *J. Org. Chem.*, **1**, 407 (1936–1937).
(40) The normal heptyl alcohols, for example, have the following boiling points: heptanol-1, 176°; heptanol-2, 159°; heptanol-3, 157° (750 mm.), and heptanol-4, 154°.
(41) Langmuir, THIS JOURNAL, **40**, 1361 (1918).
(42) Neale and Stringfellow, *Trans. Faraday Soc.*, **37**, 525 (1941).
(43) Robertson, *ibid.*, **36**, 913 (1940). No distinction was made between the hydrogen bond energies of primary and secondary alcohols.
(44) Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939, p. 307, mentions a bond energy of 6,200 cal. for methanol and ethanol.

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the sharp decrease in the heat evolved by the adsorption of additional amounts of water.[3] The thermal effects connected with the adsorption of the lower alcohols[20] would be subject to similar considerations.

It is well known that moist cellulose rapidly becomes bone dry when heated in air to slightly more than 100°.[11b] This is, therefore, the temperature range in which even the most powerfully adsorbed moisture, $R_6OH \cdot H_2O$, is expelled and in which the corresponding hydrogen bond, like that in liquid water, becomes quite unstable. The hydrogen bonds holding the cellulose crystallites together resist far higher temperatures because their strength is additive in this case. Since the bond system in an associated liquid secondary alcohol disintegrates at a temperature about 20° lower than that in the primary isomer,[40] it is reasonable to suppose that the complexes $R_2OH \cdot H_2O$ and $R_3OH \cdot H_2O$ in moist cellulose have only a transient existence at 80° or more. In other words, the moisture-adsorption isotherms at such elevated temperatures should be a function of the primary alcoholic groups alone. Urquhart and Williams[10] determined isotherms at 80° and above, one of which is reproduced in Fig. 1; plot IV. An inflection corresponding to the B point at lower temperatures is scarcely perceptible and the plot remains practically linear until distorted upward by swelling. The linearity at lower humidities is consistent with Langmuir's adsorption isotherm for surfaces containing only one kind of elementary space. It follows that plots of similar shape may be expected at *all* temperatures with high molecular materials that swell but possess only one kind of hydroxyl or other adsorbing group. If some other physical properties of cellulose, such as elasticity or rigidity, happen to be connected with hydrogen bonding between secondary alcoholic groups in the amorphous regions, such properties may alter more or less abruptly about 80°.

These general principles may eventually throw fresh light upon the mechanism of some gelations. Heymann and his collaborators, for example, provided evidence that the gelation of aqueous solutions of methylcellulose (substitution 1.59) in the temperature range 40 to 50° is accompanied by a decrease in the solvation of the macromolecules.[45] Most of this decrease might be caused by the preferential, partial desolvation of the unsubstituted, secondary alcoholic groups, rather than to the decomposition of hydrated ether complexes, as was suggested. The pasting of starch in water kept at 65 to 85°[46] may be connected with the breakdown of hydrogen bonds uniting secondary alcoholic groups in the granule and with their inability to remain extensively solvated in this temperature range. When the paste cools, its rigidity increases[47] because these groups recover their ability to hydrogen bond with each other, with the primary alcoholic groups, and with water to form a random system in dynamic equilibrium.

The Cellulose Nitrogen Adsorption Isotherm.—The percentages of the celluloses I and II theoretically accessible to nitrogen (Fig. 2) are given in Table II, column 2, together with the adsorption calculated on the basis of three nitrogen molecules for each accessible glucose residue (column 4). Column 5 shows that the gas actually adsorbed at the B point, as found by Brunauer, Emmett and Teller's method[29] was *one-seventh to one-eighth of the calculated amount*, and the surfaces calculated by the thallous ethylate and the nitrogen methods were in practically the same ratio (columns 3 and 6). This coincidence originated in the fact that the former method of calculating surface assumed an area of 52 sq. Å. for a glucose residue, which in the second method would be almost completely covered by three nitrogen molecules forming a continuous film with a total area of 3 × 17 sq. Å., or 51 sq. Å. It therefore happened that the assumed adsorption at three discrete points in each glucose residue very nearly corresponded to a continuous film that was "unimolecular" in the accepted sense of the word.[29] Although the measurements are not extensive, they are in accord with Babbitt's[3] conclusion that it is necessary to assume *six or seven* superimposed, unimolecular water layers, calculated by Emmett, Brunauer and Teller's method, in order to account for the observed moisture content of cotton and spruce wood in the region of the 20° isotherms just above the D point. The agreement suggests that nitrogen as well as water molecules are adsorbed by the exposed alcoholic groups of the cellulose and in this event the first three of the "unimolecular" layers might represent adsorption on the three different

TABLE II

CORRELATION OF ACCESSIBLE CELLULOSE WITH NITROGEN ADSORPTION

	Available to N_2[a]			N_2 adsorbed at B point	
	Cellulose %	Surface[b] cm.²/g. × 10^{-4}	Calcd. N_2[c] cc./g.	Found cc./g.	Surface[d] cm.²/g. × 10^{-4}
Cellulose I	22.0	411	91.3	11.6	53.0
Cellulose II	23.7	443	98.3	14.0	64.6

[a] Extrapolated from thallous ethylate methylation data in Fig. 2. [b] From column 2 and 52 sq. Å. as area of glucose unit in cellulose. [c] From column 2 and $3N_2$ for a glucose residue. [d] From column 5 and 17 sq. Å. as area of a nitrogen molecule.

(45) Heymann, Bleakley and Docking, *J. Phys. Chem.*, **42**, 353 (1938). The present authors thank Dr. S. L. Bass, of the Dow Chemical Company, Midlands, Michigan, for a private communication discussing Heymann's work in connection with the gelation of water-soluble methylcelluloses.

(46) Radley, "Starch and its Derivatives," D. Van Nostrand Co., New York, N. Y., 1940, pp. 29–47, discusses the literature.

(47) Kang, *Collection Czechoslov. Chem. Communs.*, **4**, 1432 (1932).

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kinds of alcoholic group present.[48] This assumption would render the areas calculated by Emmett, Brunauer and Teller's method about one half, instead of about one sixth, as large as those derived from the thallous ethylate technique. Further work is required to overcome the discrepancy. In the meantime, the suggestion that the D point, rather than the B point, of sigmoid adsorption isotherms corresponds to the complete monolayer must be restricted to the adsorption of water vapor by cellulose.

Changes in Accessible Surface Caused by Solvent-Exchange Drying and by Sorption of Water.—Samples of the highly swollen, dry cellulose II were permitted to absorb known equilibrium amounts of water before being submitted to the thallous ethylate–methylation determination. The solvents chosen for the ethylate were diethyl ether, in which water dissolves sparingly, 1,4-dioxane, which is miscible with water, and absolute ethanol, which competes effectively with cellulose for traces of moisture.[49] The usual large excess of thallous ethylate was increased to offset the decomposition of a portion by the water. Experiments 1 and 2, 5 and 6 (Table III) show that a moisture content of 9% made about three-quarters of the original surface inaccessible not only to ether, but also to dioxane. The preliminary removal of water by standard solvent-exchange drying procedures was also unsatisfactory (expts. 3 and 4) but comparison with experiments 7, 8 and 9, in which even a slight, final drying *in vacuo* was scrupulously avoided, showed that the latter step was the major cause of difficulty. The results support Kistler's conclusion that the formation of aerogels by the direct evaporation of liquids below their critical temperature must involve a collapse of surface.[50]

Figure 4 records an attempt to follow the surface changes exhibited by cellulose III during a moisture sorption cycle from zero to 47% relative humidity at 25°. The method employed thallous ethylate in absolute alcohol and involved no drying. Points 1, 2 and 3, determined during adsorption, are reliable and show that the adsorption of as little as 2.3% of moisture increases the accessible cellulose by at least one fifth, even although the original sample was highly swollen. Points 4 and 5, determined during adsorption, and point 6, after desorption was commenced, merely reveal the inadequacies of the experimental method at higher humidities because the surface was certainly not contracting during the adsorption of additional amounts of water. Point 7, determined when desorption was complete, is accurate, and comparison with point 1 shows that two-thirds of the original surface became inaccessible to ethanol during the complete sorption cycle. The experimental portion contains data showing that the obliteration of surface may amount to 98% as a result of desorption from 100%, instead of 47%, relative humidity.

(48) This idea is analogous to the opinion expressed by Brunauer and Emmett, THIS JOURNAL, **62**, 1732 (1940), concerning certain synthetic iron catalysts, the heterogeneity of whose surfaces was probably due to different developed crystal faces. See also the review by Emmett, "Twelfth Report of the National Research Council Committee on Catalysis," John Wiley and Sons, New York, N. Y., 1940, pp. 53–67.

(49) Mitchell, *Ind. Eng. Chem., Anal. Ed.*, **12**, 390 (1940).

(50) Kistler, *J. Phys. Chem.*, **36**, 52 (1932).

TABLE III

THALLATION-METHYLATION OF MOISTURE-CONTAINING CELLULOSE

Expt.	Moisture, %	Pretreatment of sample	Solvent for TlOEt	OCH_3,[a] %
1	0.0	Original sample	Ether	11.2
2	9.0	None	Ether	3.5
3	17.2	Solvent-exchanged through 100% methanol and dry benzene. Dried over solid KOH *in vacuo*	Ether	0.9
4	24.1	Solvent exchanged through 100% methanol and dry ethyl ether. Kept *in vacuo* for five minutes	Ether	1.8
5	0.0	Original sample	1,4-dioxane	8.0
6	9.0	None	1,4-dioxane	2.0
7	0.0	Original sample	Ethanol	10.2
8	9.1	None	Ethanol[b]	7.8
9	9.5	Absolute ethanol for fourteen hours. Surplus removed without drying	Ethanol	7.4

[a] Averages of concordant duplicate or triplicate estimations. [b] Twenty, instead of the usual three, hours in excess of the 0.1 *N* solution of thallous ethylate.

A more detailed experiment on the effects of drying (Fig. 5) was carried out with cellulose I,

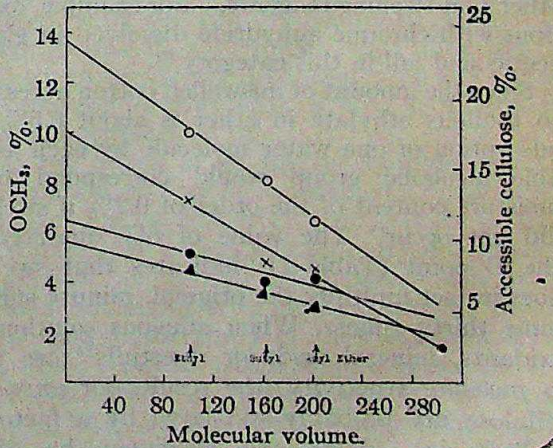

Fig. 5.—Progressive decrease in portion of cellulose I accessible to thallous ethylate in normal ethers: initially, 1.47% moisture, O; after 22 days over solid caustic potash, ×; after 53 days, ●, and after 99 days, ▲.

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whose initial moisture content of 1.47% was not sufficient to render the thallation method with ethers inaccurate. When stored in the dark and *in vacuo* over solid caustic potash, the moisture content diminished during ninety-nine days to 0.43%, while the accompanying change in the amount of cellulose accessible to an ether of zero molecular volume (amorphous cellulose[25]) was from 24% to 10%. Although experimental inaccuracies make the intermediate plots doubtful, the slopes of the initial and final plots are such as to render the percentage decrease in accessible cellulose almost independent of the molecular volume of the ether. The drying process, therefore, seems to obliterate the larger and smaller capillaries of molecular dimensions to almost the same extent. The magnitude of the effect suggests that the removal of a water molecule from the more confined spaces may make possible the formation of a hydrogen bond between two glucose residues on opposite sides of the fissure, and that the corresponding macromolecules, held together in this way at one point, then crystallize imperfectly but extensively against each other.[15,51] In this event, the mechanism may be compared to the action of the domestic "slide fastener" as it unites two serrated edges. The removal of adsorbed liquid appears to be essential for the contraction in surface because the thoroughly dry cellulose II retained its original, superficial methylation of 11.2% unchanged during storage for three months over concentrated sulfuric acid.

Interpretation of the "Mercerization Ratio" of Cellulose.—Data in this and the preceding article[25] show that the accessibility of cellulose to thallous ethylate dissolved in normal ethers may be increased perhaps a hundredfold by appropriate swelling and drying. The value of the "mercerization," "activation" or "reactivity" ratio[23] is therefore of the order of 100 in this case and ratios of similar magnitude probably describe the behavior of cellulose toward other non-swelling reagents. For example, oxidations with chromic anhydride dissolved in glacial acetic acid fall in this category.[52]

Since the amount of unswollen cotton accessible to thallous ethylate in ether is about 0.5%, an adsorption of one water molecule by each available alcoholic group would correspond to a moisture content of the order of 0.2% if swelling did not occur. The value of 6% observed at the D point (Table II) indicates that swelling does in fact multiply the original, minute surface some thirty times. When aqueous solutions of oxidants, mineral acids or dyestuffs[23] are used to measure reactivity, the results for *unswollen* cellulose are probably too large by a factor of similar size. After the specimen has been highly swollen in caustic soda, the water-wet product is usually directly dried before its reactivity is measured. The drying processes used obliterate by far the greater part of the original, swollen surface, which is then regenerated to a considerable extent during the final measurement. It follows that the reactivity ratios of approximately 1.5 obtained by these methods record only the net effect of swelling and contracting changes of much greater magnitude.

This article has profited greatly from constructive suggestions made by Professors P. H Emmett and G. Scatchard, although responsibility for the opinions expressed remains entirely with the authors.

Summary

1. Three highly swollen samples of cotton linters were immersed in solutions of thallous ethylate in normal ethers of different molecular volume. Methylation of the resulting thallium cellulosates gave products whose methoxyl contents were accepted as proportional to the penetration of the ether into the celluloses. Extrapolation of the linear methylation-molecular volume plots to volumes of 18 and 35 gave the respective percentages of cellulose theoretically accessible to water vapor and nitrogen gas.

2. The moisture adsorption isotherms, at 20 or 25°, of the same swollen samples were determined. The moisture content at the second region of inflection in the sigmoid shaped plots, occurring at a relative humidity of about 50%, was approximately that predicted from (1) by assuming the adsorption of one water molecule by each accessible alcoholic group. This region in the isotherm was considered to be approximately equivalent to a unimolecular water layer completely covering the accessible surface of the cellulose.

3. The moisture content at the first region of inflection in the isotherm, occurring at a relative humidity of about 10%, was approximately one-third of the value at the second inflection. This fact, together with other considerations cited, suggested that the avid adsorption of water up to the first inflection was mainly a function of the strong hydrogen bonding capacity of the accessible, primary alcoholic groups. The flat, intermediate portion of the isotherm represented the water less strongly hydrogen-bonded to the secondary alcoholic groups, but its shape was influenced at the higher humidities by the effects of swelling and by capillary condensation. Some physical-chemical implications of these ideas were discussed, particularly the inference that the moisture sorption characteristics of cellulose and starch at 80° or more must be those of the primary alcoholic groups exclusively.

4. Up to 98% of the surface of moist, swollen cellulose was obliterated by direct drying, but up to 75% was preserved during solvent-exchange with ethanol. The absorption of 6% to 9% of

(51) Kratky, *Angew. Chem.*, **53**, 153 (1940).

(52) Gladding and Purves, *Paper Trade J.*, **116**, No. 13, 26 (1943).

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water increased the colloidal surface of highly swollen cellulose by at least 20%, but the increase for unswollen samples was perhaps thirty-fold. These data threw fresh light upon the significance of the "mercerization" or "reactivity" ratio of cellulose, which is usually given as about 1.5.

5. The surfaces of two of the swollen cellulose samples were estimated by a standard method involving the determination of the nitrogen adsorption isotherm at −195.8° but the correlation of this method with the thallous ethylate technique requires further study.

CAMBRIDGE, MASS. RECEIVED SEPTEMBER 4, 1943

[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

Diacetone Xylitol (2,3,4,5-Di-isopropylidene-D,L-xylitol)

BY RAYMOND M. HANN, A. T. NESS AND C. S. HUDSON

Tipson and Cretcher[1] have recently prepared a crystalline diacetone xylitol by condensing the components under suitable conditions. The substance contains one free hydroxyl group and they prepared its crystalline monotosyl derivative and subjected this substance to the action of a solution of sodium iodide in acetone at 100° for two hours, conditions which have been recommended by Oldham and Rutherford[2] for use in their method of distinguishing primary and secondary hydroxyl groups in the case of the aldohexosides, where it appears to be a general rule that a tosyl group is replaced by iodine only when it is attached at the primary hydroxyl of carbon atom 6. Tipson and Cretcher found that tosyl diacetone xylitol reacts with sodium iodide, as is shown by their isolation of sodium tosylate in nearly quantitative yield; it is not mentioned whether the isolation of the expected iodo diacetone xylitol was attempted. They found on the other hand, that all four tosyl groups of tetratosyl-erythritol are removable as sodium tosylate by the acetone solution of sodium iodide under the same conditions and that the erythritol moiety undergoes extensive change to volatile products, a component of which appears to be butadiene, as shown by a test for conjugated double bonds. They concluded therefore that "Oldham and Rutherford's rule apparently does not apply to tosyl esters of the sugar alcohols." Drawing this conclusion, the position of the free hydroxyl group in diacetone xylitol was left undecided.

We have used the Oldham–Freudenberg technique for the preparation of iodo derivatives of the sugar alcohols on numerous occasions. In all but two cases, the tosyl groups of the substances which we studied were attached only to primary hydroxyl groups; these tosyl groups were replaceable by iodine in conformity with the Oldham–Rutherford rule. However, in these cases the general question of the applicability of the Oldham–Rutherford rule did not arise, because we determined the position of the iodine atom in the iodo derivative by an independent and conclusive method, namely, the replacement of the iodine by hydrogen to yield a desoxy compound, the structure of which was then determined through oxidation by per-iodic acid or lead tetraacetate and the estimation of the resulting acetaldehyde. In one of the excepted cases,[3] the 1,4-ditosyl derivative of 2,3,5,6-di-isopropylidene-D,L-galactitol has been shown to give a nearly quantitative yield of a mono-iodo monotosyl derivative, a result which agrees with the Oldham–Rutherford rule in an appropriate test case. In the second excepted case,[4] it has been shown that the substance which has the structure 1,6-ditosyl-2,3,4,5-dimethylene-D-mannitol (as proved conclusively by per-iodic acid oxidation of an appropriate derivative and the estimation of acetaldehyde) reacts with sodium iodide according to the Oldham–Rutherford directions to give the expected 1,6-di-iodo-2,3,4,5-dimethylene-D-mannitol in 98% yield. A second substance which is also a di-tosyl-dimethylene-D-mannitol, was found to be entirely unreactive toward sodium iodide even under more drastic conditions; it seems highly improbable that this second closely similar substance can have either of its tosyl groups at a primary position. We assumed from their lack of reactivity, as contrasted with the proved reactivity of the 1,6-tosyl groups in the isomer, that they are attached to secondary hydroxyl groups; our interpretation of this case is that it follows the Oldham–Rutherford rule.

In the course of studies on methylene acetals of sugar alcohols we have obtained a dimethylene-L-xylitol (m. p. 215–217° (cor.), $[\alpha]^{20}D$ −25.3° in water) and a crystalline desoxy-dimethylene-D,L-xylitol (m. p. 155–156°), which will be described further in later publications; it became important in the study of these substances that the desoxy-xylitol which would be expected to be obtainable from Tipson and Cretcher's diacetone xylitol, be prepared. Our results confirm their work in the preparation of the diacetone xylitol and its tosyl derivative. The replacement of the tosyl group by iodine was accomplished

(1) Tipson and Cretcher, *J. Org. Chem.*, **8**, 95 (1943).

(2) Oldham and Rutherford, THIS JOURNAL, **52**, 366 (1932); *cf.* Oldham, *J. Chem. Soc.*, **127**, 2840 (1925); Freudenberg and Raschig, *Ber.*, **60**, 1633 (1927).

(3) Hann, Maclay and Hudson, THIS JOURNAL, **61**, 2440 (1939).

(4) Hankins, Hann and Hudson, *ibid.*, **65**, 67 (1943).

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by a modification of the Oldham–Freudenberg technique which has been suggested by Murray and Purves,[5] namely, the use of acetonylacetone in place of acetone as the solvent of the sodium iodide. On allowing the reaction to proceed at 60° for nineteen hours the tosyl-di-isopropylidene-xylitol was converted in a yield of 88% to a crystalline iodo-di-isopropylidene-xylitol. This iodo derivative was transformed in alkaline solution by hydrogen and Raney nickel to a desoxy-di-isopropylidene-xylitol, which is a colorless, mobile and somewhat volatile liquid which could be purified by distillation (b. p. 88–90° at 6–7 mm.); its analysis for carbon and hydrogen gave correct percentages. Mild acid hydrolysis removed its acetone groups and there resulted a desoxy-xylitol, which is a colorless viscid odorless sirup, of correct carbon and hydrogen analysis. The oxidation of the desoxy-di-isopropylidene-xylitol by per-iodic acid showed that a reaction was complete in five hours at room temperature, with the consumption of 3.06 molecular equivalents of oxidant; evidently the substance is easily hydrolyzed in the acid solution to acetone and desoxy-xylitol and the latter is then oxidized according to the following equation, which represents the only course that is compatible with the consumption of three moles of the oxidant

$$CH_3(CHOH)_3CH_2OH + 3HIO_4 = CH_3CHO + 2HCOOH + HCHO + 3HIO_3 + H_2O$$

The equation limits the desoxy group to a terminal position. This inference was confirmed by the oxidation of the desoxy-xylitol with sodium periodate; each mole consumed 2.88 moles of oxidant and generated 1.96 moles of acid, 3.00 and 2.00 moles, respectively, being the theoretical values. Finally, desoxy-xylitol was oxidized by per-iodic acid and the resulting acetaldehyde was determined by the procedure of Nicolet and Shinn[6] for the estimation of acetaldehyde in the presence of formaldehyde. Each mole of desoxy-xylitol produced 0.91 mole of acetaldehyde. These quantitative results, and especially the acetaldehyde measurement, prove conclusively that the desoxy-xylitol has the terminal CH_3 in its structure, from which it follows that the free hydroxyl group of diacetone xylitol is a primary one. The acetone groups must be attached to the remaining four carbon atoms; the arrangement of these groups is left undecided. Owing to the *meso* configuration of xylitol, the desoxy-xylitol must consist of equal amounts of two enantiomorphs and the substance is to be named 1-desoxy-D,L-xylitol. This relationship would not hold for a terminal desoxy-D-arabitol because 1-desoxy- and 5-desoxy-D-arabitol are different substances. The tosyl derivative is 1-tosyl-2,3,4,5-di-isopropylidene-D,L-xylitol, the iodo derivative is 1-iodo-2,3,4,5-di-isopropylidene-D,L-xylitol and the product from its reduction is 1-desoxy-2,3,4,5-di-isopropylidene-D,L-xylitol. The question of whether any of the crystalline members of this series of racemic mixtures is a true racemate has not been investigated.

It is apparent from the foregoing that the Oldham–Rutherford rule should not be regarded as inapplicable to sugar alcohols in general. We believe that its apparent failure to hold in the case of tetratosyl-erythritol, where Tipson and Cretcher find that all four tosyl radicals are removed by sodium iodide in acetone, only discloses a special structural influence that has not been noticed in previous applications of the rule. In tetratosyl-erythritol, the tosyl groups that are on secondary hydroxyl positions are contiguous to tosyl groups on primary ones. Except for tritosyl-glycerol[7] and tetratosyl-erythritol, we are not aware that there has been any previous test of a 1,2-ditosyl derivative in considering the applicability of the Oldham–Rutherford rule. However, some evidence on the subject can be supplied at present.[8] Upon heating the known 5,6-ditosyl-1,2,3,4-dibenzylidene-D-sorbitol[9] with sodium iodide and acetone at 100° for four hours, there were formed two molecular equivalents of sodium tosylate and a crystalline compound (m. p. 187–188°; $[\alpha]^{20}D$ +19.0° in chloroform) which decolorizes bromine in carbon tetrachloride and shows a correct analysis for 1,2,3,4-dibenzylidene-D-sorbitoleen; the latter substance was reduced by hydrogen and Raney nickel to what is presumably 1,2,3,4-dibenzylidene-5,6-di-desoxy-D-sorbitol (m. p. 184–185°; $[\alpha]^{20}D$ +39.4° in chloroform. Calculated for $C_{20}H_{22}O_4$: C, 73.60; H, 6.79. Found: C, 73.84; H, 6.78). It appears, therefore, that contiguous tosyl groups, one of which is attached at a primary hydroxyl position and the other at a secondary, are both removed by treatment with sodium iodide in acetone with the ultimate production of a double bond. The behavior which Tipson and Cretcher have described falls in this category. The behavior of tritosyl-glycerol may be analogous. This method of forming a double bond in a 1,2-position opens many possibilities, particularly in the study of sugar alcohols. According to the idea which underlies the Oldham–Rutherford rule, a 1-iodo-2-tosyl derivative is to be expected as the first step in the ultimate formation of a double bond.

We express our appreciation to Dr. B. H. Nicolet and Mr. L. A. Shinn, of the Bureau of Dairy Industry, U. S. Department of Agriculture, for assistance in the acetaldehyde determinations.

(5) Murray and Purves, THIS JOURNAL, 62, 3195 (1940).

(6) Nicolet and Shinn, *J. Biol. Chem.*, 138, 91 (1941); THIS JOURNAL, 63, 1456 (1941).

(7) Levene and Mehltretter, *Enzymologia*, 4 (11), 232 (1937).

(8) Unpublished results obtained by Dr. John K. Wolfe in this Laboratory in a research which is temporarily suspended. We thank Dr. Wolfe for permission to quote the data.

(9) Wolfe, Cretcher and Hudson, THIS JOURNAL, 64, 1495 (1942).

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Experimental

2,3,4,5-Di-isopropylidene-D,L-xylitol.—Xylitol and acetone were condensed by the method which Levene and Tipson[10] used for the condensation of uridine and acetone. A mixture of 10.0 g. of crystalline xylitol,[11] 200 cc. of acetone, 20.0 g. of anhydrous copper sulfate and 0.2 cc. of concentrated sulfuric acid was agitated on a shaking machine for forty-eight hours at 25°; the copper sulfate was separated by filtration and the filtrate was shaken with 10 g. of powdery calcium hydroxide for one hour to neutralize the acid; the solids were removed by filtration and the solvent by distillation *in vacuo* at 50°. The sirupy residue, weighing 14.8 g. (97%) seems to be essentially 2,3,4,5-di-isopropylidene-D,L-xylitol. It is sufficiently pure for the preparation of derivatives, but if the crystalline substance be desired, seed crystals of it may be obtained by dissolving the sirupy product in hexane and cooling the solution in dry-ice. If seed crystals are available, the crystallization of the substance from hexane solution progresses satisfactorily at ice-box temperatures. The crystalline diacetone xylitol melted at 33–34° in agreement with the melting point of 34–34.5° reported by Tipson and Cretcher.

1-Acetyl-2,3,4,5-di-isopropylidene-D,L-xylitol.—A solution of 6.9 g. of 2,3,4,5-di-isopropylidene-D,L-xylitol in a mixture of 50 cc. of pyridine and 50 cc. of acetic anhydride was kept at 25° for eighteen hours and then poured into 500 cc. of ice-water. The acetic acid was neutralized with potassium carbonate and the solution was extracted with five 50-cc. portions of chloroform. The chloroform extracts were combined, washed successively with ice-cold 2% hydrochloric acid, 2% sodium bicarbonate solution and water, and dried over anhydrous sodium sulfate. The chloroform was removed by concentration *in vacuo* and the thin sirup which remained was brought to crystallization by dissolving it in a small amount of alcohol and cooling the solution in dry-ice. The acetyl derivative was recrystallized from 10 parts of 50% alcohol and it formed prisms which melted at 45–46°. The substance is soluble in acetone, chloroform, ether, methyl alcohol and hot water and relatively insoluble in cold water. The yield was nearly quantitative.

Anal. Calcd. for $C_{13}H_{22}O_6$: C, 56.92; H, 8.08; CH_3CO, 15.7. Found: C, 56.90; H, 8.10; CH_3CO, 15.5.

1-Benzoyl-2,3,4,5-di-isopropylidene-D,L-xylitol.—This compound was obtained in quantitative yield (10.0 g.) by the benzoylation of 2,3,4,5-di-isopropylidene-D,L-xylitol (6.9 g.) in pyridine solution with benzoyl chloride. It was recrystallized from 5 parts of alcohol and obtained in the form of stout needles which melted at 61–62°. The substance is soluble in warm methyl and ethyl alcohols, acetone and chloroform, relatively insoluble in cold alcohol, and insoluble in water.

Anal. Calcd. for $C_{18}H_{24}O_6$: C, 64.27; H, 7.19; C_6H_5CO, 31.2. Found: C, 64.47; H, 7.31; C_6H_5CO, 31.0.

1-Tosyl-2,3,4,5-di-isopropylidene-D,L-xylitol.—A solution of 14.3 g. of 2,3,4,5-di-isopropylidene-D,L-xylitol in 71.5 cc. of pyridine was cooled in ice and 14.3 g. of *p*-toluenesulfonyl chloride was added. After standing for forty-eight hours at 25° the reaction mixture was poured into 500 cc. of ice water and the precipitated tosyl derivative (21.6 g.; 91%) was separated by filtration and recrystallized from 3 parts of alcohol. The once recrystallized compound melted at 77–78° and further recrystallization did not alter this melting point; Tipson and Cretcher record 70–71°. The substance is relatively unstable which may account for the difference in melting point; it decomposed spontaneously on standing a few days at room temperature. It is readily soluble in acetone, methyl and ethyl alcohols, chloroform and ethyl acetate and insoluble in water.

Anal. Calcd. for $C_{18}H_{26}O_7S$: C, 55.94; H, 6.78; S, 8.30. Found: C, 55.82; H, 6.81; S, 8.26.

1-Iodo-2,3,4,5-di-isopropylidene-D,L-xylitol.—A solution of 15.5 g. of recrystallized 1-tosyl-2,3,4,5-di-isopropylidene-D,L-xylitol and 15.0 g. (2.5 molecular equivalents) of sodium iodide in 60 cc. of acetonylacetone,[5] was heated at 60° for nineteen hours; the cooled reaction mixture was poured into 1 liter of ice water and after standing at 5° overnight the precipitated 1-iodo-2,3,4,5-di-isopropylidene-D,L-xylitol (12.1 g.; m. p. 55–57°; 88%) was separated by filtration and recrystallized by solution in 2 parts of alcohol and the addition of 1 part of water; it was obtained in the form of thin rectangular plates which melted at 57–59°. The substance is soluble in acetone, chloroform, methyl and ethyl alcohols and dioxane and insoluble in water.

Anal. Calcd. for $C_{11}H_{19}O_4I$: C, 38.61; H, 5.60; I, 37.09. Found: C, 38.66; H, 5.72; I, 37.19.

1-Desoxy-2,3,4,5-di-isopropylidene-D,L-xylitol.—The suspension of 2.0 g. of Raney nickel in 25 cc. of absolute methyl alcohol was saturated with hydrogen at a temperature of 27° and a pressure of 5 cm. of mercury and then 2.5 g. of 1-iodo-2,3,4,5-di-isopropylidene-D,L-xylitol and 4.5 cc. of 1.8 *N* barium methylate[12] (0.55 molecular equivalent) were added and the reaction mixture was agitated in a glass bottle under a slight positive pressure of hydrogen. In thirty minutes the calculated amount of hydrogen (181 cc. at 27° and 756 mm.) was taken up and no further absorption occurred in an additional thirty minutes. The catalyst was separated by filtration and the filtrate was concentrated *in vacuo* to a thick slurry; this residue was extracted with ether and the extract, upon evaporation of the solvent, yielded a colorless liquid. The product is volatile and care must be exercised in the last stages of the evaporation to prevent loss. A sample of 4.3 g. of this sirup was distilled *in vacuo* and a 3.1 g. fraction boiling at 83–89° at 7 to 8 mm. was collected; this fraction was redistilled *in vacuo* and the major portion (2.8 g.), which distilled at 88–90° at 6 to 7 mm., was analyzed and found to agree in composition with desoxy-di-isopropylidene-xylitol. The clear mobile liquid, which had a mild and slightly pungent but rather agreeable odor, showed a refractive index $n^{21}D$ of 1.4308.

Anal. Calcd. for $C_{11}H_{20}O_4$: C, 61.08; H, 9.32. Found: C, 61.15; H, 9.32.

Per-iodic Acid Oxidation of 1-Desoxy-2,3,4,5-di-isopropylidene-D,L-xylitol.—To a solution of 0.2236 g. of 1-desoxy-2,3,4,5-di-isopropylidene-D,L-xylitol in 25 cc. of water at 25° was added 5 cc. of 0.675 *M* per-iodic acid (3.26 molecular equivalents) and the volume was adjusted to 50 cc. with water. Analysis of 5-cc. subsamples at the expiration of one, two and one-half, five and twenty-two hours showed that 2.48, 3.00, 3.06 and 3.18 molecular equivalents of oxidant had been consumed. This experimental result indicated that the diacetal was readily hydrolyzed by the per-iodic acid under the experimental conditions, and that the resulting 1-desoxy-xylitol was then oxidized in accordance with the expected reaction course, the equation for which has been given.

1-Desoxy-D,L-xylitol.—A solution of 1.6 g. of 1-desoxy-2,3,4,5-di-isopropylidene-D,L-xylitol in 25 cc. of 20% aqueous acetic acid was refluxed for four hours and the solvent then removed by concentration *in vacuo*. The sirupy reaction product was dried by the successive addition and evaporation *in vacuo* of two 25-cc. portions of absolute alcohol. The final product was a viscid odorless sirup showing $n^{21}D$ 1.4706. The yield was 0.8 g. (quantitative).

Anal. Calcd. for $C_6H_{12}O_4$: C, 44.11; H, 8.88. Found: C, 44.12; H, 8.66.

Sodium Periodate Oxidation of 1-Desoxy-D,L-xylitol.—To an ice-cold solution of 0.1255 g. of 1-desoxy-D,L-xylitol in 35 cc. of water 8.54 cc. of 0.432 *M* sodium periodate (4.00 molecular equivalents) was added and the solution was allowed to warm to 25°; the volume was then adjusted to 50 cc. with water. Analysis of 5-cc. aliquots at the expiration of one, six and twenty-four hours indicated that 2.85, 2.88 and 2.88 molecular equivalents of oxidant had

(10) Levene and Tipson, *J. Biol. Chem.*, **106**, 115 (1934).

(11) Wolfrom and Kohn, THIS JOURNAL, **64**, 1739 (1942).

(12) Levene and Compton, *J. Biol. Chem.*, **111**, 326 (1935); *cf.* Haskins, Hann and Hudson, THIS JOURNAL, **65**, 1419 (1943).

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been consumed. At the expiration of twenty-four hours the titration of a 10-cc. subsample required 3.60 cc. of 0.1 *N* sodium hydroxide (using methyl red as indicator), equivalent to 1.96 molecular equivalents of formic acid. As previously mentioned, the oxidation of 1-desoxy-xylitol should consume three molecular equivalents of sodium periodate and produce two molecular equivalents of formic acid.

Determination of the Acetaldehyde Produced in the Oxidation of 1-Desoxy-D,L-xylitol by Per-iodic Acid.—A 5-cc. aliquot (0.0737 millimole) of a solution of 0.1003 g. of 1-desoxy-D,L-xylitol in 50 cc. of water was oxidized by per-iodic acid and the acetaldehyde produced was determined by the procedures described by Nicolet and Shinn.[6] The consumption of 0.02 *N* iodine (6.68 cc.) corresponded to 0.0668 millimole of acetaldehyde, equivalent to 0.91 mole of acetaldehyde per mole of 1-desoxy-xylitol. As previously indicated, the expected production of acetaldehyde was one molecular equivalent.

Summary

Proof of the structure of the diacetone xylitol of Tipson and Cretcher is presented. Its tosyl derivative reacts with sodium iodide in acetonylacetone solution to form a crystalline iododiacetonexylitol, which is reduced by hydrogen and Raney nickel to a liquid desoxydiacetonexylitol. The latter substance, upon mild acid hydrolysis, yields a sirupy desoxyxylitol, which must be a 1-desoxy derivative because it is oxidized by per-iodic acid or sodium periodate with the consumption of three moles of oxidant and the production of one mole of acetaldehyde. Owing to the meso configuration of xylitol the substances are racemic mixtures. Their structures may now be described by the following names: 2,3,4,5-di-isopropylidene-D,L-xylitol, 1-tosyl - 2,3,4,5 - di - isopropylidene - D,L - xylitol, 1 - iodo - 2,3,4,5 - di - isopropylidene - D,L - xylitol, 1 - desoxy - 2,3,4,5 - di - isopropylidene - D,L - xylitol, 1-desoxy-D,L-xylitol. The arrangement of the acetal linkages among the 2,3,4,5-positions remains undecided.

The applicability of the Oldham–Rutherford rule to sugar alcohols is discussed.

BETHESDA, MARYLAND RECEIVED SEPTEMBER 3, 1943

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 291]

The Formation of Anhydro Derivatives by the Action of Alkali upon Some Mononitrate-acetates of Glucose and Methylglucoside

BY E. K. GLADDING[1] AND C. B. PURVES

The recognition that the organic esters of sulfonic acids not only are cleaved by alkaline reagents in the sense $R_1R_2R_3C—O\vdots SO_2R$, but also in the sense $R_1R_2R_3C\vdots O—SO_2R$, explains the frequency with which the course of the reaction resembles the hydrolysis of the corresponding alkyl chloride, $R_1R_2R_3C\vdots Cl$.[2] Walden inversions often occur in both cases[3,4] and today are attributed to the formation of a charged, asymmetric carbonium ion, $R_1R_2R_3C^+$, whose rearrangement to an electrically neutral molecule is associated with the expulsion of a proton. The final molecule may contain a double bond, an anhydro ring, or be combined with a negative group, such as alkoxyl, derived from the environment. These ideas have been very successfully used to explain the chemical behavior of sugar sulfonates in alkaline media[5,6,7] and there is evidence that *p*-toluenesulfonic esters of cellulose react in a similar way.[8]

The mechanism underlying the reaction between alkali and the esters of nitric acid has not been studied extensively and most of the published work is restricted to the identification of the products.[9] Guncotton, for example, suffers rapid oxidative degradation when immersed in aqueous caustic soda, and carbon dioxide and sodium nitrite are formed.[9] Degradation in presence of diphenylamine and traces of copper salts produces oxidized and nitrated derivatives of the base.[10,11] Degradation is marked in ammonia at 65°[12] and we have found that such a weak base as pure, dry pyridine causes a vigorous decomposition of dissolved, stabilized guncotton at steam-bath temperature. Nitrogen dioxide is evolved in this decomposition as a volatile pyridine addition complex that readily crystallizes when cooled. Nef,[13] however, has emphasized that simple, aliphatic nitrates, sulfates

(1) Du Pont Cellulose Fellow, 1942–1943. Present address, Magnolia Petroleum Co., Field Research Department, Dallas, Texas.

(2) Ferns and Lapworth, *J. Chem. Soc.*, 273 (1912).

(3) Phillips, *ibid.*, 44 (1923).

(4) Kenyon, Phillips and Turley, *ibid.*, 399 (1925). See also Day and Ingold, *Trans. Faraday Soc.*, **37**, 686 (1941), who reviewed the hydrolysis of carboxylic esters.

(5) Hirst and Peat, *Ann. Repts. Chem. Soc.*, **31**, 173 (1934); **32**, 280 (1935).

(6) Peat, *ibid.*, **36**, 258 (1939).

(7) Isbell, *Ann. Rev. Biochem.*, **9**, 65 (1940).

(8) Gardner and Purves, THIS JOURNAL, **65**, 444 (1943).

(9) Kenyon and H. LeB. Gray, *ibid.*, **58**, 1422 (1936), referred to many results concerning the decomposition of low-molecular nitrates by alkali.

(10) Maraour, *Bull. soc. chim.*, [5] **3**, 2240 (1936).

(11) Becker and Hunold, *Z. ges. Schiess- u. Sprengstoffw.*, **33**, 213, 244 (1938). Literature reviews included.

(12) Chernitskaya, Kargin and Gutenmakker, *J. Applied Chem.*, U. S. S. R., **13**, 1159 (1940); *Chem. Abs.*, **35**, 2322 (1941).

(13) Kenyon and H. LeB. Gray, *ibid.*, **58**, 1422 (1936), referred to

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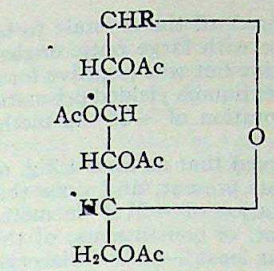
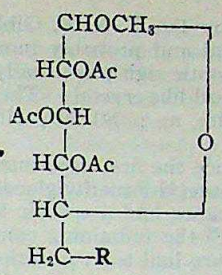
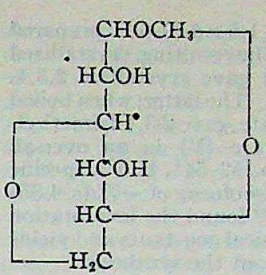


I. R, ONO_2
Ia. R, Cl or Br
Ib. R, $O—SO_2CH_3$
Ic. R, OCH_3



II. R, ONO_2
IIa. R, Cl or Br
IIb. R, $O—SO_2C_7H_7$



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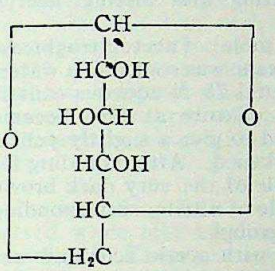
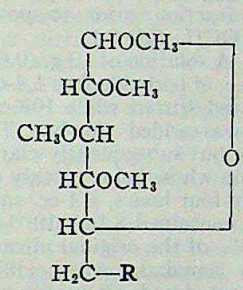
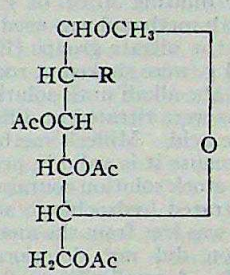


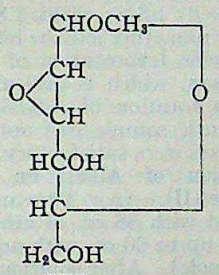
IV



V. R, ONO_2
Va. R, OH
Vb. R, Br



VI. R, ONO_2
VIa. R, $O—SO_2C_7H_7$



VII

and halides are analogous in their behavior toward alcoholic caustic potash, although in the case of the nitrates the formation of unsaturates is suppressed and an oxidation–reduction process often produces potassium nitrite and the corresponding aldehyde or ketone. This process is stated to proceed quantitatively with benzyl nitrate, glycol dinitrate and glycerol trinitrate, but to be completely suppressed with methyl nitrate, which gives large yields of methyl ether. Ethyl and higher nitrates produce ethers mixed with decomposition products derived from carbonyl compounds exposed to excess alkali. A straightforward hydrolysis to the aliphatic alcohol occurs to an extent which, although small, increases with the stability of the nitrate toward alkali. It is also known that the *beta* forms of tetraacetyl glucosyl nitrate (Structure I)[14,15] and chloride (Ia)[15,16] resemble each other in their ready isomerization to the *alpha* configurations and that the latter produce tetraacetyl-β-methylglucoside (Ic) when warmed with methanol and barium carbonate.[17] This reaction apparently involves a Walden inversion. Tetraacetyl glucosyl methylsulfonate (Ib) also gives (Ic) when dissolved in methanol.[18] Another instance of the resemblance between halides, sulfonates and perhaps nitrates is known when these groups are present in the sixth position of methylglucoside (Structures IIa, IIb and II). Aqueous or alcoholic caustic soda produces high yields of 3,6-anhydromethylglucoside (III) from the two former[5,6,7] and the rotatory change undergone by the 6-nitrate (II) suggests that the reaction follows a similar course.[19]

The foregoing illustrations tend to show that the action of alcoholic caustic soda on a carbohydrate nitrate may remove the elements of nitric acid and produce anhydro or alkoxyl derivatives, either with or without Walden inversions. Unsaturated products may possibly be encountered. An ordinary hydrolysis, leading to sodium nitrate and the parent carbohydrate, may also take place and the third possibility is that the nitrate group may be reduced to nitrite and the carbohydrate oxidized to carbonyl derivatives. The latter, of course, would quickly undergo further change in the excess alkali. The present article assesses the practical importance of these possibilities for four simple cases (Structures I, II, V and VI) and demonstrates that the analogy in principle between the behavior of corresponding halogen, *p*-toluenesulfonyl and nitrate derivatives toward alkali is probably of wide application in the carbohydrate field.

Experimental

Materials.—2,3,4,6-Tetraacetyl-α-D-glucopyranosyl nitrate (α-acetonitroglucose, I) was prepared by nitrating 10 g. of dry, commercial *beta*, not *alpha*, glucose pentacetate dissolved in 100 cc. of chloroform with an equal volume of ice-cold, chloroform-soluble nitric acid.[17,20] The observed m. p., 148–49° (cor.), and specific rotation in chloroform, 148°,[21] were each one degree less than the recorded values.

(14) Skraup and Kremann, *Monatsh.*, **22**, 1037 (1901).
(15) Schlubach, Stadler and Wolf, *Ber.*, **61**, 287 (1928).
(16) Schlubach, *ibid.*, **59**, 840 (1926).
(17) Koenigs and Knorr, *ibid.*, **34**, 957 (1901).

(18) Helferich and Gnüchtel, *Ber.*, **71**, 712 (1938). The methylsulfonate had a specific rotation of 121.4° in chloroform and in consequence was probably of the alpha configuration.
(19) Oldham, *J. Chem. Soc.*, 2841 (1925).
(20) Behrend and Roth, *Ann.*, **331**, 359 (1904).
(21) Unless otherwise stated, all specific rotations were observed at 20° with sodium light, and m. p.'s were corrected for the emergent thermometer stem.

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Crude, crystalline D-glucosan<1,5>β<1,6> prepared from starch was methylated[22] and the resulting, crystallized trimethyl derivative on nitration gave crystalline 2,3,4-trimethyl-α-glucosyl-1,6-dinitrate. The latter, when boiled with methanol and barium carbonate, gave 2,3,4-trimethyl-β-methyl-D-glucopyranoside-6-nitrate (V) in an over-all yield of 50%. The product, m. p. 52–54°, had a specific levorotation, observed at 25° in chloroform, of −7° (*c*, 4.35) and analyzed correctly. Oldham[19] found the levorotation to be −5.2° but otherwise the physical constants and yields he recorded were checked throughout the synthesis.

The preparation and properties of 2,3,4-triacetyl-α-methyl-D-glucopyranoside-6-nitrate (II) and 3,4,6-triacetyl-β-methyl-D-glucopyranoside-2-nitrate (VI) have been described elsewhere.[23]

Methods.—A solution made by diluting 30 cc. of 4 *N* aqueous caustic soda to 100 cc. with methanol was used in determining the alkali-lability of the nitrate groups (Fig. 1). Samples weighing 0.10 to 0.14 g. were shaken at room temperature with 5-cc. aliquots of the alkali until solution was complete. Duplicate solutions were titrated at different times with 0.1 *N* hydrochloric acid. Miller's method of estimating nitrite[24] was used because it is valid in presence of a large excess of nitrate. A stock solution contained 30 cc. of water, 50 cc. of concentrated hydrochloric acid and 20 cc. of dimethylaniline that was free from the monomethyl derivative. This solution did not deteriorate noticeably when stored in the dark. A small aliquot, 0.25 to 1.0 cc., of the nitrite solution was made acid to litmus with hydrochloric acid and was diluted to 10 cc. with water. The addition of 0.5 cc. of the stock solution produced intensely yellow *p*-nitrosodimethylaniline and the transmission of light by the solution became constant within two hours. A photoelectric colorimeter, a blue filter and 1-cm. glass cells were used to estimate the transmission, and distilled water in an identical cell was the standard taken for 100% transmission.

The standard nitrite solution contained 0.5050 g. of the C. P. sodium salt in 500 cc. of water, or 14.6×10^{-6} mole of nitrite in 1 cc. Dilutions were made to bracket the concentration of nitrite in the unknown. Although Beer's law did not apply exactly, a plot of log % transmission against nitrite-concentration was linear up to about 2×10^{-6} mole per cc.

Action of Alkali on α-Acetonitroglucose (I) (A).—A suspension of 5.04 g. (0.017 mole) of the acetonitroglucose in 100 cc. of methanol was mixed at room temperature with 50 cc. of absolute 1.75 *N* sodium methylate (0.088 mole). Solution was complete within five minutes and the molecular rotation of the slightly yellow liquid acquired a final constant value of −6,500 within ten minutes. The solution was acidified with glacial acetic acid after one hour and was evaporated to dryness under diminished pressure. The product obtained by acetylating the residue with pyridine, 30 cc., and acetic anhydride, 15 cc., contained constituents, 3.56 g., that were extracted from the aqueous acetylation liquors by chloroform. These constituents partly crystallized when seeded with tetraacetyl-β-methylglucopyranoside and recrystallizations from 6-cc. volumes of methanol left 1.3 g. (28%) of this substance as hexagonal plates or stout prisms with the correct elementary analysis. The m. p., 102.5–104.5° (cor.), and the specific levorotation of −18.0° in chloroform agreed with the accepted constants.[25]

A duplicate experiment gave 3.49 g. of crude, acetylated material which on this occasion crystallized completely, rather than partly, to a hard mass, m. p. 83–90°. Four recrystallizations from methanol and ethanol alternately left the main fraction still melting over the broad range of 85 to 102° and with a specific levorotation of −28.6° in methanol. A brief microscopic examination, kindly carried out by Dr. T. R. P. Gibb, showed all the crystals to be biaxial and probably monoclinic with large optic angles. The optic sign was usually positive but was negative for a few rod-like crystals. The mother liquors yielded prismatic needles, m. p. 80–90°, with a rotation of −34° in methanol.

Since the first experiment proved that at least 1.3 g. of tetraacetyl-β-methylglucoside was present, and since this substance had a specific levorotation of −21.8° in methanol,[25] the remaining constituent, or constituents, of the mixture had a levorotation of at least −40°. Triacetyl-glucosan occurs as needles and has a levorotation of −45.5° in methanol.[26] *Anal.* Calcd. for tetraacetyl-methylglucoside: acetyl, 47.5; OCH_3, 8.56. Calcd. for triacetylglucosan; acetyl, 44.8; OCH_3, 0.0. Found for main fraction prior to powdering and mixing: acetyl, 46.8; OCH_3, 3.1, 8.1.

(B) A solution of 10 g. (0.034 mole) of acetonitroglucose in 50 cc. of peroxide-free 1,4-dioxane was cooled in a water-bath and stirred while 100 cc. of 1.75 *N* aqueous caustic soda was added slowly. The mixture at first became cloudy but subsequently clarified to give a slightly yellow solution whose color quickly darkened. After standing for twenty-four hours, a 1-cc. sample of the very dark brown liquid contained 8.1×10^{-6} mole of nitrite, corresponding to 4.5% of the original nitrate groups.

The remainder was acidified with acetic acid and was evaporated under reduced pressure to a dark gum. Methylation[22] of this gum gave a chloroform-soluble product that distilled completely at 112–114° (5 mm.) and crystallized completely when nucleated with 2,3,4-trimethylglucosan <1,5>β<1,6>; yield, 1.8 g. or 33%. Two recrystallizations from ether left the long needles with m. p. 56–58° and a specific levorotation of −61.8° in water. Trimethylglucosan, which is difficult to purify, has m. p. 62–65° and a rotation of −63.5°.[27a] A mixed m. p. with an authentic sample was not depressed and the elementary analyses were satisfactory.

Action of Alkali on Triacetyl-α-methylglucoside-6-nitrate (II).—(A) The sample, 6.08 g. or 0.0167 mole, was wetted with 38 cc. of ethanol and the total volume was made up to 60 cc. with aqueous, 4 *N* caustic soda (about 0.08 mole). After solution was complete (thirty minutes), the liquid was kept at 75–80° for seventy minutes or until its molecular rotation had decreased to 9,180°. A quantitative conversion to the 3,6-anhydro derivative required M_D 9,850°. One cc. of the liquid contained 5.2×10^{-6} mole of nitrite, corresponding to 1.9% of the original nitrate.

The remaining 53 cc. was acidified with acetic acid and evaporated under reduced pressure to dryness. Five 25-cc. volumes of boiling acetone extracted the product, which was recovered and dissolved in 20 cc. of hot ethyl acetate. This solution was dried with a little anhydrous sodium sulfate and after filtration was evaporated. The residual, straw colored sirup crystallized solidly when nucleated with 3,6-anhydro-α-methylglucopyranoside (III); yield, 2.0 g. or 77%. After two recrystallizations from ethyl acetate, the m. p. of the product, 105.5–107.5°, and the specific rotation of 56.5° in water agreed with the constants of the 3,6-anhydro derivative.[28] The elementary analysis also checked.

A duplicate experiment was carried out in which the mixture of triacetyl methylglucoside-6-nitrate and alkali was kept at room temperature for two days. Since the molecular rotation decreased to 13,300 in these conditions, instead of to the proper value of 9,850, the reaction was completed by heating at 70° for thirty minutes. An 88% yield of crystalline anhydro-methylglucoside was isolated and 2% of the nitrate groups were reduced to nitrite.

(B) A suspension of 5.03 g. (0.0138 mole) of the triacetyl methylglucoside-6-nitrate in 100 cc. of absolute methanol was mixed at room temperature with 50 cc. of freshly pre-

(22) West and Holden, THIS JOURNAL, **56**, 930 (1934).

(23) Cladding and Purves, *ibid.*, **66**, 153 (1944).

(24) Miller, *Analyst*, **37**, 345 (1912). See also Snell and Snell, "Colorimetric Methods of Analysis," D. van Nostrand Co., New York, 1937, Vol. I, p. 647.

(25) Hudson and Dale, THIS JOURNAL, **37**, 1264 (1915).

(26) Tanret, *Bull. soc. chim.*, [3] **11**, 949 (1894).

(27) Irvine and Oldham, *J. Chem. Soc.*, (a) 1744 (1921); (b) 2729 (1925).

(28) Haworth, Owen and Smith, *ibid.*, 88 (1941).

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pared, 1.3 *N* sodium methylate in methanol. Solution was complete within five minutes but the molecular rotation decreased to the nearly correct value of 9,890 only after forty-eight days. The crude, crystalline product amounted to 1.72 g., or 77%, and an easy purification left it with physical constants in agreement with those already given for 3,6-anhydro-α-methylglucopyranoside.

Action of Alkali on 2,3,4-Trimethyl-β-methylglucoside-6-nitrate (V).—A 5.06 g. (0.018 mole) sample of the 6-nitrate was heated at 60° with 4.0 g. (0.10 mole) of caustic soda dissolved in 150 cc. of 50% aqueous methanol. The container was an Erlenmeyer flask with a wired-in rubber stopper. Solution of the 6-nitrate was complete within two hours but the liquid was too discolored to be observed on the polarimeter. The consumption of alkali, followed by titrating 5-cc. aliquots with standard acid, amounted to 1.17, 1.38 and 1.46 moles per nitrate group after six, twenty and twenty-four hours, respectively, of heating at 60°. These measurements were corrected by means of blank experiments containing none of the methylglucoside nitrate. Aliquots of 0.25 and 0.35 cc., withdrawn at the latter time, contained 11.5×10^{-6} and 17×10^{-6} mole of nitrite, corresponding to 19 and 20% of the original nitrate.

The remaining 59 cc. of the original solution was extracted while still alkaline with two 50-cc. volumes of chloroform. These extracts, after being combined, dried and evaporated, yielded 2.0 g. of a colorless sirup that quickly crystallized. After recrystallizations from 50 and 30 cc. volumes of warm ligroin, the long white needles melted at 92.5–93.5° and had specific levorotations at 25° of −20.8° in methanol and −21.2° in chloroform. A m. p. of 93–94°, rotations of −22.9°[27] to −25.1° in methanol,[29] and of −20.6° in chloroform,[30] have been observed for 2,3,4-trimethyl-β-methylglucopyranoside. An 0.130-g. sample of this substance would liberate 12.3 cc. of methane, corrected to N. T. P., in a Zerewitinoff estimation of active hydrogen. The value found was 12.7 cc.

The aqueous residue from the chloroform extractions was acidified with hydrochloric acid and then re-extracted with chloroform. A dark sirup, 0.5 g. recovered from the extract crystallized spontaneously and nearly completely. Recrystallization from ligroin gave long needles that were non-acidic, contained no double bonds and melted at 87–93°. Since this product was identified as slightly impure 2,3,4-trimethyl-β-methylglucopyranoside, the total crude yield of the latter was raised to 2.5 g. or to 75%.

Action of Alkali on 3,4,6-Triacetyl-β-methylglucoside-2-nitrate (VI).—A solution of 6.06 g. of the 2-nitrate in 18 cc. of peroxide-free dioxane was shaken at room temperature with 60 cc. of 1.67 *N* aqueous sodium hydroxide and precipitated material redissolved within two hours. Table I gives the subsequent change in the observed and the molecular rotation of the solution, whose volume was 77 cc.

TABLE I

ROTATORY CHANGE OF THE METHYLGLUCOSIDE-2-NITRATE IN ALKALI

Hours	α^a	$[M]_D$	Hours	α^a	$[M]_D$
2.5	−3.25°	−15,000°	5.5	−3.86°	−17,900°
3.5	3.50	16,200	8.7	4.02	18,600
4.0	3.63	16,800	10.4	4.17	19,300
4.5	3.73	17,300	23	4.58	21,200[b]

[a] Observed in a 1-dm. tube. [b] Corresponds to a specific levorotation of −120° if anhydromethylhexoside (mol. wt. 176) was the sole product.

After twenty-three hours, 3-cc. samples contained 14.7×10^{-6} mole of nitrite, equivalent to 2.3% of the original nitrate groups.

The remainder of the solution, 72 cc., was examined by the methods already described for the isolation of 3,6-anhydromethylglucoside. A clear, colorless sirup resulted in a yield of 2.30 g. or 84%, and with a specific levorotation of −101° in water at 26°. A negative test for nitrate groups was obtained with ferrous sulfate and concentrated sulfuric acid. In a test for the presence of unsubstituted, adjacent hydroxyl groups, an 0.0545-g. sample reduced 0.7 cc. of 0.1 *N* sodium periodate at *p*H 4.1 in two hours, or in circumstances where 1 mole of methylglucopyranoside reduced the correct amount of 2 mole.[31] The estimation showed that the amount of any methylhexopyranoside present in the sirup did not exceed 5 or 6%. An 0.3-g. sample of the sirup, when acetylated with acetic anhydride and pyridine, gave 0.29 g. of an uncrystallized acetate with a levorotation of −68.8° in chloroform. This acetate required 7.85 cc. of *N* sodium hydroxide per gram in an acetyl estimation. Calcd. for the diacetate of an anhydromethylhexoside, 7.73 cc.; for the tetraacetate of a methylhexoside, 11.5 cc.

The remainder of the unacetylated sirup, 1.9 g., partly crystallized. Cautious dilution of the mass with 10 cc. of ethyl acetate–ethyl ether led to the separation of 0.18 g. of long, feathery needles melting at 127–136° and with a specific levorotation of −111° in water. An 0.0493-g. sample reduced 0.765 cc. of 0.1 *N* sodium periodate or 0.07 mole per mole of crystals, calculated as anhydromethylhexoside. Evaporation of the mother liquors from the crystals gave a residual sirup with a specific levorotation of −106° in water. When a 2.58% solution in 0.01 *N* hydrochloric acid was heated on the steam-bath,[32,33] the rotations observed in a 1-dm. tube were −2.72 (calcd), −1.26, −0.85 and −0.65° after zero, thirty, one hundred and twenty and two hundred minutes, respectively. The solution had developed reducing properties and quickly deposited a yellow precipitate when treated at room temperature with 3 cc. of acetic acid and 2.5 cc. of phenylhydrazine. This precipitate was too small in amount for a detailed examination. The development of reducing power, however, showed that methylglycosidic groups in the sirup had been hydrolyzed.

Anal. Calcd. for an anhydromethylhexoside, $C_7H_{12}O_5$: C, 47.7; H, 6.8, OCH_3, 17.6. Calcd. for a methylhexoside, $C_7H_{14}O_6$: C, 43.3; H, 7.2; OCH_3, 16.0. Found for the crystals: C, 46.4, 45.9, 46.0; H, 6.9, 7.1, 6.9. Found for the residual sirup: C, 46.0, 45.7, 45.4; H, 7.1, 7.3[34]; OCH_3, 16.4. Neither the crystals nor the sirup were obtained in a pure condition. Although the sirup was volatile at 150–165° (3 mm.), an attempt to purify it by vacuum distillation failed owing to rapid decomposition.

Discussion

The quick neutralization of five moles of alkali by tetraacetyl-α-glucosyl nitrate (Structure I, Fig. 1) confirms the fact that the nitrate group in the reducing position of glucose is at least as labile as the four acetyl groups. The yellow gum obtained by dissolving the nitrate in absolute sodium methylate was acetylated prior to examination and the chloroform-soluble portion amounted to 75%. On one occasion, when the crude, acetylated product crystallized spontaneously but incompletely, there was no difficulty in isolating a 28% yield of crystalline tetraacetyl-β-methylglucoside (Ic) and in characterizing it definitely. Crystallization of the crude product was complete on a subsequent occasion and an attempt to isolate the glucoside by fractional recrystallization was unsuccessful. The physical properties of the fractions suggested that the

(29) Haworth and Wylam, *J. Chem. Soc.*, 3120 (1923).

(30) Fowler, Buckland, Brauns and Hibbert, *Can. J. Research*, **15B**, 486 (1937).

(31) *Cf.* Malaprade, *Bull. soc. chim.*, [5] 1, 833 (1934).

(32) Haworth, *Ber.*, **65A**, 43 (1932).

(33) Haworth, Porter and Waine, *J. Chem. Soc.*, 2254 (1932).

(34) These microcombustions were carried out by Miss Zelma Weiss, to whom the authors express their thanks.

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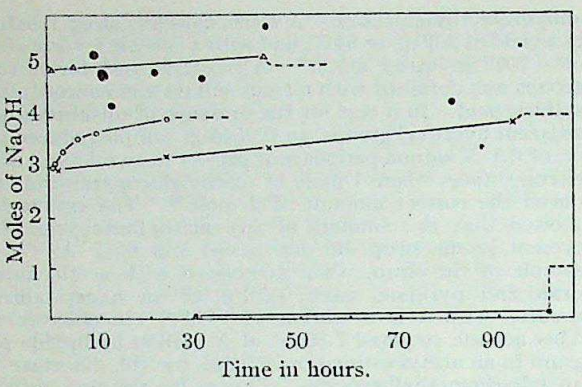

Fig. 1.—Rates of de-acylation by 1.2 *N* aqueous methanolic sodium hydroxide at 25°: 2,3,4,6-tetraacetyl-α-glucosyl-1-nitrate, Δ; 3,4,6-triacetyl-β-methylglucoside-2-nitrate, ○; 2,3,4-triacetyl-α-methylglucoside-6-nitrate, ×, .and 2,3,4-trimethyl-β-methylglucoside-6-nitrate, ●; broken lines show theoretical consumptions of alkali.

original was a mixture of almost equal amounts of tetraacetyl-β-methylglucoside and the more levorotatory triacetylglucosan <1,5>β<1,6>. This interpretation was confirmed when the formation of methylglucoside was suppressed by replacing the absolute sodium methylate with caustic soda dissolved in aqueous dioxane, glucosan (IV) being isolated in 33% yield as the crystalline, trimethyl derivative. The formation of glucosan in these reactions completes the analogy between the behavior of tetraacetyl glucosyl-α-nitrate and the corresponding α-bromide (Ia), which is known to give glucosan when treated in succession with trimethylamine and aqueous barium hydroxide.[35] The analogy, indeed, suggests that the trimethylamine step in the latter preparation may be unnecessary. It is plausible to assume that alkali forms the same carbonium ion from both the α-nitrate and the α-bromide and that a Walden inversion occurs as this ion combines with solvent methanol to give β-methylglucoside, or with the primary alcoholic group of the glucose residue to give glucosan. The explanation, however, fails to account for the formation of glucosan in similar conditions from beta, but not from alpha, phenylglucoside[36] and must at present be accepted with great reserve.

About one quarter of the tetraacetylglucosyl nitrate used in the experiments with absolute sodium methylate produced a yellow gum that was not examined in detail. A much darker colored gum comprised two-thirds of the product obtained with caustic soda in aqueous dioxane. Since only 4.5% of the nitrate groups was reduced to sodium nitrite in the latter experiment, the oxidation of carbohydrate during denitration was likewise insignificant and the gum did not originate in the action of excess alkali upon oxidized glucose residues. This action was probably exerted upon glucose, or upon a reducing intermediate at the glucose level of oxidation, that was formed during denitration. It is apparent that such substances did not reduce sodium nitrate to nitrite in the experimental conditions.

The nitrate group in 2,3,4-triacetyl-α-methylglucoside-6-nitrate (II) neutralized one mole of alkali more slowly than the three acetyl groups (Fig. 1) and only 2% was identified as sodium nitrite in the resulting, nearly colorless solution. Both aqueous alcoholic caustic soda and absolute sodium methylate caused the molecular rotation of the 6-nitrate to decrease to a value corresponding to a practically quantitative formation of 3,6-anhydro-α-methylglucopyranoside (III)[19] and in both cases 77–88% yields of this substance were isolated in a crystalline condition. The preparation of the anhydroglucoside from the 6-nitrate, therefore, proceeds at least as smoothly as those employing the 6-bromo (IIa),[37] the 6-*p*-toluenesulfonyl (IIb)[28] or the 6-sulfonyl[38] derivative.

The nitrate group in 3,4,6-triacetyl-β-methylglucoside-2-nitrate (VI) was removed by alkali somewhat more rapidly than that in the isomeric 6-nitrate (Fig. 1), and only 2.3% was reduced to sodium nitrite. Sodium hydroxide dissolved in aqueous dioxane gave an 84% yield of a clear, colorless, non-reducing, nitrate-free sirup about one-tenth of which eventually crystallized as needles, m. p. 127–136°. Analytical data and physical properties showed that both the crystals and the residual sirup were impure anhydromethylhexosides. An estimation for unsubstituted, adjacent hydroxyl groups by the periodate method showed that, if methylhexoside was present, its amount did not exceed 6% in either fraction. This denitration, therefore, followed a path fundamentally similar to that observed for the deacylation of 2-*p*-toluenesulfonyl-β-methylglucoside (VIa) to a sirup consisting mainly of 2,3-anhydro-β-methyl mannoside (VII).[39,40] The latter sirup, however, had a levorotation of −25° in water, whereas the rotations of the crystals and the residual sirup isolated from the 2-nitrate were −111 and −106°, respectively. Perhaps the discrepancy is connected with the use of sodium methylate in chloroform at 0° as the alkali in one case and sodium hydroxide in aqueous dioxane at 25° in the other. The first reagent produced an anhydro sirup with a specific levorotation of −80 to −90° from triacetyl-3-*p*-toluenesulfonyl-β-methylglucoside[41] in circumstances where a boiling solution of sodium hydroxide in aqueous acetone yielded a product with the large levorotation of −328°.[42] Ohle and Wilcke[42] are of the opinion that 2,3-anhydro derivatives may

(35) Karrer and Smirnhoff, *Helv. Chim. Acta*, **4**, 817 (1921).
(36) Montgomery, Richtmyer and Hudson, THIS JOURNAL, **65**, (1943).
(37) Fischer and Zach, *Ber.*, **45**, 456 (1912).
(38) Duff and Percival, *J. Chem. Soc.*, 830 (1941).
(39) Haworth, Hirst and Panizzon, *ibid.*, 154 (1934).
(40) Lake and Peat, *ibid.*, 1417 (1938).
(41) Peat and Wiggins, *ibid.*, 1088 (1938).
(42) Ohle and Wilcke, *Ber.*, **71**, 2316 (1938).

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sometimes rearrange to other anhydro structures, such as the 3,6, either with or without Walden inversions. Although an examination of the mixture from the methylglucoside-2-nitrate along these lines was outside the scope of the present work, it was observed that at least a portion resembled 3,6-anhydromethylhexosides to the extent that the glucosidic group was very readily removed by acid hydrolysis.[28]

The three denitrations already discussed tend to show that the preferred alkaline cleavage of carbohydrate nitrate groups takes place in the sense $R_1R_2CH\vdots O—NO_2$ and leads to the quick expulsion of the elements of nitric acid in a substantially unreduced condition. The dependence of this method of elimination upon a facile production of methylglucoside or anhydro structures is illustrated in Fig. 1, by the relatively great stability displayed toward alkali by 2,3,4-trimethyl-β-methylglucoside-6-nitrate (V), in which the methyl ether groups block anhydro formation. More drastic conditions promoted a straightforward hydrolysis to crystalline 2,3,4-trimethyl methylglucoside (Va), which was isolated in 75% yield. The alkaline hydrolyses of the "blocked" *p*-toluenesulfonyl radicals in such substances as 2-tosyl-3,4,6-trimethyl-β-methylglucoside[39], 2-methyl-3,4-isopropylidine-6-tosyl-α-methylgalactoside[43] and 2,5-dimethyl-3-tosyl-β-methylxylofuranoside[44] proceed with difficulty but often in high yield along exactly the same lines. No Walden inversions were observed[45] and the hydrolyses were therefore attributed to scission in the sense $R_1R_2CH—O\vdots SO_2C_7H_7$. It is probably legitimate to assume the similar mechanism, $R_1CH_2—O\vdots NO_2$, for the scission of the "blocked" nitrate group in the present case.

The most interesting aspect of this denitration was the reduction of no less than 20% of the organic nitrate to sodium nitrite and the decomposition of up to 25% of the methylated carbohydrate to a discolored tar that slowly neutralized some of the excess alkali. These occurrences showed unequivocally that the direct hydrolysis of "blocked" nitrate groups was slow enough to render the still slower side-reaction, $R_1CH_2—O—NO_2 \rightarrow R_1CHO + HNO_2$, of considerable importance. When it is remembered that a proton is readily expelled from the methylene group in benzyl alcohol and that the oxidative cleavage is quantitative with benzyl nitrate,[13] it appears possible that the mechanism involves the loss of a methylene proton from the scission fragment $R_1CH_2—O—$ and rearrangement to $R_1CH=O$. This mechanism resembles that advanced to explain the formation of *p*-toluenesulfinic acid when certain N-benzyl sulfonamides are heated in strong alkali,[46] although no search seems to have been made for sulfinic acids among the hydrolysis products of "blocked" sulfonyl residues in carbohydrates. The alkaline hydrolysis of 6-bromo-2,3,4-trimethyl-β-methylglucoside (Vb) is reported to yield unsaturated substances[27b]; presumably by the loss of halogen from the sixth carbon atom and of a proton from the adjacent, rather than from the same, position.

The authors wish to thank Professor R. C. Hockett for valuable advice and for several samples of seed crystals.

Summary

1. When 2,3,4-triacetyl-α-methylglucopyranoside-6-nitrate was denitrated by aqueous or alcoholic caustic soda, the product consisted almost entirely of 3,6-anhydro-α-methylglucopyranoside. An 84% yield of a semi-crystalline mixture of crude anhydro methylhexosides was recovered after submitting 3,4,6-triacetyl-β-methylglucopyranoside-2-nitrate to a similar denitration. The constitution of the mixture was not examined in detail.

2. 2,3,4,6-Tetraacetyl-α-glucosyl nitrate and absolute sodium methylate produced a 75% yield of β-methylglucopyranoside mixed with a second substance, which was supposed to be glucosan $<1,5>\beta<1,6>$. The latter was isolated in 33% yield when aqueous alcoholic sodium hydroxide was substituted for the absolute sodium methylate.

3. Aqueous alcoholic sodium hydroxide slowly hydrolyzed 2,3,4-trimethyl-β-methylglucopyranoside-6-nitrate to the 2,3,4-trimethylglucoside in 75% yield. The remainder was recovered as a discolored gum and 20% of the nitrate groups was reduced to sodium nitrite. Only 2 to 4.5% of nitrite resulted in (1) and (2) where an easy formation of methylglucoside or of anhydro derivatives was possible.

4. The very close analogy between the behavior toward alkali of these nitrates and the corresponding *p*-toluenesulfonyl, sulfonyl and halide derivatives was emphasized.

CAMBRIDGE, MASSACHUSETTS
RECEIVED SEPTEMBER 22, 1943

(43) Bell and Williamson, *J. Chem. Soc.*, 1196 (1938).
(44) Robertson and Gall, *ibid.*, 1600 (1937).
(45) Cutler and Peat, *ibid.*, 782 (1939), cite other literature references.

(46) Holmes and Ingold, *ibid.*, 1305 (1926). See also review on mechanism and kinetics of elimination reactions by Hughes and Ingold, *Trans. Faraday Soc.*, **37**, 657 (1941).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

The Preparation of Unsymmetrical Secondary Aliphatic Amines[1]

BY KENNETH N. CAMPBELL, ARMIGER H. SOMMERS AND BARBARA K. CAMPBELL

Until recently unsymmetrical secondary aliphatic amines have been difficult to prepare in quantity. One of the most promising methods of preparing these amines would appear to be by reduction of aliphatic aldimines. A survey of the literature has shown that this approach has been investigated before, with varying degrees of success. Although several workers have reported the preparation of various aliphatic aldimines,[2,3,4] there appears to be no good general description of the method of preparation. Reduction of aliphatic aldimines by sodium and alcohol has been reported to yield the secondary amines[2,4,5] but the yields are not always good; possibly considerable cleavage or polymerization of the aldimine occurs during the reduction. Skita and his co-workers[6,7] investigated the low-pressure catalytic hydrogenation of aldimines, using platinum as catalyst and acetic acid as solvent. They obtained secondary amines, but the carbon content was greater than would be expected. Winans and Adkins[8] and Henze and Humphreys[9] have shown that aldehyde-amine condensation products can be hydrogenated to secondary amines of the same carbon content at high pressures in the presence of nickel catalysts; these workers did not isolate the intermediate aldimines, and while their method gives good yields of amines, there is also need for a procedure which does not involve the use of high-pressure hydrogenation equipment.[10] We therefore undertook a study of the preparation and isolation of aliphatic aldimines, and of their catalytic hydrogenation at low pressures and temperatures.

We have found that aldimines can be obtained in a pure state and good yield from aliphatic aldehydes and amines only by observing certain precautions rather strictly. The method of Emerson, Hess and Uhle[11] could not be extended satisfactorily. The method finally adopted is a modification of the one described by Chancel[12] for propylidene propylamine; the reaction is best carried out by adding the aldehyde to the amine, without a solvent, at 0°. When the order of addition is reversed, the yields are much lower. After the addition is complete, solid potassium hydroxide is added to remove the water formed in the reaction. This step is essential; when other drying agents such as potassium carbonate or magnesium sulfate were tried, practically no aldimine was obtained on distillation, and attempts to hydrogenate the undistilled material were unsuccessful. The aldimine should be distilled from fresh potassium hydroxide. The aldimines obtained in this work were water-white when freshly distilled; they are unstable, and polymerize on standing, and should be used within a few hours after distillation.

The aldimines can be hydrogenated to secondary amines of the same carbon content at room temperature and pressures of 2–3 atmospheres with certain restrictions. The best solvent appears to be absolute ethyl alcohol. Palladium-charcoal catalyst can be used, but the hydrogenation is more rapid, and the yields of amine seem better when pre-reduced platinum oxide is used. With Raney nickel the calculated amount of hydrogen is taken up rather rapidly, but side reactions appear to predominate, and but little of the desired secondary amine is formed. The hydrogenations are best carried out in the presence of a small amount of the original primary amine in order to minimize cleavage of the aldimine.

Experimental

Preparation of Aldimines.—The aldehydes and amines were obtained from Eastman Kodak Co., and were used without further purification. Since the procedure for the condensation was the same in all cases, only a typical example is described.

A 250-ml. 3-neck conical bottom flask, fitted with reflux condenser, mercury-seal stirrer and dropping funnel, was packed in an ice-bath. It was charged with 23.6 g. (0.4 mole) of *n*-propylamine, and 28.8 g. (0.4 mole) of butyraldehyde was added gradually over a period of two hours. The reaction mixture was stirred for an additional fifteen minutes; potassium hydroxide flakes were then added, and the mixture was allowed to stand until separation into two layers appeared complete; this required about ten minutes. The organic layer was then removed, and was allowed to stand over crushed potassium hydroxide in the refrigerator overnight. The dried material was decanted into a 100-ml. conical-bottom Claisen flask, a few pellets of potassium hydroxide were added, and the material was distilled. There was a small preliminary fraction; the temperature then rose rapidly to 120°, and the bulk of the material came over at 120–124°. When the treatment with potassium hydroxide was omitted, and when another drying was substituted, the boiling point of the product rose gradually and continuously, and there was no plateau.

The data on the aldimines prepared are summarized in Table I. The indices of refraction and densities were determined on the freshly-distilled samples.

(1) This paper was presented before the Organic Division at the Pittsburgh meeting of the American Chemical Society, September, 1943.

(2) Henry, *Compt. rend.*, **120**, 837 (1895); *Bull. acad. roy. méd. Belg.*, (3) **29**, 489 (1895).

(3) Turcan, *Bull. soc. chim.*, (5) **3**, 283 (1936).

(4) Löffler, *Ber.*, **43**, 2041 (1910).

(5) Stoermer and von Lepel, *ibid.*, **29**, 2115 (1896).

(6) Skita and Wulff, *Ann.*, **453**, 190 (1927).

(7) Skita and Pfeil, *ibid.*, **485**, 152 (1931).

(8) Winans and Adkins, THIS JOURNAL, **54**, 306 (1932).

(9) Henze and Humphreys, *ibid.*, **64**, 2878 (1942). This paper appeared while the present work was in progress.

(10) In a private communication received recently, Dr. W. M. Lauer of the University of Minnesota reports that he has been able to adapt the procedure of Henze and Humphreys to low-pressure hydrogenation by using platinum oxide as catalyst.

(11) Emerson, Hess and Uhle, THIS JOURNAL, **63**, 872 (1941).

(12) Chancel, *Bull. soc. chim.*, (3) **11**, 933 (1894).

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TABLE I

PHYSICAL CONSTANTS OF ALDIMINES

Aldimine	Yield, %	B. p., °C.[a]	$n^{20}D$	d^{20}_4	MR_D obs.	MR_D calcd.
Ethylidenepropylamine[b]	72	74–81	1.4006	0.7342	28.2	28.0
Ethylidenebutylamine	83	98–106	1.4098	.7513	32.7	32.6
Propylidene-ethylamine[b]	70	70–76	1.4004	.7353	28.1	28.0
Propylidenebutylamine	78	118–127	1.4153	.7601	37.3	37.2
Butylidene-ethylamine	52	100–108	1.4082	.7558	32.4	32.6
Butylidenepropylamine	70	120–124	1.4149	.7611	37.2	37.2
Butylidene-iso-propylamine	64	100–111	1.4063	.7436	37.4	37.2
Butylidenecyclohexylamine[c]	60	78–88 (20 mm.)	1.4564	.8475	49.2	48.9
Isobutylidenepropylamine[b]	76	108–114	1.4087	.7456	37.5	37.2
Isoamylidenepropylamine	64	130–139	1.4170	.7615	42.0	41.8
Isoamylidenebutylamine	67	90–96 (100 mm.)	1.4217	.7687	46.7	46.4

[a] The boiling range given is that of the usable fractions; the bulk of the material in each case boiled over a much narrower range. [b] Henry[2] reported the following boiling points: ethylidenepropylamine, 75–77°, propylidene-ethylamine, 75–78°, butylidenepropylamine, 117–118°. [c] Skita and Pfeil[7] obtained a boiling point of 85–87° (16 mm.) for butylidenecyclohexylamine.

TABLE II

PHYSICAL CONSTANTS OF SECONDARY AMINES

Amine	Source	Yield,[a] %	B. p., °C.	Press., mm.	$n^{20}D$	d^{20}_4	MR_D obs.	MR_D calcd.
Et Pr	$PrNH_2$	40	81–83	746	1.3951	0.7319	28.5	28.9
Et Pr[b]	$EtNH_2$	43	77–80	738	1.3966	.7318	28.7	28.9
Et Bu[c]	$BuNH_2$	52	109	737	1.4056	.7391	33.6	33.5
Et Bu	$EtNH_2$	33	109	734	1.4055	.7414	33.5	33.5
Pr Bu	$BuNH_2$	54	92–93	200	1.4112	.7500	38.2	38.1
Pr Bu	$PrNH_2$	45	92–93	200	1.4112	.7509	38.1	38.1
Pr *i*-Bu	$PrNH_2$	63	83–84	200	1.4065	.7416	38.2	38.1
Pr *i*-Am	$PrNH_2$	47	106–107	200	1.4159	.7564	42.9	42.8
Bu *i*-Pr	*i*-$PrNH_2$	44	121	733	1.4069	.7412	38.3	38.1
Bu *i*-Am	$BuNH_2$	58	64–65	14	1.4202	.7641	47.5	47.4
Bu cyclohexyl	Cyclohexylamine	45	87–90	12	1.4533	.8429	49.8	49.8

[a] This is the over-all yield from the primary amine. [b] From the fractionation data this appeared to be the pure material. Nitrogen analysis (Dumas) gave N; 16.3%; calculated, N, 16.1%. [c] From the fractionation data this appeared to be the purer material. Nitrogen analysis gave N, 13.6%; calculated, N, 13.8%.

Hydrogenation of Aldimines.—Preliminary runs were carried out with a microhydrogenation machine, using 0.01-mole samples of butylidenebutylamine in absolute alcohol. With 50 mg. of platinum oxide, "pre-reduced," 0.01 mole of hydrogen was absorbed in thirty minutes; with 0.1 g. of 10% palladized charcoal, the time required was seventy-five minutes, and with Raney nickel, sixty minutes. On the basis of these results "pre-reduced" platinum was chosen as catalyst, and the following procedure is typical.

A suspension of 0.20 g. of platinum oxide[13] in 50 ml. of absolute alcohol was shaken with hydrogen at 25 lb./sq. in. for ten minutes, or until no more hydrogen was absorbed. The hydrogen pressure was then released, and 31.6 g. of freshly distilled butylidenepropylamine (0.28 mole), 50 ml. of absolute alcohol and 3 ml. of propylamine were added to the catalyst mixture. The mixture was shaken with hydrogen at an initial pressure of 51 lb./sq. in. until no more hydrogen was absorbed; this required forty minutes, and 0.26 mole of hydrogen was taken up. The catalyst was removed, and the alcoholic solution was distilled through a small Whitmore–Fenske column at atmospheric pressure and a 5:1 reflux ratio until the alcohol was removed. The residue was distilled through the same column under reduced pressure. The yield of product boiling at 92–93° (209 mm.) was 20.8 g., 65% of the theoretical amount.

In the case of ethylpropylamine the amine and the alcohol boil too close together to permit of separation by distillation. In this case, therefore, the alcoholic solution of the reduction product was acidified with hydrochloric acid and evaporated to dryness. The free base was liberated from the hydrochloride by aqueous alkali, taken up in ether and the ether solution distilled through the column.

Two attempts were made to use Raney nickel as catalyst; in both cases the correct amount of hydrogen was taken up, but distillation of the reduction product yielded little or no secondary amine.

The unsymmetrical secondary amines prepared in this work have been reported in the literature, but in many cases the data recorded are very meager. For this reason we determined the physical constants and prepared the

TABLE III

DERIVATIVES OF SECONDARY AMINES

Amine	M. p. of α naphthylthiourea,[a] °C.	M. p. of hydrochloride,[b] °C.	% Cl in hydrochloride Found	% Cl in hydrochloride Calculated
EtPr	122–123	223–224	28.61	28.68
EtBu	125	197	25.73	25.76
PrBu	136–137	267–268d	23.32	23.38
Pr-*i*-Bu	143–144	278–282d	23.29	23.38
Pr-*i*-Am	137–138	264–265d	21.37	21.40
Bu-*i*-Pr	91.5–92.5	195–196	23.37	23.38
Bu-*i*-Am	117.5–118.5	dec. 290	19.75	19.73
Bu-cyclohexyl-	107–108	278–283d	18.42	18.49

[a] After two recrystallizations from 95% alcohol. [b] After two recrystallizations from absolute alcohol–ether.

(13) Adams, Voorhees and Shriner, "Organic Syntheses," Coll. Vol. I, 2nd ed., p. 463.

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hydrochlorides and α-naphthylthioureas. The hydrochlorides were analyzed for chlorine. The data are summarized in Tables II and III. In several cases the secondary amine was prepared from both possible combinations of aldehyde and amine, and the two products shown to be identical by comparison of physical constants and derivatives.

Summary

1. A procedure has been described for the preparation of aldimines from aliphatic aldehydes and amines.

2. The catalytic hydrogenation at low temperatures and pressures of the aldimines has been studied, and several unsymmetrical, secondary aliphatic amines have been prepared, their physical constants determined and certain derivatives made.

NOTRE DAME, INDIANA RECEIVED SEPTEMBER 25, 1943

[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY[1a]]

Linear Superpolyesters from Dilinoleic Acid

BY JOHN C. COWAN AND DONALD H. WHEELER[1b]

Linear superpolymers prepared from saturated dibasic acids with other difunctional molecules have been described by Carothers.[1c] However, the preparation of linear superpolymers from dibasic acid containing non-benzoid unsaturation has not been described despite reported preparation of such α-polyesters[2] and α-polyamides.[2a]

Vorländer[3] reported the preparation of a resinous polyethylene maleate and crystalline polyethylene fumarate. Carothers[4] prepared the same polyesters, reporting that the maleate polymer was crystalline, and the fumarate resinous. In addition, Carothers reported that both polyethylene maleate and fumarate were heat-convertible to insoluble three-dimensional polymers.

Bradley[5] and Vincent[6] showed that these polyesters were oxygen-convertible and confirmed Carothers' observation on their heat-convertibility. Vincent reported that one polyester, the triethylene glycol citraconate, was very difficult to heat-convert. This observation indicated that under controlled conditions certain types of unsaturated dibasic acids might give linear superpolyesters. It was believed that the kind of unsaturation present in the acid, as well as the possible effect of steric hindrance, were important.

Dibasic acids which contain unsaturation not conjugated with the carboxyl groups, or contain unsaturation which does not easily shift to conjugation, have not been readily available until recently. By suitable polymerization,[7] and fractional distillation[8] under reduced pressures, the esters of linoleic acid of semi-drying oils can be converted to esters of dilinoleic acid.[8a] Although the structure of dilinoleic acid is not known with certainty, the following data indicate its properties[8,9]

Unsaturation	Two double bonds
Molecular weight	560
Neutral equivalent	280
Conjugation	Negligible[10]
Conjugation after alkali treatment[11]	Negligible[12]
Melting point	Non-crystalline at −60°

Bradley[8] described the preparation of the polyester of triethylene glycol dilinoleate. He obtained a viscous liquid which had an acid value of 13.1. This description indicates that the polymer was an α-polyester, having a molecular weight of approximately 4,300. No description of an attempt to prepare superpolyesters was reported. As a part of the program of the Oil and Protein Division of the Northern Regional Research Laboratory on the polymerization phenomena of semi-drying oils, an investigation of the polyesters of dilinoleic acid was undertaken.

By use of methods developed by Carothers[13] and Flory[14] superpolyesters were prepared from dilinoleic acid with ethylene, decamethylene, and hydrogenated dilinoleyl glycols.[14a] All superpolyesters were soluble in chloroform and, in

(1a) The Northern Regional Research Laboratory is one of four Regional Laboratories authorized by Congress in the Agricultural Research Act of 1938 for the purpose of conducting research to develop new uses and outlets for agricultural commodities. These Laboratories are operated by the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Not copyrighted.

(1b) New address: General Mills, Inc., Minneapolis, Minnesota.

(1c) Carothers and Hill, THIS JOURNAL, **54**, 1559 (1932); **54**, 1566 (1932).

(2) The terminology of Carothers to designate molecular weight ranges of a condensation polymer is used throughout this paper: α-polymers, 800–5,000; ω-polymers, 5,000–10,000; and superpolymers, above 10,000. This terminology is used merely for convenience in referring to the molecular weights of the polyesters.

(2a) Carothers, U. S. Patent 2,174,619 (1939).

(3) Vorländer, *Ann.*, **280**, 167 (1894).

(4) Carothers and Arvin, THIS JOURNAL, **51**, 2560 (1929).

(5) Bradley, Kropa and Johnston, *Ind. Eng. Chem.*, **29**, 1270 (1937).

(6) Vincent, *ibid.*, **29**, 1267 (1937).

(7) Bradley and Johnston, *ibid.*, **32**, 802 (1940).

(8) Bradley and Johnston, *ibid.*, **33**, 86 (1941).

(8a) This terminology is used since the product is apparently a dimer of linoleic acid and its structure is unknown.

(9) Jackson and Cowan, unpublished data.

(10) Bradley and Richardson, *Ind. Eng. Chem.*, **32**, 963 (1940).

(11) Kass and Burr, THIS JOURNAL, **62**, 1796 (1940).

(12) Teeter and Cowan, unpublished data.

(13) Carothers and Hill, THIS JOURNAL, **54**, 1557 (1932).

(14) Flory, *ibid.*, **62**, 1057 (1940).

(14a) Hydrogenated dilinoleyl glycol was prepared from dimethyl dilinoleate esters by high pressure hydrogenation, using Adkins catalyst. The sample used in this investigation was prepared by Organic Chemicals Manufacturers, University of Illinois.

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general, exhibited solubilities similar to those reported by Carothers for saturated superpolyesters. The dilinoleate superpolyesters were non-crystalline plastic solids which on continued exposure to oxygen converted to insoluble three-dimensional polymers. Also, by long heating at temperatures as high as 290–300°, conversion to insoluble three-dimensional polymers was effected. However, some doubt remains as to whether this conversion was actually caused by the high temperature or by traces of oxygen which might have come in contact with the polyesters.

Despite indications from end-group determinations; and from the general properties of the polyesters, it was believed that additional proof of the linear nature and high molecular weight of these polyesters was necessary. This proof was established by use of the relationship of the logarithm of viscosity of the molten polyesters to the square root of molecular weight from end-group determination. Flory[14] showed that this relationship is linear for polyesters from saturated dibasic acids, and he obtained molecular weights in excess of 10,000. Polyesters from dilinoleic acid with decamethylene and hydrogenated dilinoleyl glycols were readily converted to superpolyesters having molecular weights of 10,000 with little deviation from the linear viscosity relationship. However, at higher molecular weights of the order of 20,000–30,000, close correlation was not obtained. At a molecular weight of 20,000, a small deficiency or excess of either reactant makes an enormous variation in the molecular weight obtained by end-group titration (see experimental part). Therefore, failure to obtain exact correlation at high molecular weights is not surprising. Such a failure is probably due to the loss or decomposition of either reactant or to impurities present in the reactants.

Superpolyesters from ethylene glycol were obtained by means of glycolysis. In all cases where dilinoleic acid was used with a theoretical or a slight excess over the theoretical amount of ethylene glycol, deviations from the viscosity relationship occurred at molecular weights above 5,000–6,000. It was believed that the difficultly controllable loss of ethylene glycol and its decomposition[15] at temperatures used for polyesterification were responsible for the failure of dilinoleic acid and ethylene glycol to give superpolyesters when molar or approximately molar quantities of the glycol were used. However, when an excess of glycol was used with the dilinoleic acid, and a glycolysis catalyst added, a superpolyester was obtained. Viscosity determinations indicate that superpolyesters having molecular weights as high as 24,000 were obtained by this method.

(15) Gallaugher and Hibbert, THIS JOURNAL, 59, 2514 (1937); 59, 2521 (1937).

Direct comparison of preparations of polyesters from dilinoleic acid and hydrogenated dilinoleic acid showed that the unsaturation did not contribute to the viscosity of the final products. This behavior was maintained when an inert atmosphere was kept over the reaction mixture and oxygen excluded from the reaction. This work shows that essentially linear superpolymers can be obtained containing nonconjugated unsaturation, and therefore this type of unsaturation is not functional under proper preparative conditions.

Bradley[5] studied the properties of triethylene glycol maleate and triethylene glycol succinate. He obtained relative viscosities and molecular weights by end-group titration of the polyesters at various stages of reaction up to molecular weights of approximately 3,000. Application of Flory's relationship to Bradley's data indicates that under special conditions, *i. e.*, under an atmosphere of pure nitrogen, linear α-polyesters having molecular weights of 2,500 were obtained with triethylene maleate. This work indicates that superpolyesters from maleic and citraconic anhydride and other unsaturated dibasic acids or anhydrides might be obtained by suitable methods. However, conditions required for the preparation of superpolyesters may cause heat conversion too readily to make possible preparation of such superpolyesters. Investigation of the use of unsaturated dibasic acids other than dilinoleic acid for the preparation of superpolyesters is planned, to determine whether essentially linear superpolymers can be obtained which contain conjugated aliphatic unsaturation. This work will determine if conjugated aliphatic unsaturation is functional under preparative conditions necessary for formation of superpolyesters.

Experimental

Dilinoleic Acid.—The acids used in this investigation were prepared from corn or soybean oil. The method used was essentially that described by Bradley[8] for the preparation of methyl dilinoleate from dehydrated castor oil. Corn or soybean oil was converted by methanolysis to methyl esters. The distilled methyl esters were polymerized at 300° with 0.3% anthraquinone catalyst for sixteen to twenty-four hours. Unpolymerized esters were removed by distillation under reduced pressure of 1–5 mm., and the residual methyl dilinoleate carefully fractionated in a short path pot still (a modified alembic flask)[16] at 2 to 50 microns, or in a cyclic molecular still.

Middle cuts of the main methyl dilinoleate fraction were taken as pure dilinoleate for the preparation described. The presence of about 5% linolenic acid in soybean oil resulted in a dimeric product of slightly higher refractive index and iodine value, but otherwise it was very similar to the methyl dilinoleate from corn and dehydrated castor oil.

Methyl dilinoleate from corn oil had the following analysis: Calcd. for $C_{38}H_{68}O_4$: C, 77.20; H, 11.64. Found: C, 77.46; H, 11.68.

The acid was prepared from the ester by usual methods; neutral equivalent varied slightly with each preparation.

Hydrogenated Dilinoleic Acid.—To 3 liters of anhydrous ethanol was added 346 g. of methyl dilinoleate and approximately 20 g. of Raney nickel catalyst[17] suspended in anhy-

(16) Falkenburg, Teeter and Cowan, unpublished work.

(17) Adkins and Covert, THIS JOURNAL, 54, 4116 (1932).

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drous ethanol. The material was hydrogenated in a high pressure bomb at 100° and 1,400 pounds for two and one-half hours. Two additional treatments with fresh catalyst were carried out at 150° and 1,000 pounds for three hours each. The final product had an iodine value of 15.6, $n^{30}D$ 1.4705, and d^{30}_4 0.9306. It is possible that some alcoholysis occurred, giving a mixed ester. On saponification and neutralization the hydrogenated dilinoleic acid was obtained: neutral equivalent, calculated, 282.4; found, 299, 286.9, on two different preparations.

Hydrogenated Dilinoleyl Glycol.—Methyl dilinoleate from corn oil was hydrogenated, using Adkins catalyst, copper chromium oxide.[5,18]

Anal. Calcd. for $C_{36}H_{66}(OH)_2$: sapon. no., 0.0; OH no., 209.5; I no., 0. Found: sapon. no., 6.8; OH no., 204.1; I no., 11.3.

Original Preparations of Polyesters.—The first preparations of the polyesters from dilinoleic acid were made from the acid and ethylene glycol without catalyst. Several preparations were made with a variation in the amount of reactants used, and all of the polyesters prepared exhibited properties somewhat similar to superpolyesters. However, later work showed that these esters were probably ω-polyesters, although some preparations such as the following may have higher molecular weights.

A mixture of 328 g. of dilinoleic acid (neutral equivalent 288) and 45 g. of ethylene glycol was heated under carbon dioxide ebullition in a Claisen flask for seventy-two hours and for one hundred and forty-six hours in a pot still (Corning 3480). Table I shows the temperatures used and neutral equivalent of the polyester.

TABLE I

PREPARATION OF ETHYLENE GLYCOL DILINOLEIC ACID POLYESTER

Sample	Time, hours	Temp., °C.	Neutral equivalent
1	24	125	817
2	72	150	2200
3	120	240	3620
4	162	240	4240
5	170	250	4700
6	194	250	4900

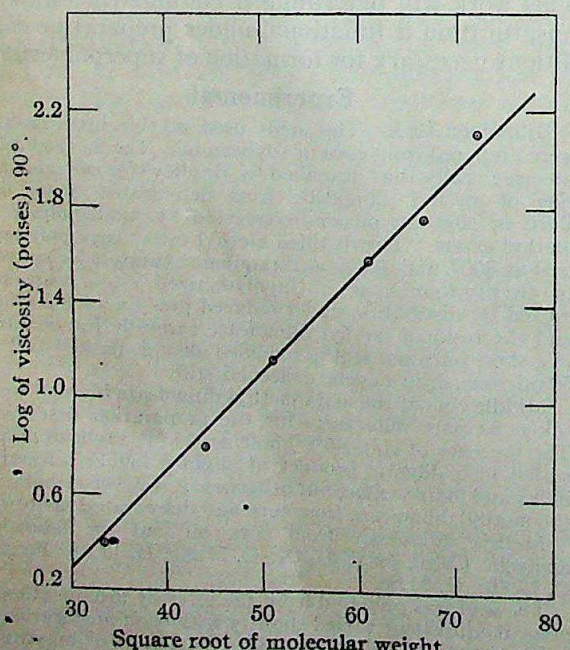

Fig. 1.—Viscosity–molecular weight relationship, polyester from dilinoleic acid with ethylene glycol.

(18) Folkers and Adkins, THIS JOURNAL, 54, 1146 (1932).

The polyester at the end of one hundred and ninety-four hours dissolved slowly but completely in chloroform. After twenty-four more hours heating at 300 to 320°, the polyester converted to a gel and only a portion of it was soluble in chloroform. The method used to remove samples from the reaction chamber permitted air to enter. Although the increased temperature appeared to be responsible for this gelation, oxygen conversion cannot be ruled out. A film of the soluble polyester having a neutral equivalent of 4,900 was exposed to the atmosphere. After sixty days, the film was only partly soluble in chloroform.

Despite repeated attempts with catalysts to obtain superpolyesters using molar or slightly greater quantities of ethylene glycol, no polyester was obtained which could be classified with certainty as a true superpolyester. Therefore, a study based on Flory's work[14] was undertaken.

Preparation of Superpolyesters and Viscosity Studies.—The esterifications were carried out in a vapor-jacketed vessel fitted with an inlet tube for introducing inert gas (purified nitrogen or carbon dioxide) below the surface of the reaction mixture, and an exit tube sealed with a bubbler to prevent back-diffusion of oxygen. Viscosities were usually measured by the rolling ball method, using 6 mm. i. d. tubes and an 1/8 inch steel ball. The relative kinematic viscosities thus obtained were converted to approximate values in poises by standardizing the viscosimeter with an oil of known viscosity. In several cases, viscosities were measured at reaction temperature with pipets or tubes in the reaction vessel, following the methods described by Flory.[14]

Molecular weights were determined by titrating samples in chloroform with alcoholic sodium hydroxide, using phenolphthalein or brom thymol blue indicator.

1. Ethylene Dilinoleate.—An ethylene glycol polyester of approximately 6,000 molecular weight was obtained as follows. A mixture of 50.8 g. (0.1810 equivalent) of dilinoleic acid (neutral equivalent, 286.4) and 5.82 g. (0.1877 equivalent) of ethylene glycol was heated for twenty-four hours at 100°, and then at 155–160° for another twenty-four hours, and then the temperature was raised to 195° for one hundred and fifty hours. Samples taken during the run showed the following neutral equivalents and viscosities.

Sample	Total hours	Molecular weight (neutral equivalent)	30° poises	90° poises
1	30	1142	70.8	2.47
2	42	1960	195	6.15
3	50	2630	514	14.8
4	65	3920	1295	37.7
5	77	4480	2120	56.6
6	140	5190	4650	125.5
7	over 200	5690	12140	....

The relationship of the log of viscosity at 90° to the square root of the equivalent weight is shown in Fig. 1. The values at 30° showed the same degree of agreement with a straight line relationship up to molecular weights of 5,000. Repeated attempts failed to obtain polyesters of much higher molecular weight which correlated with viscosity. Apparently ethylene glycol was lost or decomposed so that the reaction could not proceed above a molecular weight of 5,000 when equivalent amounts of reactants were used.

The experience with the polyesters just described led to the use of excesses of ethylene glycol with the addition of a small amount of alcoholysis catalyst. A mixture of 33.8 g. of dilinoleic acid (0.1205 equivalent), 4.86 of ethylene glycol (0.1567 equivalent, 30.5 % excess), and 15 mg. of *p*-toluenesulfonic acid was heated with purified nitrogen passing through the mixture. The reaction was run at 195° with the viscometer pipet in the reaction vessel, and was followed by viscosity values only since acid end-group determinations would be meaningless with such a large excess of glycol. After eighteen days, the viscosity had reached a

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value of 4,600 poises at 195°, which corresponds to a molecular weight of approximately 24,000. This value is arrived at by extrapolating to 195° from the viscosities at 30 and 90°, as described in the previous run, making use of the fact that the log of viscosity is a linear function of the reciprocal of absolute temperature (*cf.* Flory, *loc. cit.*). The calculated values for log of viscosity at 195° plotted against the square root of molecular weight showed good agreement with linear relationship. Extension of this curve indicates that a viscosity of 4,600 poises at 195° corresponds to a molecular weight of 24,000. This superpolyester was a soft elastic material which was soluble in chloroform at room temperature.

2. **Polyester of Ethylene Glycol with Hydrogenated Dilinoleic Acid.**—A mixture of 25.48 g. (0.0852 equivalent) of dilinoleic acid (equivalent weight found, 299) and 2.67 g. (0.086 equivalent) of ethylene glycol was heated at 195° under purified nitrogen with the results shown in Fig. 2. The linear relationship was again retained to a molecular weight of approximately 5,000.

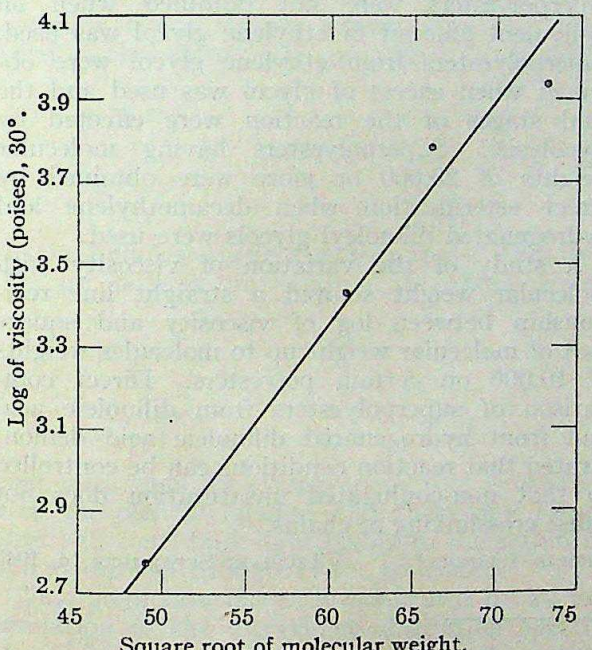

Fig. 2.—Viscosity–molecular weight relationship, polyester from hydrogenated dilinoleic acid with ethylene glycol.

3. **Decamethylene Dilinoleate.**—One method which served to minimize loss of reactants was to use a high molecular weight glycol such as decamethylene glycol with the dilinoleic acid. Although an observable loss of decamethylene glycol occurred, it was much less than when ethylene glycol was used.[18a] A mixture of 31.27 g. (0.115 equivalent) of dilinoleic acid and 9.72 g. of decamethylene glycol (0.116 equivalent) reacted at 195°, and the data obtained on viscosity and molecular weights are shown in Fig. 3. The values up to molecular weights of 10,000 are in excellent agreement with the linear relationship expected. The last two values deviate from an extension of the line for the first four. According to relationships developed by Flory, the deviation of the last two points would correspond to a deficiency of about 0.7% of glycol. Such a deficiency would not appreciably affect the previous points, and is in accord with the qualitative observation of some loss of glycol. The last sample was chloroform soluble, and represents a superpolyester of molecular weight of at least 20,000 or about 28,000, according to viscosity by extrapolation of the first four points.

4. **Polyester from Decamethylene Glycol and Hydrogenated Dilinoleic Acid.**—A mixture of 36.99 g. (0.1289 equivalent) of hydrogenated dimer acid (neutral equivalent found, 286.9) and 11.230 (0.1289 equivalent) of decamethylene glycol was heated at 195° with the results (see Fig. 4) similar to those of the decamethylene dilinoleate run. The deviation of the points beyond the fourth (10,400 molecular weight) corresponds to a loss of 0.8 to 0.9% of glycol. The final sample, with molecular weight of 15,500 by titration, or about 22,000 by vicosity, was also soluble in chloroform.

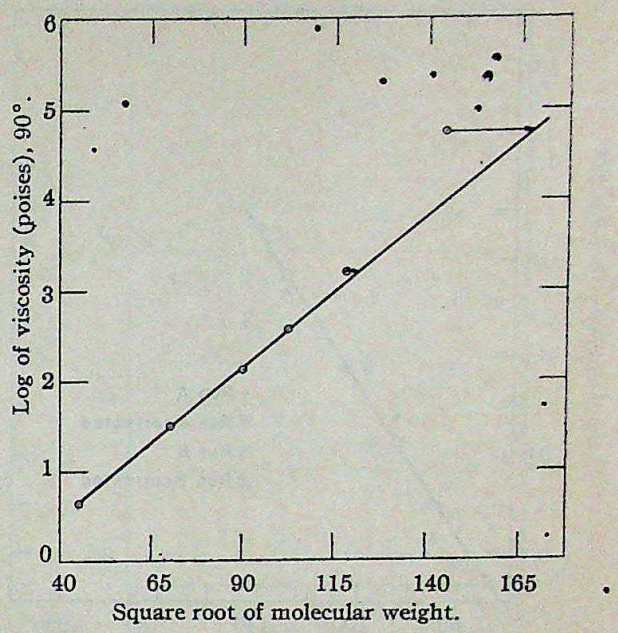

Fig. 3.—Viscosity–molecular weight relationship, polyester from dilinoleic acid with decamethylene glycol.

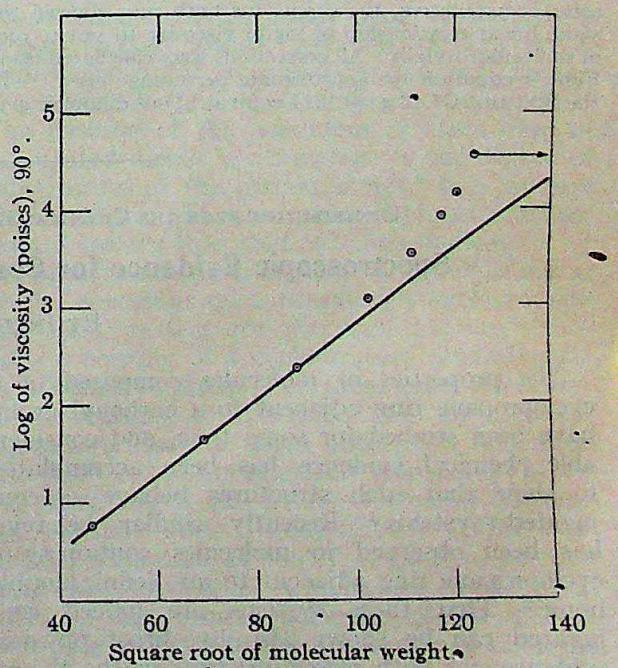

Fig. 4.—Viscosity–molecular weight relationship, polyester from hydrogenated dilinoleic acid with decamethylene glycol.

5. **Polyester from Dilinoleic Acid with Hydrogenated Dilinoleyl Glycol.**—In the first run, an excess of acid was used due to an error in calculations. In the second run, equivalent amounts of glycol and acid were used, assuming

(18a) Flory[14] reports a similar experience with decamethylene glycol.

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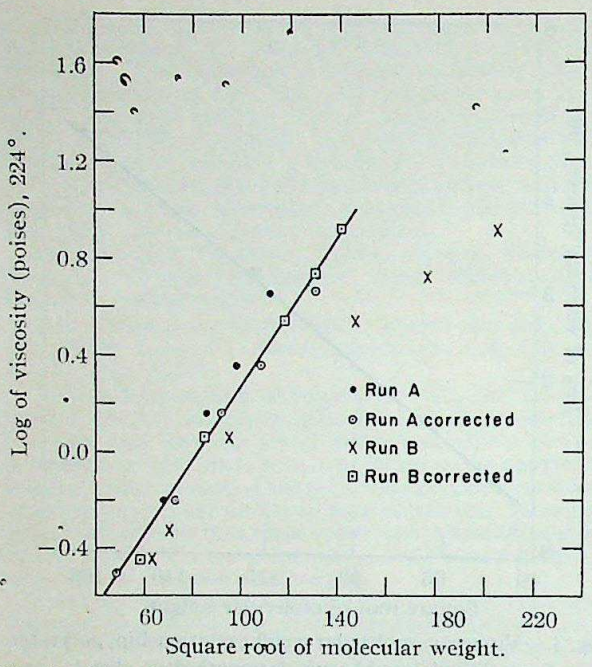

Fig. 5.—Viscosity–molecular weight relationship, polyester from dilinoleic acid with dilinoleyl glycol.

that the ester present in the glycol would be reactive by glycolysis and should be allowed for in calculating the required amount of acid to be used. The viscosity–molecular weight relationships of samples taken during this run indicated that an excess of glycol was present, and since no catalyst was present, it would appear that the ester had not reacted. When the results of both runs were corrected for the excess of acid or glycol present, assuming that the ester is unreactive, the points for both runs showed the same linear relationship of log of viscosity to square root of molecular weight. All corrections were calculated using Flory's equation for approximate percentage error.[14] In the first run, 34.42 g. (0.1214 equivalent) of dilinoleic acid (from soybean oil; neutral equivalent, 283.8) and 32.76 g. (0.1193 equivalent, based on OH no.) of hydrogenated dilinoleyl glycol reacted at 224°. In the second run, 31.14 g. (0.1098 equivalent) of dilinoleic acid and 31.09 g. (0.1131 equivalent) of the same glycol reacted at 224°. The results for viscosity molecular weight relationship are identified as Run A and Run B, respectively, in Fig. 5. The corrected values lie on the same straight line, and again indicate linear superpolyesters of molecular weights up to 20,000. Final samples from both runs were soluble in chloroform.

Summary

Superpolyesters were prepared from an unsaturated dibasic acid, dilinoleic acid, with ethylene, decamethylene and hydrogenated dilinoleyl glycols.

Loss and decomposition of ethylene glycol at reaction temperatures occurred and therefore superpolyesters were not obtained when an equivalent amount of ethylene glycol was used. Superpolyesters from ethylene glycol were obtained when excess of glycol was used and the final stages of the reaction were effected by glycolysis. Superpolyesters having molecular weights of 20,000 or more were obtained by direct esterification when decamethylene and hydrogenated dilinoleyl glycols were used.

A study of the variation of viscosity with molecular weight showed a straight line relationship between log of viscosity and square root of molecular weight up to molecular weights of 10,000 on certain polyesters. Direct comparison of superpolyesters from dilinoleic acid and from hydrogenated dilinoleic acid demonstrated that reaction conditions can be controlled so that non-conjugated unsaturation does not cause crosslinking of chains.

PEORIA, ILLINOIS RECEIVED SEPTEMBER 14, 1943

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Spectroscopic Evidence for Conjugation in Cyclopropane Systems

BY IRVING M. KLOTZ

The properties of molecules composed of a cyclopropane ring adjacent to a carbonyl group have been studied for some time, and considerable chemical evidence has been accumulated to show that such structures behave as conjugated systems.[1] Recently similar behavior has been observed in molecules containing a cyclopropane ring adjacent to an olefinic double bond.[2] That these systems are indeed conjugated can be shown also by direct physical evidence, for with recent progress in the theory of absorption spectra[3] it is now possible to interpret ultraviolet spectra in terms of molecular structure.

The intense absorption bands of single ethylenic linkages lie in the region near 1800 Å., and if the carbon atoms are highly substituted, strong absorption may extend somewhat beyond 2000 Å.[4] However, when two double bonds are conjugated to each other a pronounced shift in the absorption toward the red end of the spectrum is observed. Wave-mechanical considerations[3] have shown that high intensity ultraviolet absorption spectra are due to transitions from a neutral ground state of the molecule to an ionic excited state. Conjugation permits the existence of a number of ionic structures which contribute appreciably to the resonance in

(1) R. C. Fuson, "Organic Chemistry, An Advanced Treatise," Vol. I, second edition, edited by H. Gilman, John Wiley and Sons, Inc., New York, 1943, p. 102.

(2) B. Riegel, M. F. W. Dunker and M. J. Thomas, THIS JOURNAL, 64, 2115 (1942).

(3) R. S. Mulliken, *J. Chem. Phys.*, 7, 121 (1939); 7, 339 (1939).

(4) A. Lüthy, *Z. physik. Chem.*, 107, 285 (1923).

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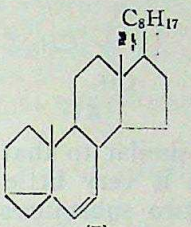
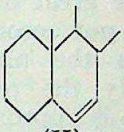
the excited state, but not to that in the ground state, and hence lower the energy of the former relative to that of the latter.

Since it is now recognized that conjugation may also occur between a saturated group and a double bond (hyperconjugation[3]) it would be expected that a compound such as Δ^6-*i*-cholestadiene (I) should have an ultraviolet absorption

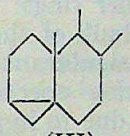


(I)

spectrum much farther toward the red than either 6-cholestene (II) or *i*-cholestene (III).

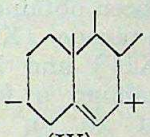


(II)

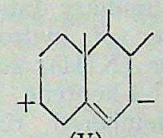


(III)

For in *i*-cholestadiene the structures (IV) and (V) are possible in addition to those which



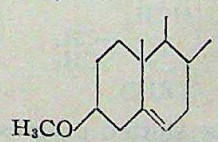
(IV)



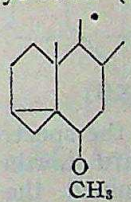
(V)

exist even when the cyclopropane ring is isolated from the olefinic linkage, and these new structures will contribute appreciably to the stabilization of the excited state of the molecule.

This prediction has been confirmed by an examination of the ultraviolet absorption spectra of Δ^6-*i*-cholestadiene (I), cholesteryl methyl ether (VI) and *i*-cholesteryl methyl ether (VII).



(VI)



(VII)

The two methyl ethers show no significant absorption, when examined in thickness and concentration comparable with Δ^6-*i*-cholestadiene (I), as low as 2230Å., the limit of our present instrument. These latter compounds correspond to structures (II) and (III) except for slight, non-influential differences in the position of the double bond and in the presence of a methoxy group. The *i*-cholestadiene, on the other hand, shows appreciable absorption below 2500Å. and gives strong indications of a peak near 2100Å. The spectrum of the compound has been plotted in Fig. 1 in conjunction with some mono- and di-

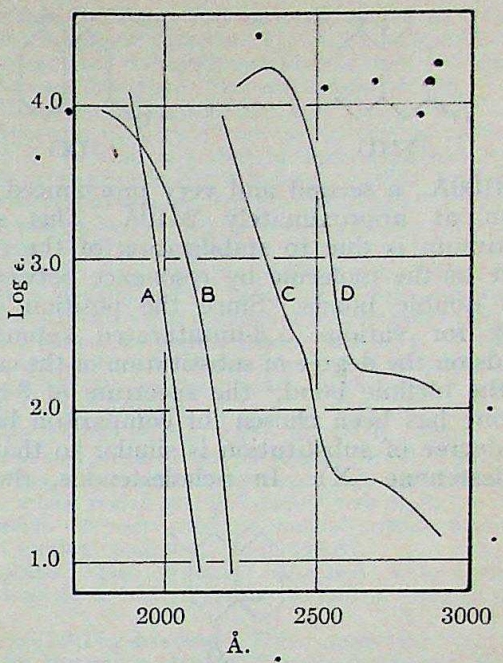


Fig. 1.—Absorption spectra of diallyl, A, trimethylethylene, B, Δ^6-*i*-cholestadiene (I), C, and cholestadiene, D. A and B from G. Scheibe and R. Pummerer, *Ber.*, **60**, 2163 (1927), and D from E. L. Skau and W. Bergmann, *J. Org. Chem.*, **3**, 166 (1938).

olefins for comparison. The unconjugated diolefin absorbs far to the left of *i*-cholestadiene, as is predicted by quantum mechanics.[3] Cyclopropane absorbs at even shorter wave lengths. Cholestadiene, on the other hand, absorbs in a region farther toward the red than even *i*-cholestadiene, for hyperconjugation is a second order effect compared to ordinary conjugation.[5] The position of the maximum of absorption of conjugated dienes is a function of the degree of substitution of the carbon atoms,[6] but for any cholestadiene, the absorption is much farther toward the red than that of *i*-cholestadiene.

The considerations leading to an explanation of the spectrum of a conjugated cyclopropane ring–olefin system are also applicable to structures consisting of a cyclopropane ring adjacent to a carbonyl group. In these cases, however, it is necessary to recognize that all carbonyl compounds show a small absorption maximum near 3000Å., but are relatively transparent below this wave length unless some degree of conjugation exists. Thus 3-cholestanone (VIII) exhibits a maximum at 2860Å. (Fig. 2), a position quite close to that for acetone despite the great bulk of the former molecule. Below 2860Å. there is a decrease in the absorption of cholestanone down to about 2600Å. and a slight rise thereafter. In contrast, 3-cholestenone (IX) which has a conjugated olefinic and carbonyl group, shows, in addition to the carbonyl peak

(5) R. S. Mulliken, C. A. Rieke and W. G. Brown, THIS JOURNAL **63**, 41 (1941).

(6) R. B. Woodward, *ibid.*, **64**, 72 (1942).

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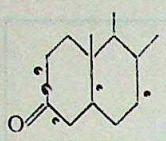
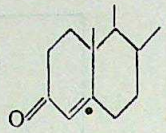
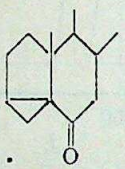

(VIII)


(IX)

at 3100Å., a second and very pronounced maximum at approximately 2410Å. This second maximum is due to stabilization of the excited state of the molecule by resonance between the two double bonds. Since the position of the peak for various α,β-unsaturated ketones depends on the degree of substitution of the carbons in the olefinic bond,[7] the spectrum of 3-cholestenone has been chosen for comparison because its degree of substitution is similar to that of *i*-cholestenone (X). In *i*-cholestenone, the con-


(X)

jugation of cyclopropane ring and carbonyl group introduces a number of ionic structures, in addition to those possible when the groups are isolated, which stabilize the excited state sufficiently to produce the spectrum shown in Fig. 2.

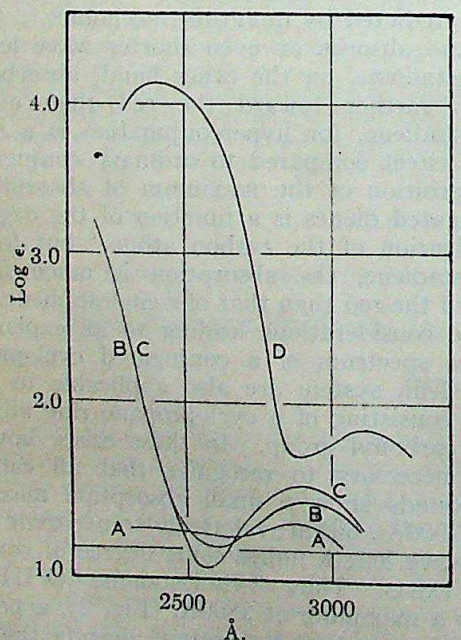
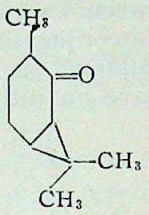


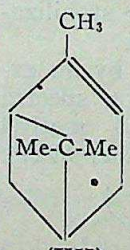
Fig. 2.—Absorption spectra of 3-cholestanone (VIII), A, carone (XI), B, *i*-cholestenone (X), C, and Δ^4-3-cholestenone, D. D is from H. Mohler, *Helv. Chim. Acta*, 20, 289 (1937).

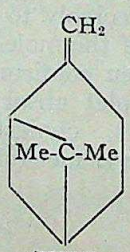
Spectroscopic evidence of conjugation between a cyclopropane ring and a carbonyl group is not limited to the steroid series. There are a number of terpene molecules which have similar conjugated structures, and we have examined the ultraviolet absorption of one of these substances, carone (XI). This compound exhibits a spec-

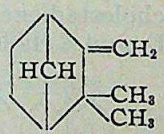

(XI)

trum extremely similar to that of *i*-cholestenone (Fig. 2). There is very little difference in the spectra of the two substances despite the fact that the cyclopropane ring in the terpene is relatively flexible whereas that in the steroid is locked in very rigidly because it is attached to two other rings. Similarly, the great difference in the bulk of the molecules is not accompanied by a significant difference in the ultraviolet absorption spectra. Apparently the resonance energy due to hyperconjugation is approximately the same in both the steroid and terpene and is influenced but little by the remainder of the molecule.

Preliminary data also have been obtained for a number of hydrocarbons, α-pinene (XII), β-pinene (XIII), camphene (XIV) and bicyclo-[2,2,1]-2-heptene (XV), containing a four- or five-membered ring adjacent to an olefinic linkage. In these cases the effect of hyperconjugation (or of strain in the classical point of view) is less than in the cyclopropane compounds


(XII)


(XIII)


(XIV)

(XV)

and the spectrum should be shifted progressively toward shorter wave lengths. In the compounds examined, the pinenes absorb in the region between the cyclopropane and cyclopentane compounds. The separation between the spectra is rather large, and there are indications that it may be possible to determine ring size in hydrocarbons by examining the spectrum of the compound containing the ring conjugated to an olefinic bond. However, the region farther in the ultraviolet must be investigated, and many more substances must be studied to substantiate this correlation. The necessary work is now in progress.

Experimental

The ultraviolet absorption spectra were obtained with a Beckmann quartz spectrophotometer. This instrument

(7) R. B. Woodward, THIS JOURNAL, 63, 1123 (1941); 64, 76 (1942).

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uses a hydrogen arc as a source of ultraviolet radiation and a photocell-amplifier combination as a detector. The spectral region covered was from 2230 to 4000Å.

Solutions of known concentration were made by dissolving weighed quantities of solute in ethyl ether in a volumetric flask. At least two different concentrations of solute were used in most cases since a wide range in molecular extinction coefficient was encountered. The solution was poured into one of two matched silica absorption cells and the second cell was filled with solvent. Both cells were then inserted into the spectrophotometer and the intensity of light passing through each of them was recorded. The temperature of the solutions was maintained between 22 and 25°.

Extinction coefficients were calculated from the familiar equation

$$\epsilon = \frac{1}{cd} \log_{10} (I_0/I)$$

where I_0 is the intensity of the light passing through the solvent, I, the intensity of the light passing through the solution, c, the concentration of solute, in moles per liter, and d the thickness of the cell, in centimeters.

The compounds examined were prepared in the following ways.

Cholesteryl Methyl Ether.—The normal ether was prepared by the reaction of cholesteryl *p*-toluenesulfonate with methanol. Repeated crystallization from acetone gave platelets melting at 84–84.5°.

***i*-Cholesteryl Methyl Ether.**—The isomeric methyl ether was prepared from cholesteryl *p*-toluenesulfonate by the method of Stoll.[8] The crude ether was crystallized many times from acetone. Long, thin rods were obtained and melted at 79–79.8°.

***i*-Cholestenone.**—3(α)-Chlorocholestanone-6 was converted into *i*-cholestenone by the method of Windaus and Dalmer.[9] After several crystallizations from methanol, the ketone was sublimed at 75–80° at 10^{-4} mm. Crystallization of the sublimate from methanol gave a product melting at 93–96°. The above compounds were prepared by Dr. Edwin W. Meyer.

3-Cholestanone.—The method used for the preparation of 3-cholestanone was that described by Bruce.[10] The compound was crystallized from dilute ethanol until spectrographically pure. Dr. Irving Allan Kaye prepared this ketone.

(8) W. Stoll, *Z. physiol. Chem.*, **207**, 147 (1932).
(9) A. Windaus and O. Dalmer, *Ber.*, **52**, 168 (1919).
(10) W. F. Bruce, "Org. Syntheses," Coll. Vol. II, p. 139.

Δ⁶-*i*-Cholestadiene.—This material melted at 73–73.5° and gave a specific rotation of −60.9°. Its method of preparation and chemical characterization will be described in a publication[11] that will appear shortly.

***d*-5-Carone.**—Dihydrocarvone, b. p. 116–118° (17 mm.), was prepared in 62% yield from carvone by the method of Wallach.[12] It was converted to dihydrocarvone hydrochloride by passing in dry hydrogen chloride until 120% of the theoretical amount had been absorbed. This crude product was converted directly to *d*-5-carone by the method of Richter, Wolff, and Presting.[13] The crude *d*-5-carone was dissolved in 5 to 6 volumes of Skellysolve F (petroleum ether, b. p. 30–60°) and the resulting solution was washed with an excess of neutral potassium permanganate solution (20 g. of potassium permanganate and 25 g. of sodium bicarbonate per liter of solution), heated on the steam-bath to remove the Skellysolve F, and distilled under reduced pressure. The yield was 67%, b. p. 115–116° (15 mm.), d^{26}_4 0.933, $[\alpha]^{25}D$ +155.6° ($\alpha^{25}D$ 143.3°, *l*, 1 dm.). The *d*-5-carone was prepared and purified by Dr. R. I. Jackson.

α-Pinene.—A commercial product was distilled and a fraction which boiled at 158.5–159.0° was used.

β-Pinene.—A very pure commercial sample was used without further treatment; b. p. 165.8°.

Camphene.—The product examined was obtained from *i*-borneol by dehydration. It had a melting point of 50°.

Bicyclo-[2,2,1]-2-heptene.—This compound was obtained by treating cyclopentadiene and ethylene by the method described by Joshel and Butz.[14] A sample was redistilled and then recrystallized twice from an ethyl alcohol–water mixture. The product melted at 53°.

The samples of α-pinene, β-pinene, camphene and bicyclo-[2,2,1]-2-heptene were supplied by Dr. H. Pines.

Summary

The absorption spectra of a number of compounds containing a cyclopropane ring adjacent to an olefinic or carbonyl group have been examined and have been interpreted in terms of resonance due to hyperconjugation.

(11) Unpublished results of B. Riegel, G. P. Hager and B. L. Zenitz.
(12) O. Wallach, *Ann.*, **279**, 377 (1894).
(13) F. Richter, W. Wolff and W. Presting, *Ber.*, **64**, 877 (1931).
(14) L. M. Joshel and L. W. Butz, THIS JOURNAL, **63**, 3350 (1941).

EVANSTON, ILLINOIS RECEIVED JULY 8, 1943

[COMMUNICATION NO. 951 FROM THE KODAK RESEARCH LABORATORIES]

Ascorbic and Iso-ascorbic Acids as Photographic Developing Agents

BY T. H. JAMES

Ascorbic and iso-ascorbic acids represent a type of developing agent chemically quite distinct from the conventional aromatic agents. The developer activity of ascorbic acid was first reported by Maurer and Zapf[1] in 1934. Shortly afterwards, Bills[2] published formulas in which ascorbic acid was the active developing agent, and Rzymkowski[3] and Pavolini[4] published similar formulas for iso-ascorbic acid. Reaction mechanism studies have not been reported.

The present paper is concerned chiefly with establishing the general kinetics of development by ascorbic and iso-ascorbic acids, preliminary to using these substances in an investigation of the electric charge effect[5] in development. They show certain definite advantages over the aromatic agents usually employed for this purpose. The most important advantage is that the oxidation products of the ascorbic acids do not

(1) K. Maurer and G. Zapf, *Ber.*, **67**, 1239 (1934); *Phot. Ind.*, **33**, 90 (1935).
(2) C. E. Bills, *Science*, **81**, 257 (1935).
(3) J. Rzymkowski, *Phot. Ind.*, **33**, 91 (1935).
(4) T. Pavolini, *Il Corr. Fot.*, **32**, 33 (1935).
(5) T. H. James, *J. Phys. Chem.*, **43**, 701 (1939).

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interfere with the development process. The kinetic conditions are thus considerably simplified.

Materials and Methods

Ascorbic Acids.—Eastman Kodak Company *l*-ascorbic acid and *d*-iso-ascorbic acid were used.

Alkali and Salts.—General Chemical Company reagent grade potassium hydroxide and salts were used.

Water was redistilled in an all-Pyrex glass apparatus.

All development operations were carried out at 20 ± 0.05° under an atmosphere of oxygen-free nitrogen, using the general procedure previously described.[5] A series of development tests made on solutions which had been kept in the development apparatus for times varying from ten minutes to twenty-four hours gave satisfactorily constant results.

The photographic material was a normal motion picture positive (silver bromide) emulsion. Strips of film were given standard exposures in the Eastman Type IIb sensitometer. The step corresponding toan exposure of $\log E = 1.15$ (where E is in meter-candle-seconds) was employed in general for rate determinations. This exposure step was consistently on the "straight-line" portion of the exposure curve.[6] Rates are given in terms of R, the slope of the density–time curve of development at $D = 0.80$; and $1/t$, where t is the time required to obtain a density of 0.20.

Comparison of Ascorbic and Iso-ascorbic Acids.—At *p*H 10.3, the R values for iso-ascorbic acid in several experiments varied from 1.30 to 1.37 times those of ascorbic acid, with an average of 1.32. The ratio of $1/t$ values varied from 1.34 to 1.50, with an average of 1.45. In 0.04 M excess potassium hydroxide solution, the R values for iso-ascorbic acid varied from 1.0 to 1.09 times those of ascorbic acid, with an average of 1.03. The ratio of $1/t$ values varied from 1.1 to 1.2, with an average of 1.14. Thus, the iso-ascorbic acid develops appreciably faster than the ascorbic at *p*H 10.3, but only slightly faster in the caustic solution. No difference was noted in the rate of fog formation by the two substances.

Experiments carried out under varying conditions showed no significant difference in the general developing properties of the two acids. More complete data were obtained for the iso-ascorbic acid, and only these results will be reported subsequently.

Effect of Bromide Ion.—The addition of potassium bromide to the developing solution decreased the rate of image development, but had a much greater effect in depressing the rate of fog formation. Data are listed in Table I. The rate of fog formation is indicated by the last column. In the subsequent work, sufficient bromide was employed to suppress fog formation to a small, and generally negligible, quantity.

TABLE I

EFFECT OF BROMIDE ON DEVELOPMENT BY ISO-ASCORBIC ACID

*p*H	KBr concn.	R	$1/t$	Time for fog D = 0.10
10.33	.....	0.030	....	36
10.33	0.00067	.025	0.0125	110
10.33	.00667	.018	.0085	192
KOH				
0.04 M	.00067	.07	.048	22
.04 M	.0020	.065	.050	28
.04 M	.0067	.05	.040	>42

(6) Details on the standard exposure treatment and general photographic terminology are given in "The Theory of the Photographic Process," by C. E. K. Mees, the Macmillan Co., New York, N. Y., 1942.

Effect of Concentration and *p*H.—The variation in rate with concentration of iso-ascorbic acid is given in Table II. The salt environment was maintained essentially constant. The solutions of *p*H 10.34–10.38 contained 0.167 M potassium carbonate and sufficient bicarbonate or hydroxide to adjust the *p*H. The caustic solutions contained 0.333 M potassium nitrate. The total potassium-ion concentration was approximately 0.35 in the carbonate solution and 0.39 in the caustic solution.

The variation in rate with *p*H is given in Table III. A carbonate buffer was used in all experiments except the one at *p*H 7.96, where a phosphate buffer was employed.

TABLE II

VARIATION OF DEVELOPMENT RATE WITH ISO-ASCORBIC ACID CONCENTRATION

Iso-ascorbic concn.	*p*H	R	$1/t$	KBr concn.
0.0025	10.34	0.038	0.021	0.00067
.0050	10.34	.064	.041	.00067
.0100	10.36	.112	.083	.00067
.0150	10.38	.170	.125	.00067
.0025	0.04 M KOH	.062	.050	.00667
.0050	.04 M KOH	.126	.105	.00667
.0100	.04 M KOH	.235	.23	.00667

TABLE III

EFFECT OF *p*H UPON DEVELOPMENT RATE

Iso-ascorbic acid, 0.005 M; KBr, 0.00067 M

*p*H	R	$1/t$	% A⁻
7.96	...	0.002	...
10.08	0.042	.025	3.5
10.25	.051	.036	5.1
10.35	.065	.041	6.3
10.55	.083	.056	9.6

Effect of Oxidation Products and Copper.—The oxidation products of iso-ascorbic acid were without any effect upon the rate of development, so far as could be detected. The addition of partially oxidized iso-ascorbic acid and the admission of small amounts of oxygen were without effect other than a minor one due to some alteration in the concentration of the developing agent. The addition of copper salts, which markedly catalyze the oxygen oxidation of ascorbic acid (at least in acid and neutral solutions), produced, if anything, a slight *decrease* in the development rate.

Temperature Coefficient.—At *p*H 10.15, the 10° temperature coefficient over the range 8–20° was about 2.55 for R rates, and 1.85 for $1/t$ rates. In the caustic solution, the coefficient

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was 1.90 for R, and 1.75 for $1/t$ over the same temperature range. In each case, the solution contained 0.333 M potassium nitrate and approximately 0.04 N potassium carbonate or potassium hydroxide.

Neutral Salt Effect.—A careful control of the salt environment proved to be essential to the kinetic investigation. The rate of development is markedly dependent upon the concentration of neutral salts. The magnitude of this effect is indicated by the results given in Tables IV and V.

The increase in the development rate was accompanied by some increase in the photographic emulsion speed. The nature of this increase, together with a more complete investigation of the salt effect, will be considered in a subsequent paper. Both have a bearing upon the general question of the effect of the electric charge upon the over-all kinetics of development.

TABLE IV

NEUTRAL SALT EFFECT

K_2CO_3, 0.033 M; iso-ascorbic acid, 0.005 M

Salt	Concn.	pH	R	$1/t$	KBr
..	..	10.33	0.0246	0.0125	0.00067
KNO_3	0.167	10.25	.052	.0345	
	.333	10.18	.073	.045	
	.667	10.12	.085	.067	
NaAc	.167	10.26	.047	.027	
Na_2SO_4	.0667	10.26	.0346	.023	
	.1333	10.22	.043	.029	
	.333	10.13	.051	.0345	
$Na_2C_2O_4$	.167	10.22	.046	.033	
$K_2C_2O_4$	.167	10.18	.062	.043	
K_2SO_4	.167	10.19	.063	.043	
K_2CO_3 + $KHCO_3$	.133 + .0067	10.33	.065	.040	
..	..	10.33	.0182	.0085	.00667
KNO_3	.1333	10.27	.036	.020	
	.333	10.18	.064	.031	
	.667	10.12	.072	.043	
	1.333	10.13	.090	.054	

TABLE V

NEUTRAL SALT EFFECT

Iso-ascorbic acid, 0.005 M; excess KOH, 0.04 M; KBr, 0.00667 M.

Salt	Concn.	R	$1/t$
..	....	0.050	0.040
KNO_3	0.1333	.086	.071
	.333	.166	.105
	.667	.186	.156
	1.333	.235	.217

Discussion

In the presence of a suitable amount of bromide ion, ascorbic and iso-ascorbic acids yield good image development with only slight fog formation. The acids show no unusual properties as developing agents. In general, they resemble hydroquinone. The one important point of difference is the lack of any measurable effect of the oxidation products upon the course of development.

At pH 8.0, where the ascorbic acid exists almost entirely as the univalent ion, development is feeble. In the more alkaline solutions, the bivalent ion is responsible for almost all of the developing activity. This is shown by the data in Table III. A plot of log R against log $A^=$, where $A^=$ is the percentage of bivalent ion calculated on the basis of a dissociation constant of 3×10^{-12}, yields a nearly straight line of slope 0.75. A similar plot of log R against log C for varying concentrations of the acid at pH 10.35 gives a straight line of slope 0.78. Thus, the rate is determined by the concentration of the bivalent ion. The fact that the dependence is less than linear suggests adsorption of the ion prior to reaction with the silver halide. Similar results were obtained previously with hydroquinone.[7]

The $1/t$ rates are nearly proportional to the ascorbic acid concentration, but show a somewhat smaller dependence upon the $A^=$ values for varying pH. It is possible that the rate of diffusion through the double-layer region of the silver bromide grain is already of importance in determining the measured rate during this initial stage of development. The lower temperature coefficient of the $1/t$ values in comparison with the R values supports this possibility.

Diffusion rates become important in the caustic solution. The rates of development are only about one-fourth as great as those expected on the basis of the rates at pH 10.35. Comparisons must be made, of course, at equal salt concentrations, but the necessary data are available in Tables IV and V. Moreover, R is nearly proportional to the ascorbic acid concentration in the caustic solution. This is in contrast to the situation in the lower pH region, and is not to be expected if reaction rates are the determining factor. The decrease in temperature dependence observed in passing from pH 10.3 to a caustic solution is in line with the preceding interpretation, although the temperature dependence in development is complex and theoretical interpretations based upon it at the present time are of doubtful value. Finally the fact that ascorbic and iso-ascorbic acids show nearly equal rates in the caustic solution, in contrast to the observations at lower pH, favors diffusion as an important rate-determining factor. An alternative interpretation, that the second dissociation constant of iso-ascorbic acid is larger than that of ascorbic acid, is not supported by published data.[8]

The data on the effect of neutral salts show how important this factor can be in determining the rate of development by ascorbic acid (and other doubly-charged negative ions). Increases in rate up to five- and sixfold were produced solely by added neutral salt. Trace catalysis

(7) T. H. James, *J. Phys. Chem.*, **44**, 42 (1940).

(8) *Cf.* G. E. Carpéni, *J. chim. phys.*, **35**, 193 (1938).

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produced by impurities in the salts is not involved in this effect. Samples of potassium nitrate obtained from three very different sources gave identical salt effects. Two samples of sodium sulfate, one impure, the other highly purified, gave results identical within the limit of experimental error.

The salt effect is caused by a depression of the double-layer zeta-potential of the silver bromide.[5] This permits a greater penetration of the bivalent ascorbic acid ions through the double-layer region to the surface of the grain, where the development reaction takes place.

Summary

The course of photographic development by *l*-ascorbic and *d*-iso-ascorbic acids is not affected by the oxidation products. The iso-ascorbic acid reacts at a somewhat greater rate than the ascorbic acid.

At *p*H 10 or above, the active developer consists almost entirely of the bivalent ion. This ion is adsorbed prior to reaction with the silver bromide. In caustic solution, diffusion rates become important in determining the measured development rate.

The rate of development is markedly dependent upon the nature and concentration of the salts present. The rate increases with increasing salt concentration.

ROCHESTER, N. Y. RECEIVED OCTOBER 4, 1943

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

The Molecular Structures of Dimethyl Silicon Dichloride, Methyl Silicon Trichloride and Trifluoro Silicon Chloride[1]

BY R. L. LIVINGSTON AND L. O. BROCKWAY

Previous study of the mutual interaction of groups attached to a central silicon atom left several unanswered questions. For example, the substitution of one or two hydrogen atoms into silicon tetrachloride has no detectable effect on the length of the Si–Cl bond,[2] but in silicon tetramethyl the replacement of one methyl group by a silicon atom (as in the molecule $(CH_3)_3SiSi(CH_3)_3$[3] apparently shortens the Si–C bonds by one and one-half per cent. An extension of the study of the interaction between atoms attached to silicon was made possible by the availability of samples of methyl silicon trichloride and dimethyl silicon dichloride. Another question of interest in silicon compounds is the interaction of attached fluorine atoms. In the organic fluorides the presence of two or more fluorine atoms on the same carbon shortens the C–F bond by 0.06Å. below the length observed in the monofluorides,[4] while the effect of the CF_3 group in CF_3Cl[5] on the attachment of the chlorine atom is equally marked in comparison with the bond lengths in carbon tetrachloride. This effect in the analogous silicon compound has now been studied. The methyl silicon chlorides were supplied by W. F. Gilliam of the General Electric Research Laboratories, and the trifluoro silicon chloride was supplied by H. S. Booth of Western Reserve University.

Electron diffraction photographs of the vapors were prepared in the usual way using an electron wave length of 0.0592Å. and a camera distance of 10.29 cm. The specimens were handled on a vacuum line and transferred to the camera without admitting air in order to reduce possible hydrolysis by water vapor. For each compound the s_0 values $(4\pi(\sin\theta/2)/\lambda)$ calculated from the visually measured ring diameters are tabulated together with the coefficients used in the radial distribution function, $D(r) = \Sigma C_k \sin s_k r/s_k r$. The radial distribution curves (Fig. 1) indicate by their stronger maxima the values of interatomic distances associated with the more important scattering terms.

Methyl Silicon Trichloride.—Photographs of methyl silicon trichloride taken with the sample held near 25° show nine rings in the range out to $s = 23$. The measurements on the last eight are listed in Table I. The fourth maximum appears as a satellite to the stronger third maximum; its measured position is accordingly unreliable. The sixth maximum is broad with a faint inner shelf which was not measured. The eighth minimum is broad without a well-defined lightest point.

Scattering curves were calculated for four models in each of which the Si–C bond was assumed to lie on an axis of trigonal symmetry, the methyl group was assumed to have the regular tetrahedral bond angles with C–H = 1.09 Å., and the Si–Cl distance was set at 2.00 Å. to fix the scale of the models. In three models the Si–C/Si–Cl ratio was 0.970 with the ∠ClSiCl equal to 113° (model A), to 109½° (model B) and to 106° (model D). In model C the bond distance ratio was 0.935 with a chlorine bond

(1) This paper represents part of a dissertation submitted to the Horace H. Rackham School of Graduate Studies by R. L. Livingston in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the University of Michigan.

(2) L. O. Brockway and I. E. Coop, *Trans. Faraday Soc.*, **34**, 1429 (1938).

(3) L. O. Brockway and N. R. Davidson, THIS JOURNAL, **63**, 3287 (1941).

(4) L. O. Brockway, *J. Phys. Chem.*, **41**, 747 (1937).

(5) L. O. Brockway and John H. Secrist, in publication.

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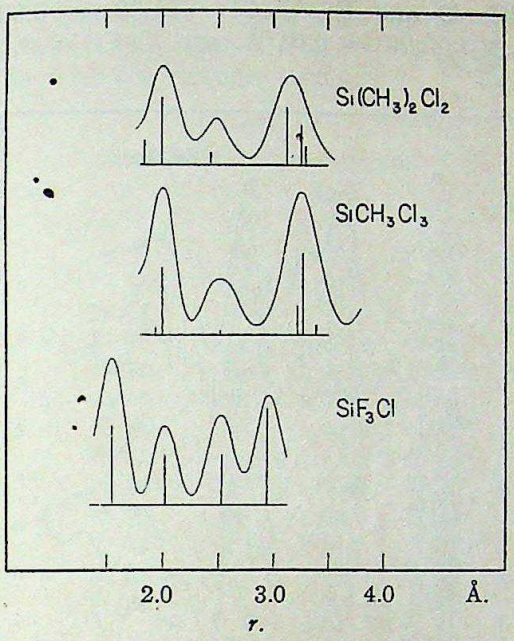

Fig. 1.—Radial distribution curves. The vertical lines show the relative scattering power associated with the interatomic distances in the final models.

angle of $109^1/_2°$. The coefficients of the Si–C and C–Cl terms were so small relative to those for the SiCl and Cl–Cl terms that the change from model B to C is scarcely detectable in the curves (Fig. 2). This means that the scattering power of the carbon atoms is so small in comparison with the silicon and three chlorine atoms that its position cannot be fixed by the diffraction data.

Curves B and C reproduce the characteristic features of the photographs: the weaker fourth ring, the sixth with the inner shelf, and the indefinite eighth minimum observed in the photographs falling on a very weak peak in both of the curves. The $3^1/_2°$ change in bond angle either up or down leads to curves which are somewhat less satisfactory. Curve A (113°) shows the fourth peak too strong, no inner shelf on the sixth and the seventh is followed by an equally prominent ring which does not appear on the photographs, curve D shows faults of the opposite sense at the same positions although its deviations from B are not as marked as those of A. Accordingly, we choose for the Cl–Si–Cl angle the value 109 ± 3°. The comparison of observed and calculated s values (Table I) leads to the value 3.27 ± 0.03 Å. for the Cl–Cl distance and to 2.01 ± 0.02 Å. for the Si–Cl distance. No definite value is given for the Si–C distance since the uncertainty in its direct determination would be greater than 0.1 Å. The values reported here are shown by vertical lines in the radial distribution figure together with a line marking the position of C–Cl if Si–C were 1.9 Å.

TABLE I

METHYL SILICON TRICHLORIDE

Max.	Min.	s_0	c_k	s_B/s_0	s_c/s_0
	2	3.33	− 1	(0.940)	(0.946)
2		4.30	17	(.972)	(.986)
	3	5.43	−13	.985	.981
3		6.44	17	1.002	1.002
	4	7.19	−12	1.013	1.017
4		(8.14)	15	(0.977)	(0.983)
	5	9.07	−34	0.994	1.011
5		10.07	25	1.005	1.012
	6	11.22	− 7	1.005	1.009
6		13.66	16	1.007	1.012
	7	14.83	−24	1.005	1.006
7		16.07	8	1.000	1.002
	8	(17.76)	− 7		
8		19.45	7	1.015	1.014
	9	21.00	− 6	0.994	0.995
9		(22.45)	5		
			Average	1.002	1.006
			Average deviation	0.007	0.008
			Cl–Cl, Å.	3.27	3.28
			Si–Cl, Å.	2.00	2.01

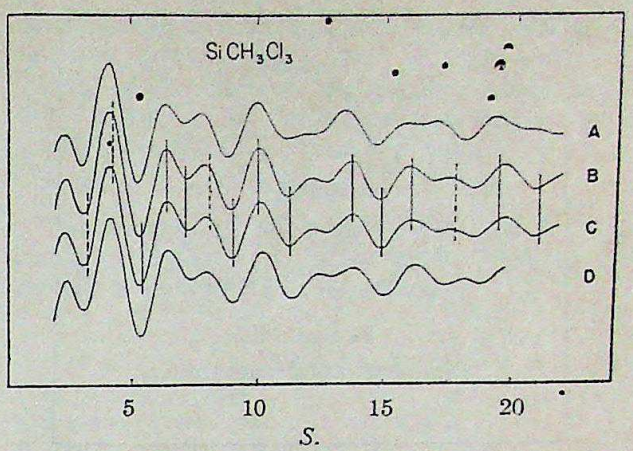

Fig. 2.—Theoretical electron scattering curves for $SiCH_3Cl_3$. The positions of the maxima and minima observed on the photographs are indicated.

Dimethyl Silicon Dichloride.—The dimethyl silicon dichloride was photographed at temperatures from 0 to 40°. Fifteen maxima and minima were measured out to $s = 19.3$ as listed in Table II. The less reliable s_0 values are enclosed in parentheses and shown on the curves (Fig. 3) by dotted lines. The radial distribution curve (Fig. 1) shows strong peaks at 1.98 Å. and 3.16 Å. The first is due to the bonded pairs, Si–Cl and Si–C, while the second is due mainly to C–Cl and Cl–Cl.

Scattering curves were calculated for the seven models in Table III, the Si–Cl distance being fixed at 2.00 Å. and the methyl group with the regular $109^1/_2°$ bond angle and C–H = 1.09 Å. in each. Of the five curves with $109^1/_2°$ angles on the Si atom only D and E show the right qualitative features. The fourth maximum is too strong in B and C and too weak in F; the inner shelf on the sixth is too small in B and C and does not appear at all in F. Model A

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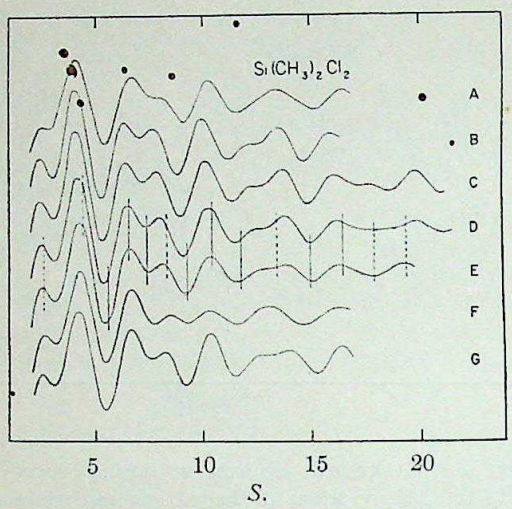

Fig. 3.—Theoretical scattering curves for $Si(CH_3)_2Cl_2$.

with a Cl–Si–Cl angle of 113° is also not good while Model G (∠Cl–Si–Cl = 106°) shows fair qualitative agreement. No systematic variation of the C–Si–C angle was attempted because of the small contributions of the Si–C and C–C terms. The quantitative comparison of observed and calculated s values given in Table II makes model G unsatisfactory because of the large average deviations from the mean value of the s/s_0 ratios. Definite values are reported for the three strongest terms on the basis of models D and E; Si–Cl = 1.99 ± 0.03 Å.; Cl–Cl = 3.25 ± 0.04 Å. and C–Cl = 3.12 ± 0.06 Å.

TABLE II

DIMETHYL SILICON DICHLORIDE

Max.	Min.	s_0	C_k	s_D/s_0	s_E/s_0	s_G/s_0
1		(2.56)	6	(0.977)		
	2	(3.37)	− 5	(.926)		
2		(4.40)	17	(.950)		
	3	5.58	−17	.970	0.975	0.984
3		6.53	19	1.003	1.008	1.025
	4	7.37	− 7	0.996	1.019	1.042
4		(8.29)	13	(.962)		
	5	9.25	−14	.984	0.995	0.997
5		10.40	20	.991	1.001	.999
	6	11.73	−20	.981	0.991	.983
6		(13.40)	15	(1.036)		
	7	14.95	− 9	1.008	1.013	1.023
7		16.43	4	0.992	0.992	1.002
	8	(17.87)	− 3			
8		(19.34)				
		Average		0.991	0.999	1.007
		Average deviation		0.009	0.011	0.017

TABLE III

MODELS FOR $Si(CH_3)_2Cl_2$

	Si–C	∠Cl–Si–Cl	∠C–Si–C
A	1.87Å	113°	105½°
B	2.04	109½	109½
C	1.94	109½	109½
D	1.87	109½	109½
E	1.80	109½	109½
F	1.67	109½	109½
G	1.87	106	112½

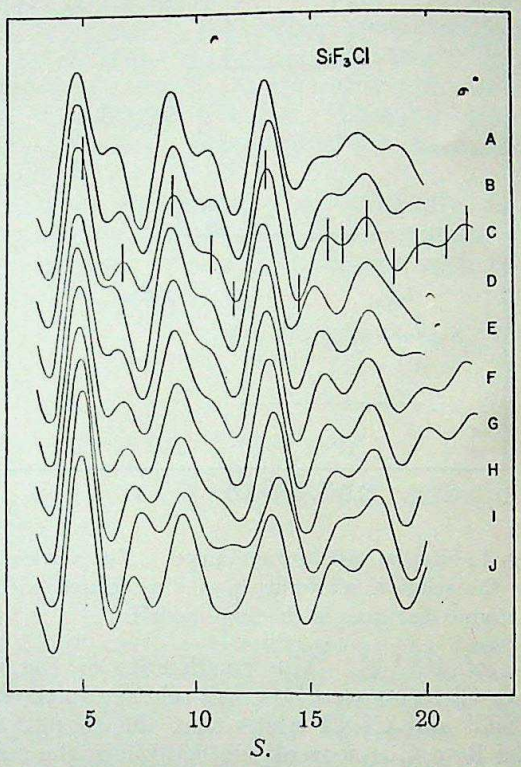

Fig. 4.—Theoretical scattering curves for SiF_3Cl.

The carbon atom positions are somewhat indefinite, although the relative importance of the carbon atom scattering is more favorable than in the trichloride. The carbon–chlorine term is nearly equal to the silicon–chlorine term, and the C–Cl distance reported above is reliable within the range given. The Si–C distance, however, can be calculated only if one of the bond angles involving carbon can be fixed. It may be supposed that since the Cl–Si–Cl angle has the regular tetrahedral value within 2 or 3° the bond angle between the two Si–C bonds will also not differ much from the regular value. With the assumption of 109½° for the angle C–Si–C, the Si–C distance becomes 1.83 Å. with an estimated uncertainty of ±0.06 Å., allowing some for a deviation of the angle from the assumed value.

Trifluoro Silicon Chloride.—Nine distinct rings appear in the photographs of trifluorosilicon chloride taken with the sample at temperatures from −115 to −85°. The distinctive features of the pattern are a faint shelf on the outer edge of the third and a very faint second maximum followed by successively stronger third and fourth peaks. The measured s_0 values are given in Table IV.

The radial distribution curve (Fig. 1) has two strong peaks at 1.55 and 2.95 Å. and two weak ones at 2.02 and 2.53 Å. These may be immediately recognized as associated with the distances Si–F, Cl–F, Si–Cl and F–F in the order

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given. The weaker terms are probably less reliable since they lack about 1% of being compatible with the stronger terms.

TABLE IV

TRIFLUOROSILICON CHLORIDE

Max.	Min.	s_0	C_k	s_c/s_0	s_F/s_0	s_G/s_0
1		5.06	45	0.958	0.961	0.966
2		6.86	8	1.001	.999	1.020
3		9.03	44	1.007	1.010	1.023
4		10.78	7			
	5	11.79	−77	1.005	0.995	1.003
5		13.12	75	1.007	1.002	1.013
	6	14.61	−68	0.996	0.995	1.004
6		15.88	30	.996	0.998	1.000
	7	16.51	−15	.999	1.000	1.007
7		17.56	28	.998	1.001	1.007
	8	18.70	−26	1.007	1.009	1.014
8		19.69	12	1.016	1.016	1.023
	9	20.92	− 5	0.984	0.981	1.002
9		21.80	5	.996	.998	1.012
			Average	.998	.997	1.007
			Average deviation	.009	.009	.009

TABLE V

MODELS FOR TRIFLUOROSILICON CHLORIDE

Model	∠F–Si–Cl	Si–Cl/Si–F
A	112°	1.350
B	112°	1.312
C	110½	1.312
D	109½	1.390
E	109½	1.350
F	109½	1.329
G	109½	1.312
H	109½	1.270
I	109½	1.230
J	106	1.312

Ten models were calculated having a trigonal axis through the Si–Cl bond and the bond angles and bond distances given in Table V. The Si–F distance was set at 1.54 Å. except in models C and F where it was 1.55 Å. None of the curves D to I (109½° models) is entirely satisfactory. In D the weak second maximum is not sufficiently resolved from the first and the shelf on the third is too weak. The other 109½° models in order get better in the first respect but worse in the second while the fifth and sixth peaks merge into one. Of these curves G is the best. A decrease in the F–Si–Cl angle to 106° (J) leads to a worse curve than any of the 109½° models. Three models (A, B and C) with larger angles were tried and of these model C (∠F–Si–Cl = 110½°) is entirely satisfactory. From the way in which changes in the two shape parameters affect the scattering curves it is possible to fix the F–Si–Cl angle at 110½ ± 1° and the Si–Cl/Si–F ratio at 1.31 ± 0.02. The s values for the best model C and for models F and G are compared with the s_0 values in Table IV. The average s/s_0 ratio for model C leads to the following values: Si–F = 1.55 ± 0.02 Å., Cl–F = 2.94 ± 0.03 Å., Si–Cl = 2.03 ± 0.03 Å., F–F = 2.50 ± 0.05 Å. These agree well with the corresponding radial distribution results, the largest discrepancy being a little more than 1% in the F–F term.

Discussion

The results on the three compounds are collected in Table VI together with distances observed in some related compounds.

TABLE VI

OBSERVED BOND DISTANCES

	Si–Cl	Si–C	Si–F
$Si(CH_3)_2Cl_2$	1.99 ± 0.03 Å.	1.83 ± 0.06 Å.	
$Si(CH_3)Cl_3$	2.01 ± 0.02		
SiF_3Cl	2.03 ± 0.03		1.55 ± 0.02 Å.
SiF_4[a]			1.54 ± 0.02
$SiCl_4$[a]	2.02 ± 0.02		
$Si(CH_3)_4$[b]		1.93 ± 0.03	
$Si_2(CH_3)_6$[c]		1.90 ± 0.02	
SiC (carborundum)[d]		1.90 ± 0.005	
Radius sum		1.94	
Radius sum with electronegativity correction[e]		1.88	

[a] L. O. Brockway and F. T. Wall, THIS JOURNAL, **56**, 2373 (1934). [b] L. O. Brockway and H. O. Jenkins, *ibid.*, **58**, 2036 (1936). [c] Ref. 2. [d] Ewald and Hermann, "Strukturbericht," 1931, p. 146. [e] V. Schomaker and D. P. Stevenson, THIS JOURNAL, **63**, 37 (1941).

The silicon–chlorine distances in the new compounds are not much different from the values previously observed. This result is especially interesting in the case of SiF_3Cl where the Si–Cl bond length is the same as in $SiCl_4$. In the corresponding carbon compounds the C–Cl bond length in CF_3Cl is 0.05Å. or 3% shorter than in CCl_4.[5] This effect of the substitution of three fluorine atoms on the attachment of the remaining chlorine is apparently specific to the carbon compound since it does not occur in the silicon compound. The stabilizing effect of CF_3 groups on organic molecules is therefore not to be expected in analogous silicon compounds. The Si–F distance is the same in SiF_3Cl as in SiF_4.

The dimethyl silicon dichloride has the smallest Si–Cl distance yet observed but the uncertainty in the determination (0.03 Å.) is as large as the decrease below the most common value (2.02 Å.). The Si–C bond length, however, is apparently much shorter than in other silicon–carbon compounds. The value reported depends on the assumption of a regular tetrahedral angle between the two Si–C bonds. If this indeterminate angle is 115 or 120°, the bond distance is fixed at 1.87 Å. or 1.90 Å., respectively. Since an angle as large as 120° seems improbable the bond distance is probably less than that in $Si_2(CH_3)_6$ and certainly less than that in $Si(CH_3)_4$. Accordingly it appears that when a methyl group in $Si(CH_3)_4$ is substituted by Cl or $Si(CH_3)_3$ the Si–C bond length decreases; when a second Cl is substituted a further decrease takes place.

It is noted in the table that the covalent

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radius sum for Si and C is 1.94 Å., or 1.88 Å. if an empirical correction is made for the electronegativity difference; but neither of these values can be correlated with the several Si–C distances observed. If the repulsion between Cl and CH_3 both attached to a silicon atom were less than between two methyl groups, the decrease in the Si–C length when two chlorines are substituted in $Si(CH_3)_4$ could be accounted for. In that case, however, an increase in the Si–Cl distance and a decrease in the Cl–Si–Cl angle would be expected in $Si(CH_3)_2Cl_2$ as compared with $SiCl_4$; this is not observed.

Summary

Electron diffraction measurements have been made on the vapors of dimethyl silicon dichloride, methyl silicon trichloride and trifluoro silicon chloride with the results shown in Table VI.

The observed Si–C distance is shorter than in $Si(CH_3)_4$, while the Si–Cl distances are not much different from the values observed in other silicon chlorides. The SiF_3 group in SiF_3Cl does not bind the chlorine more tightly than in $SiCl_4$ in contrast to the effect observed in CF_3Cl compared with CCl_4.

ANN ARBOR, MICHIGAN RECEIVED OCTOBER 11, 1943

[CONTRIBUTION FOR THE CONTINENTAL CARBON COMPANY]

Hysteresis and the Capillary Theory of Adsorption of Vapors[1]

BY LEONARD H. COHAN

Introduction

The Zsigmondy capillary theory[1a–6] was one of the earliest of the theories[7–13] which have been proposed to explain the adsorption of vapors on solids. It will be the purpose of this paper to reëxamine, in the light of recent experiments, how satisfactory an explanation this theory offers.

The Zsigmondy capillary theory is based on the Kelvin equation

$$P = P_0 e^{-2\sigma V\cos\theta/r_c RT} \qquad (1)$$

which relates r_c, the radius of a capillary, to P, the pressure of a vapor in equilibrium with liquid condensed in the capillary. P_0 is the normal saturation vapor pressure of the liquid at the temperature T; σ and V are, respectively, the surface tension and molal volume of the liquid; and θ is the angle of contact between the surface of the liquid and the walls of the capillary. If the liquid wets the walls of the capillary completely, $\theta = 0°$ and $\cos\theta$ is one and drops out of the equation.

Due to the presence of capillary pores of varying radii, a solid can hold a condensed liquid at vapor pressures below the normal condensation pressure. The distribution of pore sizes in the solid will determine the amount of liquid held at any vapor pressure, *i. e.*, it will determine the adsorption isotherm. Objections to this theory are, first, the difficulty of explaining adsorption results at low relative pressures which in some cases[14] require r_c to be smaller than the diameter of the adsorbed molecule; and, second, the scarcity of quantitative predictions which could be tested experimentally.

Some investigators have reasoned that the first objection is not critical because σ and V of equation (1) might be much larger for liquids in small capillaries than for the same liquids in bulk. If this were the case P/P_0 might reach very low values even in capillaries where r_c is much larger than molecular dimensions. Shereshefsky[15] determined the rate of evaporation from capillaries only 2 μ in radius. From the rate of evaporation, $\Delta P = P - P_0$ was calculated and found to be about eight times that predicted by equation (1). On this basis, there would be but little difficulty in ascribing adsorption at low relative pressures to condensation in capillaries. However, the usefulness of equation (1) as an aid in determining the structure of sorbents would largely disappear since σ and V would have to be known as a function of r_c before pore radius distribution could be calculated from adsorption isotherms.

More recently, Cohan and Meyer[16] determined σ and V in capillaries 2 μ in radius and found no deviation from normal values for the liquids used by Shereshefsky. In view of these results, Shereshefsky's experiments cannot be considered a serious limitation to the usefulness of equation

(1) Original manuscript received September 18, 1941.

(1a) Lord Kelvin, *Proc. Roy. Soc., Edinburgh*, **7**, 63–68 (1870).

(2) R. Zsigmondy, *Z. anorg. Chem.*, **71**, 356–377 (1911).

(3) W. Bachmann, *ibid.*, **73**, 125–172 (1912).

(4) R. Zsigmondy, W. Bachmann and E. F. Stevenson, *ibid.*, **75**, 189–197 (1912).

(5) J. S. Anderson, *Z. physik. Chem.*, **88**, 191–288 (1914).

(6) W. A. Patrick and J. McGavack, THIS JOURNAL, **42**, 946–978 (1920).

(7) A. Eucken, *Verhandl. deut. physik. Ges.*, **13**, 345–352 (1914).

(8) M. Polanyi, *Z. Elektrochem.*, **26**, 370–377 (1920).

(9) I. Langmuir, THIS JOURNAL, **38**, 2221–2295 (1916); **40**, 1361–1403 (1918).

(10) J. H. DeBoer and C. Zwicker, *Z. physik. Chem.*, **B3**, 407–418 (1929).

(11) R. S. Bradley, *J. Chem. Soc.*, 1467–1474 (1936); 1799–1804 (1936).

(12) S. Brunauer, P. H. Emmett and E. Teller, THIS JOURNAL, **60**, 309–319 (1938).

(13) S. Brunauer, L. S. Deming, W. E. Deming and E. Teller, *ibid.*, **62**, 1723–1732 (1940).

(14) A. G. Foster, *Trans. Faraday Soc.*, **28**, 645–657 (1932), also ref. 10, p. 1800, and ref. 6, p. 973.

(15) J. L. Shereshefsky, THIS JOURNAL, **50**, 2966–2985 (1928).

(16) L. H. Cohan and G. E. Meyer, *ibid.*, **62**, 2715–2716 (1940).

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(1) in the study of sorbent structure; neither, on the other hand, can they help to eliminate our first objection to the Zsigmondy capillary theory. One must conclude that the capillary theory can only be applied to vapor adsorption provided we consider that an adsorbed layer is formed on the surface of the sorbent before capillary condensation begins.

Evidence will be presented in this paper to show that a great many experimental results can be explained if we assume that the mechanism of adsorption on a porous solid consists in the formation of a monomolecular layer followed by capillary condensation. In the following, this mechanism will be referred to simply as the capillary theory. While such a model is too simple to be more than a first approximation, a considerable amount of experimental data can be correlated. It will also be shown in a subsequent paper that fairly accurate surface area values can be determined on the basis of this hypothesis.

The above mechanism is free from the first objection to the Zsigmondy capillary theory at least in so far as the necessity for considering pores smaller than molecular dimensions is concerned. There may still be some difficulty in visualizing the application of the concepts on which equation (1) is based, such as surface tension and angle of wetting to capillaries of a few molecular diameters in radius. Nevertheless, the results reported in this paper indicate that a relation of the same form as equation (1) in which σ and V are approximately equal to the normal surface tension and molar volume and $\cos \Theta = 1$, appears to hold for capillaries whose radius is only twice the diameter of the sorbate molecule.

Turning now to the second objection, the only prediction that has been made on the basis of the Zsigmondy capillary theory is that at relative pressures equivalent to equal values of r_c as calculated from equation (1), the volume of liquid adsorbed should be constant for all sorbates and should be independent of the temperature. In some systems, this has been found to be the case, but discrepancies have occurred.[5,6,14,19] In fact, considering the capillary theory mechanism given above, the volumes need be strictly constant only if monomolecular adsorption is negligible compared to capillary condensation. Other predictions are, however, possible on the basis of the capillary theory. As will be shown below, these predictions are in good agreement with experimental data.

In the light of the foregoing discussion, reconsideration of the capillary theory certainly appears in order. This is all the more true since the capillary theory is the only adsorption theory which at present can offer an explanation for sorption hysteresis in rigid gels. The importance of such an explanation has been greatly increased by recent work[17,18] which demonstrate that hysteresis is a reproducible phenomenon and is not, as thought by previous workers,[13,20,21] merely due to the presence of gases in the apparatus or to failure to obtain true equilibrium.

Theories of Hysteresis

Three explanations, all based on the capillary theory of adsorption, have been advanced to explain hysteresis in rigid sorbents.[22]

1 **Incomplete Wetting Theory.**[2,6]—Hysteresis is due to θ of equation (1) being greater during adsorption than during desorption probably due to the presence of permanent gases. In favor of this theory is the fact that in some systems[23-26] it has been found possible to eliminate hysteresis by the painstaking removal of permanent gases. However, the sharply reproducible results of Rao and Higuti can hardly be explained in this way.[27]

2. **Bottle Neck Theory.**[28,29]—For a pore having a narrow neck of radius, r_n, and a wider body of radius, r_b, adsorption occurs in accordance with equation (1) with $r_c = r_b$. Once the pore is filled, provided no break in the liquid column occurs, desorption cannot take place until the pressure falls to the value corresponding to equation (1) with $r_c = r_n$ and, therefore, hysteresis occurs.

(17) K. S. Rao, *J. Phys. Chem.*, **45**, 500–538 (1941).

(18) I. Higuti, *Bull. Inst. Phys. Chem. Research* (Tokyo), **18**, 657–684 (1939); **19**, 951–975 (1940); **20**, 130–136 (1941).

(19) B. Gustaver, *Kolloidchem. Beihefte*, **15**, 185–338 (1922).

(20) J. R. Katz, *Proc. Acad. Sci. Amsterdam*, **26**, 548–560 (1923).

(21) A. S. Coolidge, THIS JOURNAL, **46**, 596–627 (1924), p. 600; also ref. 6, p. 961–977.

(22) The theories of W. W. Barkas, *Trans. Faraday Soc.*, **38**, 194–209 (1942); R. S. Bradley, *J. Chem. Soc.*, 1798–1804 (1936), p. 1801; A. R. Urquhart, *J. Textile Inst.*, **20**, 125–32T (1929); A. E. Benton and T. S. White, *ibid.*, **53**, 2807–2808 and 3301–3314 (1931); G. H. Piper, *Trans. Faraday Soc.*, **29**, 538–543 (1933); C. O. Seborg and A. J. Stamm, *Ind. Eng. Chem.*, **23**, 1271–1275 (1931); and M. Gordon, I. Lavine and L. C. Harrington, *ibid.*, **24**, 928–932 (1932), would apply only to non-rigid systems. The theory of B. Von Il'in, *Z. physik. Chem.*, **A155**, 403–416 (1931), is a mathematical statement of the observed facts for a given isotherm and not a mechanism on the basis of which general predictions can be made. The hypothesis of H. Engelhard and W. Stiller, *Z. Elektrochem.*, **40**, 833–836 (1934), does not apply to a system which has reached equilibrium. The explanation proposed by A. G. Foster, *Proc. Roy. Soc. Edinburgh*, **A146**, 129–140 (1934), and also by A. R. Urquhart and A. M. Williams, *J. Textile Inst.*, **15**, 433–42T (1924), p. 440, is a qualitative statement similar to the quantitative deductions of the third theory discussed in the text.

(23) S. J. Gregg, *J. Chem. Soc.*, 1494–1512 (1927).

(24) W. A. Patrick and J. McGavack, ref. 6, p. 961–967.

(25) R. Fricke and H. Marquhardt, *Kolloid-Z.*, **60**, 124–129 (1932).

(26) H. A. Hamm and W. A. Patrick, *Textile Research*, **6**, 401–409 (1936).

(27) The bulk of the evidence in the literature indicates that in systems containing permanent gases hysteresis extends over the entire isotherm while hysteresis observed in the absence of permanent gases extends only over a limited portion of the isotherm. Thus there appears to be at least two phenomena involved; namely, unlimited hysteresis which can be in part explained by this theory and limited hysteresis which cannot. It is only the latter type (see Fig. 3) in which we are interested in this paper.

(28) E. O. Kraemer, "A Treatise on Physical Chemistry," edited by H. S. Taylor, D. Van Nostrand Co., New York, N. Y., 1931, Chap. XX, p. 1661.

(29) J. W. McBain, THIS JOURNAL, **57**, 699–700 (1935).

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3. Open Pore Theory.—In the case of a pore open at both ends, liquid cannot condense at the equilibrium vapor pressure given by equation (1) because a meniscus cannot form. As previously shown,[30] the pressure, P_a, at which the meniscus forms depends on the radius of curvature, r, of the cylindrical film on the wall of the capillary, that is

$$P_a = P_0 e^{-\sigma V/rRT} = P_0 e^{-\sigma V/(r_c - D)RT} \qquad (2)$$

where r_c is the radius of the pore and D the thickness of the adsorbed film which according to the capillary theory would be monomolecular; *i. e.*, D would be the height of a sorbate molecule in a direction perpendicular to the surface.[31]

Once condensation has occurred a meniscus is present and the pressure, P_d, at which evaporation occurs is given by equation (1).[32] Assuming that wetting is complete, $\cos\theta = 1$ and

$$P_d = P_0 e^{-2\sigma V/r_c RT} \qquad (3)$$

Some objection has been offered to the open pore theory because the theory as originally stated applied only to pores open at both ends, a type of structure which would not be expected to occur very commonly.[33] In this connection it is important to point out that the above considerations also apply to closed capillaries possessing constrictions. Such constrictions could be of the hour-glass type or merely the upper portion of a cavity. For example, in the cavity depicted in Fig. 1 a meniscus cannot form in the upper portion of the cavity until the lower of the two pressures $P_{a_1} = P_0 e^{-2\sigma V/r_v RT}$ or $P_{a_2} = P_0 e^{-\sigma V/(r_s - D)RT}$ is reached. P_{a_1} corresponds of course to the pressure at which the meniscus finally reaches the widest part of the cavity at r_v and P_{a_2} corresponds to the pressure in equilibrium with the cylindrical film at the smallest radius, r_s, of the upper half of the cavity. Thus P_a equals the lower of P_{a_1} or P_{a_2} and P_d is given by equation (3). For P_{a_1} equal to or less than P_{a_2} hysteresis will only occur in accordance with the bottle neck theory. However, for P_{a_2} less than P_{a_1} hysteresis will occur in accordance with the open pore theory.

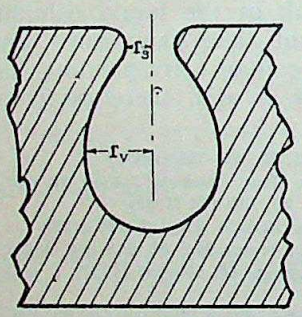

Fig. 1.

Based on the open pore theory, and, hence, on the capillary theory, two important predictions can be made. The first concerns the point on the isotherm at which hysteresis begins, and the second, the relation between adsorption and desorption pressures obtained on scanning the hysteresis loop.

Point of Hysteresis Inception

Considering equations (2) and (3), it is seen that for $r_c > 2D$, P_a is greater than P_d and hysteresis results but that for $r_c = 2D$

$$P_a = P_d = P_0 e^{-\sigma V/(r_c - D)RT} \qquad (4)$$

and no hysteresis occurs.[34] Thus if sufficiently small open or constricted capillaries are present the pressure, P_h, at which hysteresis begins should correspond to the equilibrium pressure for $r_c = 2D$. From equation (4)

$$P_h = P_0 e^{-\sigma V/DRT} \qquad (5)$$

or

$$D = \frac{-\sigma M}{dRT \ln P_h/P_0} \qquad (6)$$

where M is the molecular weight of the sorbate and d the density.

In Table I the values of D calculated by means of equation (6) from experimentally determined values for P_h are compared with D_{cubic} calculated for the sorbate in question from the expression $(M/Nd)^{1/3}$ and $D_{\text{spherical}}$ calculated from the molecular weight and density of the sorbate assuming spherical molecules and hexagonal close packing in the normal liquid. Except where otherwise indicated, room temperature was used. All available experimental evidence applying to hysteresis of the limited type in rigid sorbents has been included. However, it is felt that the greatest weight should be attached to the results of Higuti as in this series of experiments the point of hysteresis inception was specifically investigated for a great many sorbates on the same sorbent.

The author's value for P_h for water on silica gel was obtained at 28 ± 0.2°. The isotherm

(30) L. H. Cohan, *ibid.*, **60**, 433–435 (1938).

(31) In reference 30, it was assumed that D was negligible compared to r_c and therefore $r_c = r$. For the purposes of the present work, this assumption is not justified.

(32) Since an adsorbed layer of thickness D forms prior to capillary condensation and is more stable than the condensed liquid there is some argument for assuming that the curvature of the meniscus is independent of this adsorbed layer and therefore $r_c - D$ should be substituted for r_c in equation (1). If this assumption is made hysteresis would occur whenever capillary condensation in open pores occurs and the limited nature of hysteresis would then have to be explained by the fact that surface adsorption or capillary adsorption in wedge shaped pores is entirely responsible for adsorption below the hysteresis region. This in itself is perfectly plausible; however, the equation that would arise in place of equation (7) below is not in as good agreement with experimental results. Furthermore, as will be shown in a later paper, surface area values determined on the basis of this theory would not be in as good agreement with other methods. For these reasons, we will assume for the present that the curvature of the meniscus is not independent of the adsorbed layer and that equation (1) applies.

(33) P. H. Emmett and Thomas W. DeWitt, THIS JOURNAL, **64**, 1253–1262 (1942).

(34) If $r_c < 2D$ adsorption and desorption occur at the same pressure regardless of whether the sorbate is held by surface adsorption or capillary condensation. If capillary condensation is assumed to take place in pores of this size adsorption would occur at P_a' given by equation (4). Likewise desorption must also occur at this same pressure since a comparison of equation (3) with equation (4) shows that the pressure calculated by means of equation (3) is actually higher than P_a. That is, the vapor pressure of the cylindrical film is less than for the spherical meniscus and equation (3) cannot apply to capillary condensation in this case.

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for this system appears in Fig. 2. The reversible hysteresis region is bounded by the desorption and resorption curves (heavy lines).[35] Although insufficient points were taken in the region of hysteresis inception, the true inception point cannot be far from that indicated in the figure.

TABLE I

Sorbent	Sorbate	D cubic, Å.	D spherical, Å.	D, Å., calcd. from Eq. 6	Investigator
TiO_2 gel	C_6H_6	5.3	5.9	6.1	Higuti[18]
TiO_2 gel	C_6H_5Cl	5.5	6.2	5.8	Higuti[18]
TiO_2 gel	$C_6H_5CH_3$	5.6	6.3	5.9	Higuti[18]
TiO_2 gel	CH_3OH	4.1	4.6	6.2	Higuti[18]
TiO_2 gel	C_2H_5OH	4.6	5.2	6.2	Higuti[11]
TiO_2 gel	n-C_3H_7OH	5.0	5.6	6.2	Higuti[11]
TiO_2 gel	i-C_3H_7OH	5.0	5.6	6.3	Higuti[18]
TiO_2 gel	n-C_6H_{14}	6.0	6.8	7.1	Higuti[18]
TiO_2 gel	n-C_7H_{16}	6.2	7.0	7.2	Higuti[18]
TiO_2 gel	$CH_3COOC_2H_5$	5.4	6.1	6.6	Higuti[18]
TiO_2 gel	CCl_4	5.4	6.1	6.3	Higuti[18]
TiO_2 gel	$CHCl_3$	5.1	5.8	6.3	Higuti[18]
TiO_2 gel	CH_2Cl_2	4.7	5.3	5.2	Higuti[18]
TiO_2 gel	$(C_2H_5)_2O$	5.5	6.2	6.8	Higuti[18]
TiO_2 gel	CS_2	4.6	5.2	5.6	Higuti[18]
TiO_2 gel	H_2O	3.1	3.5	4.4	Higuti[18]
TiO_2 gel	NH_3	3.2	3.6	4.3	Higuti[18]
TiO_2 gel	SO_2	3.8	4.3	5.9	Higuti[18]
SiO_2 gel	H_2O	3.1	3.5	4.3	Cohan
SiO_2 gel B	C_2H_5OH	4.6	5.2	6.6	Foster[36]
SiO_2 gel B	CH_3OH	4.1	4.6	7.6	Foster[36]
SiO_2 gel B	n-C_3H_7OH	5.0	5.6	6.1	Foster[37]
SiO_2 gel B	i-C_3H_7OH	5.0	5.6	7.0	Foster[37]
SiO_2 gel B	n-C_4H_9OH	5.3	6.0	7.8	Foster[37]
SiO_2 gel	H_2O	3.1	3.5	6.1	Anderson[5]
SiO_2 gel 7	C_2H_5OH	4.6	5.2	6.1	Anderson[5]
SiO_2 gel 7	C_6H_6	5.3	5.9	6.8	Anderson[5]
SiO_2 gel 6	C_2H_5OH	4.6	5.2	8.0	Anderson[5]
SiO_2 gel	H_2O	3.1	3.5	4.8	Van Bemmeln[38]
Fe_2O_3 gel	CH_3OH	4.1	4.6	8.1	Foster[39]
Fe_2O_3 gel	n-C_3H_7OH	5.0	5.6	8.9	Foster[39]
Fe_2O_3 gel	n-C_4H_9OH	5.3	6.0	8.6	Foster[39]
Fe_2O_3 gel	C_6H_6 (40°)	5.3	6.0	6.1	Lambert and Clark[40]
Fe_2O_3 gel	C_6H_6 (50°)	5.3	6.0	6.2	
Fe_2O_3 gel	C_6H_6 (60°)	5.4	6.1	7.6	
Fe_2O_3 gel	C_6H_6 (40–60°)	5.3	6.0	6.5	Foster[14]
Fe_2O_3 gel	C_2H_5OH (60–70°)	4.7	5.3	7.5	Foster[14]
Fe_2O_3 gel A	C_2H_5OH (60°)	4.7	5.2	7.0	Lambert and Foster[41]
Fe_2O_3 gel A	C_6H_6 (60°)	5.4	6.1	7.6	
Fe_2O_3 gel A	C_6H_6 (50°)	5.3	6.0	7.5	
Fe_2O_3 gel A	C_6H_6 (40°)	5.3	6.0	6.8	
Fe_2O_3 gel B	C_2H_5OH (60°)	4.7	5.3	16.1	
Fe_2O_3 gel B	C_6H_6 (60°)	5.4	6.1	16.3	
Fe_2O_3 gel B	C_6H_6 (50°)	5.3	6.0	17.0	
Fe_2O_3 gel B	C_6H_6 (40°)	5.3	6.0	14.6	
Charcoal A[42]	H_2O	3.1	3.5	4.2	Burrage[43]
Charcoal, birchwood air activated	CH_3OH	4.1	4.6	2.5	Burrage[44]
Charcoal, birchwood air activated	CCl_4	5.4	6.1	4.0	Burrage[44]

(35) The initial adsorption curve illustrates an unlimited and irreversible type of hysteresis possibly due to imperfect rigidity in the gel structure. This latter type of hysteresis is a different phenomena from that under discussion here.

(36) A. G. Foster, *Proc. Roy. Soc.* (London), **A146**, 129–140 (1934).

(37) *Ibid.*, **A150**, 77–83 (1935).

(38) Van Bemmeln, *Z. anorg. allgem. Chem.*, **13**, 233–356 (1897).

(39) A. G. Foster, *Proc. Roy. Soc.* (London), **A147**, 128–140 (1934).

(40) B. Lambert and A. M. Clark, *ibid.*, **A123**, 497–512 (1929).

(41) B. Lambert and A. G. Foster, *ibid.*, **A136**, 363–377 (1932).

(42) P. G. T. Hand and D. O. Shiels, *J. Phys. Chem.*, **32**, 441–455 (1928).

(43) L. J. Burrage, *Trans. Faraday Soc.*, **29**, 665–678 (1933). These and the following results on charcoal are presented with reservations as the adsorption mechanism on charcoal may be due to monolayer adsorption and the hysteresis caused by lack of rigidity or interference of foreign materials such as carbon oxides.

(44) *Ibid.*, **30**, 317–325 (1934).

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TABLE I (*Concluded*)

Sorbent	Sorbate	D_{cubic}, Å.	$D_{spherical}$, Å.	D, Å., calcd. from Eq. 6	Investigator
Charcoal, birchwood air activated	CS_2	4.6	5.2	4.0	Burrage[44]
Charcoal Nl	CH_3OH	4.1	4.6	2.5	Burrage[44]
Charcoal, $ZnCl_2$ activated	C_2H_5OH	4.6	5.2	3.0	Burrage[44]
Charcoal, almond shell[45]	C_3H_7OH	5.0	5.6	4.0	Burrage[44]
Charcoal, almond shell	HCOOH	4.0	4.5	4.0	Burrage[44]
Charcoal	H_2O	3.1	3.5	4.5	Gustaver[19]
TiO_2 gel	H_2O	3.1	3.5	6.8	Rao[17]
TiO_2 gel	H_2O	3.1	3.5	5.4	Rao[17]
SiO_2 gel	H_2O	3.1	3.5	4.6	Rao[17]
SiO_2 gel	CCl_4	5.4	6.1	5.8	Rao[17]
Fe_2O_3 gel	H_2O	3.1	3.5	6.8	Rao[17]
Fe_2O_3 gel	CCl_4	5.4	6.1	6.4	Rao[17]
SiO_2 gel	H_2O	3.1	3.5	3.9	Pidgeon[46]
SiO_2 gel (heated at 300°)	H_2O	3.1	3.5	3.9	Pidgeon[46]

In judging the agreement obtained in Table I between D calculated from equation (6) and D_{cubic} or $D_{spherical}$ calculated from the density of the liquid sorbate the following points must be considered:

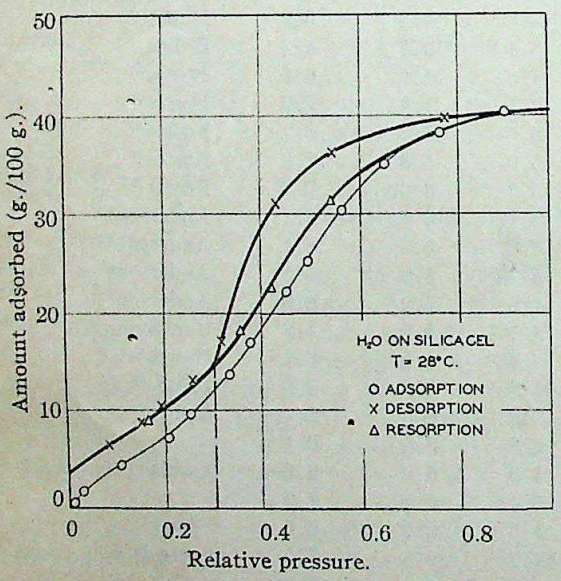

Fig. 2.

1. In order to apply the open pore theory to the determination of the point of hysteresis inception, open (or constricted) pores of radius just larger than 2D must be present in the sorbent. If pores in this region are absent, hysteresis cannot begin until pressures are reached corresponding to the open pores which are present. In such a case, the value of $D(= r_c/2)$ calculated from equation (6) would be larger than either D_{cubic} or $D_{spherical}$ and would be a measure not of the thickness of the adsorbed layer but of the radius, r_c, of the smallest open pores present. This may be the case for some of the Fe_2O_3 gels and particularly for Lambert and Foster's[40] Fe_2O_3 gel B which was prepared by heating gel A several hours at 148° in the presence of water vapor. On the other hand, the behavior of Higuti's TiO_2 gel with many different sorbates indicates that for this sorbent sufficiently small pores are present.

2. The capillary theory according to which adsorption consists of monolayer formation followed by capillary condensation is, as stated in the introduction, only a first approximation. Depending on the conditions—specific nature of the sorbent and sorbate, temperature, etc.—more or less than a monolayer could conceivably form prior to capillary condensation. For example, suppose that conditions are such that the multilayer adsorption mechanism yields a value P_3 for the equilibrium pressure for the essential completion of the third adsorbed molecular layer. Now if P_3 is less than P_d calculated from equation (3) with $r_c = 3D$ then generally speaking condensation will occur at P_3 instead of P_a, evaporation will also occur at P_3 instead of P_d and no hysteresis will be present at this pressure. In such cases, if one should try to calculate P_h from equation (5) the result would be lower than the observed value for P_h. Conversely if the observed value for P_h were used in equation (6) to calculate D, a higher value than the molecular diameter would be obtained. This is another possible explanation of the behavior of some of the Fe_2O_3 gels.

3. Equation (6) assumes that wetting is complete ($\theta = 0$) and that true equilibrium is attained. Any impurity, such as permanent gases in the apparatus, which would prevent the realization of these conditions would exclude the system as a suitable one for testing the theory. For this reason, isotherms determined in the presence of permanent gases are not included in Table I. As pointed out previously, such isotherms usually show an unlimited hysteresis which is not completely reversible. The low results for charcoal may be due to the presence of gases which could not be removed by ordinary evacuation.

4. For sorbents which cannot be considered

(45) *Ibid.*, **29**, 564–576 (1933).
(46) L. M. Pidgeon, *Can. J. Research*, **10**, 713–729 (1934).

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rigid, both the surface area and pore volume are different on adsorption than on desorption and hysteresis cannot be explained on the open pore theory alone. Hysteresis in such a system is likely to be unlimited and will be further complicated by drift if the swelling is not entirely reversible. Because of these difficulties systems which swell markedly such as wood and cotton cellulose have not been included.

5. Finally, exact agreement between D and D_{cubic} or $D_{\text{spherical}}$ should not be expected for unsymmetrical molecules. For molecules oriented perpendicularly to the surface, D should be greater than D_{cubic} or $D_{\text{spherical}}$. Examination of the table shows that molecules such as CH_3OH which might be expected to orient perpendicular to an oxide surface do have higher values for D than indicated by D_{cubic} or $D_{\text{spherical}}$.[47]

Examination of Table I reveals that except for the few cases pointed out in the preceding discussion, equation (6) is in good agreement with the experimental results and in particularly good agreement with Higuti's series of measurements on TiO_2 gel.

Additional support for equation (6) is found in the effect of temperature on the point of hysteresis inception. As long as temperature changes are not so great that the way in which the molecule is attached to the surface is altered, D should not vary with the temperature to a greater extent than does the density. Higuti has determined P_h for most of the systems reported in Table II from 0 to 30°. Although P_h/P_0 varies in this range by 25% or more for some of the sorbates, D, in most cases, varies by less than 5%, which may be considered within experimental error.

Scanning the Hysteresis Loop

"Scanning" the hysteresis loop is the name given by Rao[17] to the experimental process in which desorption is begun from an adsorption equilibrium point below saturation such as point (1), Fig. 3. The system follows the path labeled "b" in Fig. 3 and meets the desorption branch of the isotherm at some point (2) above the point of hysteresis inception.[48]

Considering a sorbent system consisting of a continuous range of open cylindrical pores and also a range of conical pores, the equilibrium pressure, P_a/P_0, at the point (1) will correspond to a capillary radius, r_c given by equation (2).

(47) It is worth noting that higher alcohols such as C_2H_5OH and C_3H_7OH have values for D closer to D spherical than does CH_3OH. Possibly chain bending may result in the former molecules occupying a less unsymmetrical volume element. It so happens as will be shown in another paper that the values for the area of Higuti's TiO_2 gel calculated from the data for the 18 different sorbates in Table I are remarkably consistent if one uses the asymmetry factor indicated by the value of D for the different sorbates. Consistency is not nearly so good if the sorbates are assumed symmetrical.

(48) On adsorbing from a desorption equilibrium point, a similar scanning curve, "a" in Fig. 3, is obtained. Rao found that for the sorbents he used scanning curves of this type did not rejoin the adsorption curve until saturation was reached.

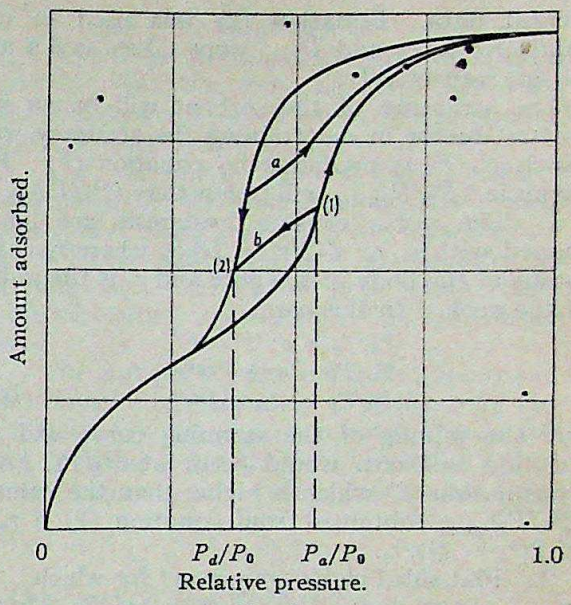

Fig. 3.

In this case, r_c is the radius of the largest open capillary to have filled at point (1). As the pressure is reduced, desorption occurs at once from the conical pores but not from the open pore of radius r_c until the pressure, P_d/P_0, given by equation (3) is reached.[49] At this point, the system will be in the same condition in which it would have been had desorption occurred from saturation. In other words, P_d/P_0 is the pressure at point (2) where curve "b" meets the desorption branch of the isotherm. From equations (2) and (3) the relation between P_d/P_0 and P_a/P_0 is[50]

$$P_d/P_0 = (P_a/P_0)^{2(r_c-D)r_c} \qquad (7)$$

In Table II values for P_d/P_0 calculated from equation (7) are compared with available experi-

TABLE II

Sorbent	Sorbate	$(P_a/P_0)_{exp.}$	$(P_d/P_0)_{exp.}$	$(P_d/P_0)_{calcd.}$	Investigator
TiO_2 gel	H_2O	0.88	0.78	0.79	Rao[17]
TiO_2 gel	H_2O	.86	.75	.76	Rao[17]
TiO_2 gel	H_2O	.82	.73	.71	Rao[17]
TiO_2 gel	H_2O	.79	.71	.67	Rao[17]
SiO_2 gel	H_2O	.60	.38	.49	Rao[17]
SiO_2 gel	H_2O	.53	.36	.44	Rao[17]
SiO_2 gel	H_2O	.47	.35	.40	Rao[17]
SiO_2 gel	CCl_4	.32	.25	.26	Rao[17]
Fe_2O_3 gel	CCl_4	.57	.43	.43	Rao[17]
Fe_2O_3 gel	CCl_4	.49	.40	.37	Rao[17]
SiO_2 gel	H_2O	.55	.42	.44	Van Bemmeln[38]
SiO_2 gel	H_2O	.53	.39	.43	Van Bemmeln[38]

(49) Sorbate held reversibly in mono or polylayers would also begin to desorb as soon as the pressure is reduced. For an adsorption equation including both polylayer adsorption and capillary condensation see A. A. Schuchowitzki, *Kolloid-Z.*, 66, 139–147 (1934). A small amount of sorbate would also be lost from open capillaries due to a change in curvature of the meniscus.

(50) In a previous paper[30] the relation $P_a^2 = P_0P_d$ was given for D negligible compared to r_c. In this case equation (7) reduces to the simple form.

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mental data. Equation (2) was used to calculate r_c; D_{H_2O} and D_{CCl_4} were taken as 4.4 and 6.3 Å., respectively.

The structure of the sorbent will be an important factor in determining the accuracy with which P_d/P_0 is predicted by equation (7). For example, $(P_d/P_0)_{calcd.}$ will be less than $(P_d/P_0)_{exp.}$ if:

1. The pores causing hysteresis are bottle shaped with $r_b/r_n < 2(r_c - D)/r_c$ where r_b is the radius of the body of the pore and r_n is the radius of the neck. In this case

$$P_n/P_0 = e^{-2\sigma V/r_b RT}$$
$$P_d/P_0 = e^{-2\sigma V/r_n RT}$$
$$P_d/P_0 = (P_n/P_0)^{r_b/r_n} \quad (8)$$

and the joining of the scanning curve and desorption isotherm would occur at P_d/P_0, given by equation (8) which is higher than the value—$(P_d/P_0)_{calcd.}$—obtained from equation (7) if $r_b/r_n < 2(r_c - D)/r_c$.

2. Flat sided clefts are present for which

$$W < r_v < 2(W - D) \text{ or approximately } W < r_v < 2W \quad (9)$$

where W is the distance between walls in the flat sided cleft and r_v is the largest radius in the cavity below the cleft, the cavity being assumed to have a circular cross section. For the flat sided cleft portion of the pore shown in Fig. 4

$$P_n/P_0 = e^{-2\sigma V/r_v RT} \quad (10)$$
$$P_d/P_0 = e^{-\sigma V/(W/2)RT} \quad (11)$$

whence

$$P_d/P_0 = (P_n/P_0)^{r_v/W} \quad (12)$$

Thus P_d/P_0 will be greater than $(P_d/P_0)_{calcd.}$ obtained from equation (7) when $r_v/W < 2(r_c - D)/r_c$. Comparing equations (2) and (10) an open cylindrical pore which will have the same P_n/P_0 as the cleft of Fig. 4 must have $r_c - D = r_v/2$. Substituting for r_c in terms of r_v the cleft will have a higher P_d/P_0 than $(P_d/P_0)_{calcd.}$ when

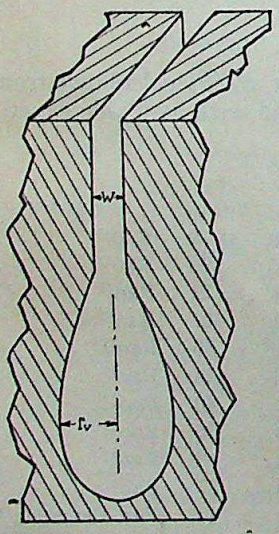

Fig. 4.

$$r_v/W < r_v/(r_v/2 + D) \quad (13)$$

or

$$r_v < 2(W - D) \quad (14)$$

from which equation (9) follows since for $r_v \gtrless W$ the cleft does not contribute to hysteresis.

In the above instances almost all the pores present must be of type (1) or (2) since even a small fraction of open cylindrical pores would prevent the scanning curve from actually joining the desorption branch until $(P_d/P_0)_{calcd.}$ is reached. A glance at Table II shows that in the few cases in which $(P_d/P_0)_{calcd.}$ differs from $(P_d/P_0)_{exp.}$ by more than experimental error, $(P_d/P_0)_{calcd.}$ is greater, not less than $(P_d/P_0)_{exp.}$[51]

On the other hand $(P_d/P_0)_{calcd.}$ will be greater than $(P_d/P_0)_{exp.}$ if:

3. Bottle shaped pores having $r_b/r_n > 2(r_c - D)/r_c$ are present.

4. Clefts are present for which

$$r_v > 2(W - D) \text{ or approximately } r_v > 2W \quad (15)$$

where W and r_v have their previous meaning. Equation (15) can be derived in the same manner as equation (9) by replacing the less than signs by greater than signs.

For pores of type (3) and (4), P_d/P_0 as given by equations (8) and (12), respectively, is lower than $(P_d/P_0)_{calcd.}$ from equation (7). Thus the scanning curve will join the desorption branch below the point corresponding to $(P_d/P_0)_{calcd.}$. Moreover the presence of only a small fraction of either of these pore types even in a system of predominantly open or constricted pores will prevent joining at $(P_d/P_0)_{calcd.}$ thus causing $(P_d/P_0)_{exp.}$ to be less than $(P_d/P_0)_{calcd.}$.[52]

In assuming that bottle shaped pores of type (1) and (3) above affect the scanning curves it is assumed that the bottle neck theory of hysteresis is valid, *i. e.*, that during desorption the liquid column in a bottle shaped pore remains intact and equilibrium is not reached. This may be open to argument; however, the effect of clefts on the scanning curve is, of course, quite independent of the validity of the bottle neck theory.

The results in Table II provide a fairly good check on equation (7). The tendency for $(P_d/P_0)_{calcd.}$ to be larger than the experimental value for Rao's SiO_2 gel may indicate presence of some clefts of type (4) even down to fairly small pore sizes. Additional data with other systems would be desirable. The preceding discussion also indicates how scanning curves may be used to throw light on the structure of the pores of a sorbent.

The evidence presented in support of equations (6) and (7) implies that: (1) The capillary theory is a satisfactory first approximation for most of the systems considered. (2) Both σ and V are about the same in capillaries as fine

(51) The experimental values in Table II had to be taken from published curves as tables of data were not available. The accuracy of determining P_n and P_d is probably not much better than several per cent. of the saturation pressure.

(52) Clefts for which $r_v >> W/2$ are not likely to affect type "b" curves (Fig. 3) because r_v is so large that adsorption cannot occur until close to saturation. However, such structures would markedly influence type "a" curves (Fig. 3) since they would remain filled until fairly low pressures and would prevent the coincidence of the "a" curves with the adsorption branch until close to saturation. The behavior of Rao's type "a" curves can be explained in this way. A. J. Allmand, P. G. T. Hand and J. E. Manning, *J. Phys. Chem.*, **33**, 1694–1712 (1929), pp. 1706–1708, report type "a" scanning curves for charcoal which rejoin the adsorption isotherm at pressures below the upper end of the hysteresis loop. Unfortunately, no data are given from which calculations can be made. It appears plausible that clefts and large cavities are more likely to be present in oxide gels such as used by Rao than in charcoal.

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as $r_c = 2D$ as they are in bulk. (3) The open pore theory appears to be in most cases a satisfactory explanation of hysteresis. However, departure of experimental values from predicted values in a few instances indicates that the presence of other factors must also be considered.

The author wishes to thank J. F. Mackey and M. Steinberg of the Continental Carbon Company staff for their assistance in the preparation of the tables and figures. The helpful criticisms of P. H. Emmett, Johns Hopkins University; S. Brunauer, U. S. Dept. of Agriculture (at present U. S. Navy); C. R. Johnson, Ridbo Corp.; and T. Brownyard, Portland Cement Association (at present U. S. Navy); who were kind enough to review a preliminary draft of this paper, are gratefully acknowledged.

Summary

1. Several predictions based on the capillary theory of adsorption and the open pore theory of hysteresis have been shown to agree reasonably well with experimental data.

2. The agreement between theory and experiments indicates that the capillary theory of adsorption which postulates the formation of a monomolecular layer followed by capillary condensation is a fairly good first approximation for the adsorption mechanism in the systems considered.

3. The surface tension and molal volume of a liquid confined in a capillary of radius only twice the diameter of the liquid molecule appear to be about the same as for the liquid in bulk.

CHICAGO, ILLINOIS RECEIVED OCTOBER 21, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, WAYNE UNIVERSITY]

Molecular Surface Energy of Sulfur Dioxide Addition Compounds. III[1]

BY JOSEPH J. JASPER AND J. RUSSELL BRIGHT[2]

The effect of temperature on the molecular surface energy of several liquid addition compounds of tertiary aliphatic amines with sulfur dioxide has been described in earlier articles.[3]

A more complete interpretation of the temperature effects described necessarily involves the extension of this series of studies to tertiary amine–sulfur dioxide addition compounds of still greater molecular weight. The purpose of this investigation, therefore, was to determine, for comparison with those preceding, the same physico-chemical constants for the respective equi-molecular mixtures of tripropylamine and tributylamine with sulfur dioxide.

Preparation of the Liquid Molecular Addition Compounds

The methods for purifying the materials were similar to those previously described.[3] Pure anhydrous sulfur dioxide was bubbled slowly through a known quantity of the best grade of Eastman Kodak Company tripropylamine ($n^{25}D$ 1.4151) until equi-molar quantities of the reactants were present. Since considerable heat was evolved during the reaction, the temperature was maintained at about 18° to prevent decomposition of the product. Upon further cooling, the product crystallized into light yellow needles, which melted at 15.3°. Distillation, even under reduced pressure, was impossible. The freshly prepared addition compound ($n^{25}D$ 1.4740) was analyzed for nitrogen by a modified Kjeldahl method; calculated for $(C_3H_7)_3N:SO_2$, N, 6.76. Found: N, 6.35, 6.46.

This compound is stable for an indefinite period as a light yellow solid at ice-box temperatures. It is very hygroscopic, changing to a red-brown liquid upon exposure to moist air. At temperatures above 45°, it changed to a black liquid whose density and surface tension deviated considerably from the linear relations given in a following paragraph.

Cryoscopic determination of the molecular weight, using purified benzene (f. p. 5.4°) as the solvent, gave 207.7, 208.4, 207.6 in 0.0327 weight molal solutions; theoretical 207.27. Increasing concentrations gave the molecular weights; 0.163 M, 2115.5; 0.327 M, 318.3; 0.411 M, 322.5. Similar association was observed by Bright and Fernelius[4] with the addition compound dimethylaniline–sulfur dioxide in the solvent dimethylaniline. Since the addition products are very hygroscopic, special precautions were used in their transfer to the various apparatus employed. Density and surface tension measurements were made, using the same apparatus and technique previously described.[3b] The viscosimeter used was constructed according to the design and specifications of Jones and Fornwalt.[5]

Experimental data are presented in Tables I and II. From these it is evident that the density d and surface tension γ are linear functions of the temperature for the compound tripropylamine-sulfur dioxide over the range 18 to 45°. These relations are given by the following equations

$$d = 1.0174 - 1.069 \times 10^{-3}t$$
$$\gamma = 32.72 - 0.125t$$

The average deviation of the data from the d-curve and γ-curve is, respectively, 0.02 and 0.08%. The Eötvös constant is −3.77 and, therefore, is less than the average value of −2.12, which is commonly assigned to non-polar liquids. This would seem to indicate considerable association, according to the criteria of Walden and Swinne.[6]

An observed value of 488.7 for the parachor of the $(C_3H_7)_3N:SO_2$ compound is in good agreement with the value of 503 obtained from the sum of

(1) Abstracted in part from material presented before the Symposium on Molecular Addition Compounds of the Division of Physical and Inorganic Chemistry at the Pittsburgh meeting of the American Chemical Society, September 6, 1943.

(2) Present address: Gelatin Products Co., Detroit, Michigan.

(3) Bright and Jasper, THIS JOURNAL, (a) 63, 3486 (1941); (b) 65, 1262 (1943).

(4) Bright and Fernelius, THIS JOURNAL, 65, 637 (1943).

(5) Jones and Fornwalt, *ibid.*, 60, 1683 (1938).

(6) Walden and Swinne, *Z. physik. Chem.*, 82, 271 (1913).

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TABLE I

DENSITY DATA FOR THE ADDITION COMPOUND $(C_3H_7)_3N:SO_2$

Temp., °C.[a]	Density, g./ml.
18.8	0.99710
22.1	.99369
23.8	.99158
24.9	.99065
27.3	.98818
30.5	.98465
33.5	.98139
36.0	.97869
40.0	.97406
45.0	.96919

[a] Precision of all temperature measurements reported in this paper is ±0.02°.

TABLE II

SURFACE TENSION AND PARACHOR DATA FOR $(C_3H_7)_3N:SO_2$

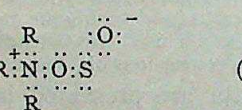
Temp., °C.	$(h + r/3)$, cm.	$(d_l - d_a)$	Surface[a] tension, dynes, cm.$^{-1}$	Parachor
17.0	3.257	0.9980	30.542	488.3
21.7	3.211	.9930	29.959	488.4
25.0	3.187	.9895	29.631	488.8
30.0	3.132	.9841	28.961	488.7
35.0	3.088	.9788	28.411	488.9
40.0	3.033	.9730	27.729	488.8
45.0	2.979	.9679	27.093	488.6

[a] Values for surface tension were calculated from the equation

$$\gamma = \frac{(h + r/3)(d_l - d_a)\, gr}{2}$$

where h is the capillary rise, r is the capillary radius, and d_l and d_a, respectively, are the densities of the liquid and air during the experiment.

the atomic and structural parachors[7] for the structure



$(R = C_3H_7)$

At room temperature the viscosity of this compound decreases approximately 3% for each degree rise in temperature. The temperature–viscosity relations are satisfactorily expressed by the following equation, from which the average deviation of the data is 1.6%

$$\log \eta = 1797.75T^{-1} - 4.96534$$

TABLE III

VISCOSITY DATA OF THE ADDITION COMPOUND $(C_3H_7)_3N:SO_2$

Temp., °C.	Viscosity, centipoises
19.1	15.16
25.0	11.78
30.0	9.50
38.0	6.57
44.0	4.98

(7) Sugden, "The Parachor and Valency," Alfred A. Knopf, New York, N. Y., 1930, p. 38.

Similarly, an equi-molar mixture was prepared from tributylamine and sulfur dioxide. The liquid was orange in color; a slight excess of sulfur dioxide changed it to deep red, while a correspondingly small additional quantity of tributylamine restored the orange color. The product was very viscous. It was found impossible to distil this equi-molar mixture, even at very low pressures, and attempts to crystallize it resulted in the formation of a glass. Efforts to crystallize it from benzene solution were likewise unsuccessful.

The following linear relationships exist for the temperature range 0 to 40° for the equi-molecular mixture of tributylamine and sulfur dioxide, *viz.*

$$d = 0.9915 - 9.562 \times 10^{-4}t$$
$$\gamma = 33.25 - 0.1317t$$

Average deviations from the data of the d-curve and γ-curve are, respectively, 0.03 and 0.11%. The Eötvös constant −4.24 is less than any of the preceding lower molecular weight addition compounds studied. The observed parachor, 602.8, agrees satisfactorily with the theoretical 620.

TABLE IV

DENSITY AND SURFACE TENSION DATA FOR THE EQUI-MOLECULAR MIXTURE $(C_4H_9)_3N$ AND SO_2

Temp., °C.	Density, g./ml.	Surface tension, dynes, cm.$^{-1}$
0	0.99084	33.232
5	.98659	32.647
10	.98205	31.914
15	.97745	31.299
20	.97293	30.592
25	.96792	29.947
30	.96247	29.246
35	.95803	....
40	.95308	28.032

Summary

The effect of temperature on the molecular surface energy of the addition compounds, $(C_3H_7)_3N:SO_2$, and the equi-molar mixture of $(C_4H_9)_3N$ and SO_2 has been determined. Data are presented for the density, surface tension and viscosity over the temperature range of 17 to 45° for the former and 0 to 40° for the latter.

The Eötvös constants were calculated and found to be less than any of the lower molecular weight addition compounds studied. Thus, the temperature coefficient of the molecular surface energy seems to decrease with increasing molecular weights of the addition compounds, and the tendency to associate increases.

Parachor data furnish additional evidence for the existence of a nitrogen to oxygen to sulfur (N–O–S) linkage in this type of compound.

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[CONTRIBUTION FROM THE HAYDEN LABORATORIES OF NORTHEASTERN UNIVERSITY]

The Conductance of Some Salts in Ethylenediamine[1]

BY WILLIAM H. BROMLEY, JR.,[2] AND W. F. LUDER

I. Introduction

In considering various solvents for use in an investigation of the ionization of metallic salts as acids according to the Lewis theory of acids and bases,[3,4] ethylenediamine seemed to offer interesting possibilities. However, due to the present emergency the work had to be abandoned after securing conductance measurements on three salts: silver nitrate, silver iodide and potassium iodide. The data obtained are presented herewith.

Ethylenediamine is a stronger base than ammonia, having a dissociation constant of 8.5×10^{-5} in water.[5] One would expect then that acidic metallic salts would be soluble in it. However, its high basicity makes it extremely difficult to work with because of its rapid absorption of carbon dioxide and water.

Some conductivity measurements have been made in ethylenediamine,[6] but at concentrations much too high to permit evaluation of Λ_0 or K. Apparently none of these have been made below 0.2 molar; our measurements go down to 1×10^{-4} molar or below.

Because of the reactivity of the ethylenediamine the solvent conductance becomes an appreciable factor in the conductance of solutions at such low concentrations. This introduces considerable uncertainty in the extrapolated values of Λ_0, as compared with the very precise results which may be obtained with such relatively inert solvents as ethylene chloride.[7] In such solvents it is possible to reduce the solvent conductance to a value entirely negligible in comparison with the conductance of the lowest concentration of solution measured. This is impractical in ethylenediamine. The best previously reported solvent conductance[6] is 1.4×10^{-6} mho. With the most drastic drying methods carried out in the absence of air in an all-glass sytem, we were only able to reduce this value to 9×10^{-8} mho.

This is not surprising since from the structure of ethylenediamine one would expect a rather high conductivity even if carbon dioxide and water could be completely removed. But such a value of solvent conductance means that its value may be as much as 5% of the total conductance of a solution at 1×10^{-4} molar. Since there is considerable uncertainty as to how the solvent correction should be made this will affect the reliability of Λ_0 values. In our data the solvent conductance was subtracted from the conductance of the solution at each concentration.

II. Apparatus, Materials and Method

The bridge[8,9] and procedure of conductance runs[7] have been described previously. The temperature of the oil thermostat was held at $25 \pm 0.01°$ by an electronic relay.

Salts.—C. P. potassium iodide was recrystallized from conductivity water. C. P. silver nitrate was dissolved in hot conductivity water and recrystallized by slowly adding freshly distilled ethyl alcohol. Silver iodide was prepared by mixing equivalent silver nitrate and potassium iodide solutions and washing the precipitate repeatedly with conductivity water. No further precautions were considered necessary because of the high solvent conductance.

Solvent.—95% ethylenediamine was stored over sodium hydroxide and barium oxide for several days, kept over sodium for a day, then fractionated off freshly activated alumina into a receiver containing alumina and sodium hydroxide. This receiver was provided with a ground glass cap carrying a tube through which the solvent could be discharged by dry nitrogen pressure. The solvent was kept from contact with moisture and carbon dioxide by a slow stream of dry nitrogen coming through a side arm and out the top of the receiver. About three-fourths of the ethylenediamine came over at constant temperature. This portion was used for runs.

The solvent thus obtained was placed in an all-glass system consisting of two stills, a solvent conductance cell, and a closed receiver. Each still was fitted with a fractionating column. The only opening to the atmosphere during the distillation was through a drying train consisting of phosphorus pentoxide, soda lime, and calcium chloride tubes and a concentrated sulfuric acid trap. This train was also used to dry nitrogen flowing through the system and out the filling tube of the first still while it was being loaded with solvent. The two successive distillations were carried out over alumina in an atmosphere of moisture and carbon dioxide-free nitrogen. The conductance was read from a sealed-in cell as the solvent was collected in the receiver from the second still. The best value was 9×10^{-8} mho. Solvent was forced into the cell[7] used in runs by nitrogen pressure while a slow stream of nitrogen emerged from the top of its long neck to prevent the entrance of air. The same procedure was followed when making dilutions. Solvent constants used were: d_{25} 0.891,[6] n_{25} 0.0154,[10] and D_{25} 12.9.[11]

III. Results

The experimental results are given in Tables I–III and are shown graphically in Fig. 1. It was hoped that potassium nitrate could also be measured to enable comparison of Λ_0 values, but it proved to be too insoluble. Λ_0 and K were calculated according to the method of

(1) Abstracted from a thesis submitted by William H. Bromley, Jr., to the faculty of Northeastern University in partial fulfillment of the requirements for the M. S. degree, April, 1943.

(2) Present address: Shawinigan Resins Corp., Springfield, Mass.

(3) G. N. Lewis, *J. Franklin Inst.*, **226**, 293 (1938).

(4) W. F. Luder, *Chem. Rev.*, **27**, 547 (1940).

(5) Britton and Williams, *J. Chem. Soc.*, 796 (1935).

(6) Putnam and Kobe, *Trans. Electrochem. Soc.*, **74**, (preprint), (1938).

(7) Mead, Fuoss and Kraus, *Trans. Faraday Soc.*, **32**, 594 (1936).

(8) W. F. Luder, THIS JOURNAL, **62**, 89 (1940).

(9) W. F. Luder, *Rev. Scientific Inst.*, **14**, 1 (1943).

(10) Dunstan, Hilditch, and Thole, *J. Chem. Soc.*, **103**, 133 (1913).

(11) Drs. J. L. Oncley and Paul Gross of the Harvard Medical School very kindly determined the dielectric constant at 25° using a sample of ethylenediamine prepared by us.

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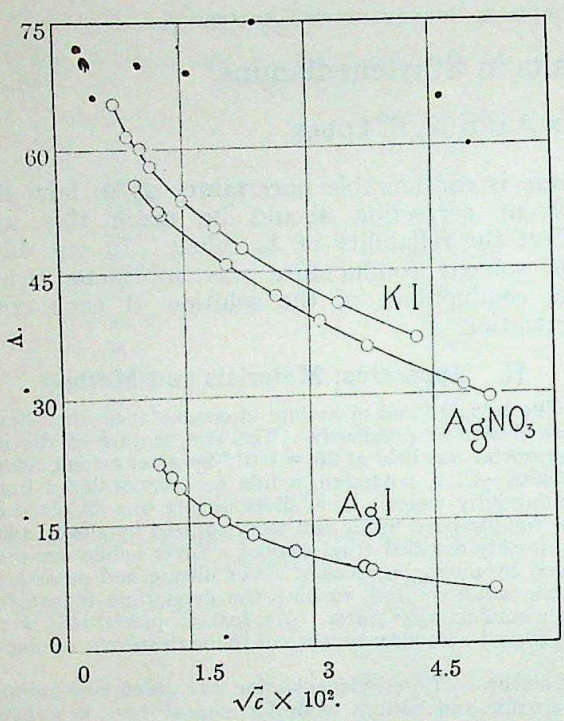

Fig. 1.

Fuoss.[12] The resulting extrapolations are shown in Fig. 2. The values obtained together with the "ion sizes" calculated from K[13] are given in Table IV. The accuracy of the measurements was probably about 0.1%, but, due to the uncertainty in the solvent conductance correction, values of Λ_0 may be off several per cent. However the values of K are apparently as good as most of those in the literature.

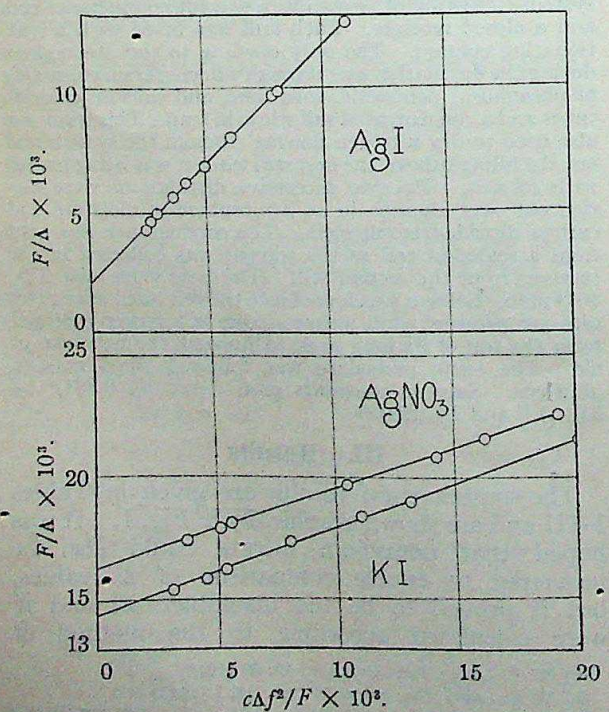

Fig. 2.

(12) R. M. Fuoss, THIS JOURNAL, 57, 488 (1935).
(13) Fuoss and Kraus, *ibid.*, 55, 1019 (1933).

TABLE I

POTASSIUM IODIDE IN ETHYLENEDIAMINE AT 25°

$C \times 10^3$	Λ	$C \times 10^3$	Λ
4.595	27.8	3.140	31.5
1.696	37.1	0.950	41.4
0.348	50.2	.453	48.1
.122	58.1	.216	53.9
.062	62.2	.099	60.1
.049	65.5		

TABLE II

SILVER NITRATE IN ETHYLENEDIAMINE AT 25°

$C \times 10^3$	Λ	$C \times 10^3$	Λ
3.340	29.7	2.378	32.1
1.351	36.1	0.980	38.8
0.736	40.8	.586	42.8
.363	46.1	.148	52.1
.147	52.6	.087	56.0

TABLE III

SILVER IODIDE IN ETHYLENEDIAMINE AT 25°

$C \times 10^3$	Λ	$C \times 10^3$	Λ
6.615	4.79	4.490	5.36
2.748	6.91	1.355	9.30
1.420	9.11	0.525	13.51
0.794	11.51	.287	16.91
.380	15.24	.194	19.36
.167	20.48	.140	21.95

TABLE IV

Salt	Λ_0	$K \times 10^4$	$a \times 10^8$
KI	69.2	6.02	5.34
$AgNO_3$	61.4	8.07	5.98
AgI	48.8	0.431	3.84[a]

[a] This value has no meaning since other than coulomb forces are involved.

The purpose of the investigation was to secure data relevant to the electronic theory of acids and bases.[3,4] In spite of the fact that only three salts were measured, due to the premature termination of the work, some interesting conclusions may be drawn. It is not surprising that the solubility of potassium nitrate is too low for conductance measurements. The potassium ion has very little tendency to associate with bases. Silver nitrate because of the acidic silver ion, and potassium iodide because of the acidic nature of the iodide ion (in expanding its valence shell to form coördinate bonds with bases) behave about as expected. "Normal" conductance behavior is observed in that greater ion size as indicated by lower Λ_0 is associated with a larger value of K (Table IV).

At first glance, the behavior of silver iodide seems rather surprising. The low Λ_0 value indicates larger ions as would be expected since both ions should be solvated rather than only one as in the case of potassium iodide and silver nitrate. But instead of a larger value of K it

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is actually only about one-fifteenth the values for the other two salts. The explanation doubtless lies in the fact that the model, upon which the expectation of a high K value accompanying low mobility is based, assumes only the presence of coulomb forces between the ions.[13] In the case of silver iodide there are additional forces present which make K less than predicted when coulomb forces alone are involved. These forces are of the acid–base type.[3,4] The amphoteric nature of the iodide ion is well known[14] and is here substantiated. The results for silver nitrate and potassium iodide indicate that both silver and iodide ions are acting as acids in their association with the highly basic solvent. But toward the acidic silver ion the iodide ion acts as a base, tending to donate a pair of electrons to give partial covalent character[15] to the bond between the two ions. The presence of these additional forces decreases K to a value far below that expected from the low value of Λ_0.

(14) R. B. Sandin, *Chem. Rev.*, **32**, 249 (1943).

IV. Summary

The conductances of three salts, potassium iodide, silver iodide, and silver nitrate in ethylenediamine have been measured, at concentrations low enough to permit calculation of Λ_0 and K. The best solvent that could be obtained had a conductance of 9×10^{-8} mho. An explanation based on the electronic theory of acids and bases is offered for the extraordinarily low value of K for silver iodide.

(15) L. Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939.

BOSTON, MASS. RECEIVED OCTOBER 8, 1943

[CONTRIBUTION FROM THE CENTRAL RESEARCH DEPARTMENT, MONSANTO CHEMICAL CO.]

Isomerization of Tri-alkyl Phosphites

BY GENNADY M. KOSOLAPOFF

The isomerization of tri-alkyl phosphites in the course of the reaction with alkyl halides, according to the scheme

$$(RO)_3P + R'X \longrightarrow (RO)_3PR'X \longrightarrow RX + R'P(O)(OR)_2 \quad (1)$$

was first studied rather extensively by Arbuzov,[1] who utilized this reaction as an elegant method of preparation of a number of phosphonic acid esters.

Usually the reaction is carried out by heating the reagents in a sealed tube, followed by distillation of the products. Under these conditions there are usually formed varying, and sometimes considerable, amounts of $RP(O)(OR)_2$, apparently formed through interaction of RX with either unreacted $(RO)_3P$ or the intermediate $(RO)_3PR'X$. It was felt that if the RX formed in the reaction were to be removed as rapidly as possible from the reaction mixture, not only should the course of the reaction be cleaner, but the measurement of RX evolved should offer a ready method for following the course of the reaction.

It was also felt that a technique employing the above principle could be utilized in obtaining additional information on the course of the reaction between tri-alkyl phosphites and paraffin dihalides. This reaction may be expected to follow both of the possible courses

$$2(RO)_3P + X(CH_2)_nX \longrightarrow \begin{matrix} RO \\ RO \\ RO \end{matrix}\!\!>\!P(CH_2)_nP\!<\!\begin{matrix} OR \\ OR \\ OR \end{matrix} \longrightarrow 2RX + (RO)_2P(O)(CH_2)_nP(O)(OR)_2 \quad (2)$$

(1) A. E. Arbuzov, "On the Structure of Phosphorous Acid," N. Alexandria, 1905.

and

$$(RO)_3P + X(CH_2)_nX \longrightarrow \begin{matrix} RO \\ RO \\ RO \\ X \end{matrix}\!\!>\!P(CH_2)_nX \longrightarrow RX + (RO)_2P(O)(CH_2)_nX \quad (3)$$

Actually, the literature data are rather meager as to information on the course of this reaction. Thus, Arbuzov and Kushkova[2] isolated from the reaction of methylene iodide and triethyl phosphite only the iodomethanephosphonic acid diethyl ester, *i. e.*, the product of reaction (3), among other substances. More recently, Parfent'ev and Shafiev[3] investigated the reaction of triethyl phosphite and trimethylene bromide, obtaining a product corresponding to the γ-bromopropanephosphonic acid diethyl ester, which could not be distilled without decomposition, and was apparently formed according to reaction (3). Nylen[4] studied the reaction between sodium diethylphosphite and methylene chloride, ethylene bromide and trimethylene bromide, obtaining $CH_2(PO(ONa)(OEt)_2)_2$, ethylene and tetraethyl trimethylenediphosphonate, respectively, as the identifiable reaction products.

From consideration of the available information it was evident that a further study of this reaction was desirable with variation of the proportions of the reactants as a means of influencing the predominance of either reaction (2) or (3).

(2) Arbuzov and Kushkova, *J. Gen. Chem.* (U. S. S. R.), **6**, 283 (1936).

(3) L. N. Parfent'ev and M. Kh. Shafiev, *Trudy Uzbesksk. Gos. Univ., Sbornik Rabot Khim.*, 87–94 (1939).

(4) P. Nylen, "Studien über organische Phosphorverbindungen," Upsala, 1930.

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Triethyl phosphite was selected as the alkyl phosphite, while *n*-butyl bromide and *n*-hexyl bromide were selected as the alkyl halides for the study of reaction (1), while ethylene bromide was taken for the study of reactions (2) and (3).

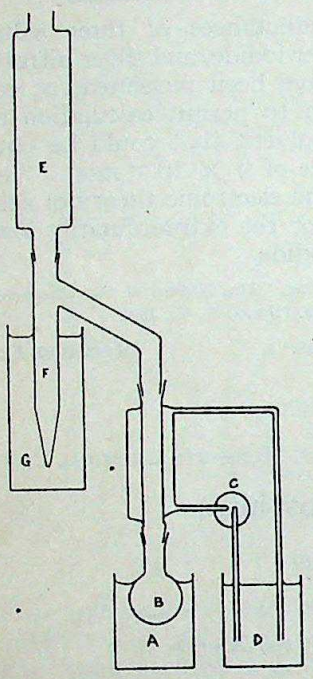

Fig. 1.—A, Oil-bath; B, reaction flask; C, circulating pump; D, heated water reservoir; E, reflux condenser; F, Stark–Dean trap; G, ice-water bath.

Experimental.—The reactants were heated, after mixing, in a small round-bottomed flask connected to an upright condenser, through the jacket of which water, heated to 50°, was circulated by a pump. The upper end of the condenser was connected to a Stark–Dean trap which was immersed in ice-water, while the exit from the trap was surmounted by an efficient spiral condenser. The reaction flask was heated by a thermostatically controlled oil-bath. The amount of ethyl bromide collected in the trap in the course of the reaction was read periodically. The apparatus is shown on Fig. 1.

***n*-Hexyl Bromide.**—Triethyl phosphite (16.6 g., 0.1 mole) and *n*-hexyl bromide (16.5 g., 0.1 mole) reacted at 133 and 150°. The results are shown in curves 1 and 2, respectively, of Fig. 2.

***n*-Butyl Bromide.**—Triethyl phosphite (16.6 g., 0.1 mole) and *n*-butyl bromide (13.7 g., 0.1 mole) reacted at 150°. The results are shown on curve 3, Fig. 2.

Ethylene Bromide.—Triethyl phosphite (16.6 g., 0.1 mole) reacted with the following amounts of ethylene bromide: 0.5 mole (94 g.), 0.2 mole (37.6 g.), 0.1 mole (18.8 g.) and 0.05 mole (9.4 g.) at 150°. The results are shown on curves 4, 5, 6 and 7, respectively, of Fig. 2. The reaction mixtures were subjected to vacuum distillation after completion of the runs. In the first three cases after distillation of excess ethylene bromide there was collected a very small amount of a liquid corresponding in boiling point to diethyl ethylphosphonate. Distillation from that point became impossible due to decomposition even at 1 mm. The last run, however, gave approximately 7 g. of diethyl ethylphosphonate, b. p. 50° at 1 mm., 194–198°.

Discussion of the Results.—In view of the fact that the over-all reaction in all of the cases studied must consist of at least two steps, *i. e.*, the formation of the intermediate addition compound, followed by thermal decomposition of the latter, it is not possible to calculate the reaction constants from our data. However, it is interesting to note the considerable effect of temperature upon both the induction period and the over-all reaction rate in case of *n*-hexyl bromide. The former is apparently the "accumulation" period of the phosphonium compound. The behavior of *n*-butyl bromide may be explained on a similar basis: while appreciable amounts of free butyl bromide exist in the mixture, the temperature of the latter is conditioned by the refluxing butyl bromide, while after the latter had combined substantially with the phosphite, the mixture attains bath temperature and the greater decomposition rate of the butyl phosphonium compound (in comparison with the hexyl compound) is evidenced by the generally steeper reaction curve.

In order to bring the reaction curve of the 0.05–0.1 molar mixture of ethylene bromide and triethyl phosphite to the same scale as that of the other three runs for more apparent visual comparison, the ordinates of curve 7 were multiplied by two and the resultant "hypothetical" curve is shown as curve 8, Fig. 2. It is evident that the suppression of di-substitution is sharply pronounced with greater excess of ethylene bromide. It is conceivable that the use of overwhelmingly large excess of the ethylene bromide may lead to almost complete suppression of di-

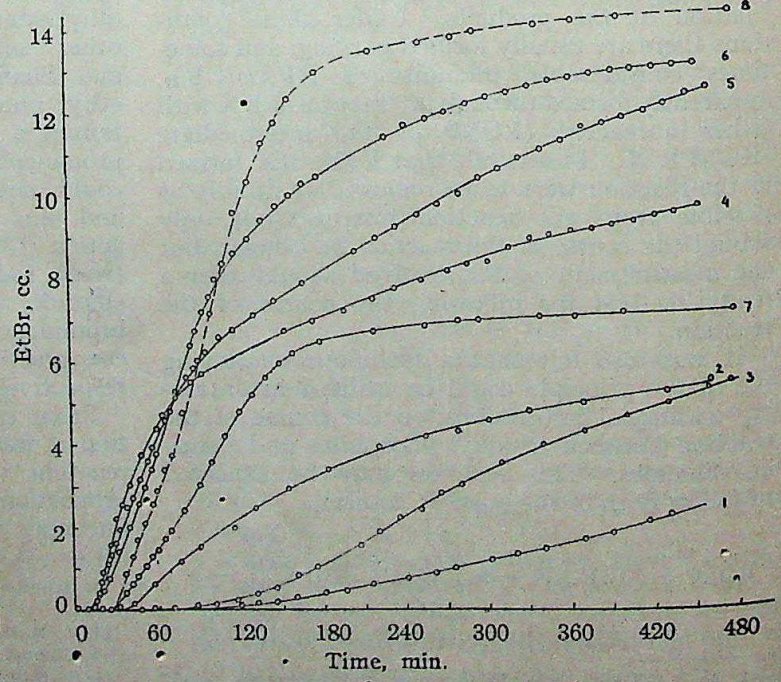

Fig. 2.

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substitution (excess of the order of 20–1 molar ratio). Such a mixture, however, was not practicable for our experimental set-up due to the relatively large bulk of such a reaction mixture. The results obtained from the 0.05–0.1 molar mixture show, apparently, a somewhat different reaction course from the other three runs. The amount of ethyl bromide collected corresponds very closely to the theoretical for complete disubstitution (*i. e.*, 7.25 cc.) according to reaction (2), while the distillation of the reaction mixture yielded approximately one-half of the triethyl phosphite used in the form of diethyl ethylphosphonate. It appears that the amount of the bromoethyl ester formed is very small, but due to its ready decomposition, on attempted distillation, and evolution of hydrogen bromide, the tetraethyl ester, which apparently forms by a normally expected reaction (2), suffers decomposition, either *per se* or influenced by the hydrogen bromide, with diethyl ethylphosphonate being one of the decomposition products. The mechanism of this decomposition is obscure and appears to require a form of disproportionation. The results with ethylene bromide are in general accord with the above cited work of Nylen, who was able to isolate only decomposition products. It is curious to note that the methane member of the series yields a halomethyl product of some stability, as well as the di-substitution product (in modified form), as shown by Arbuzov (see above) and Nylen (see above). It is now shown that the ethane derivative apparently undergoes the normal reaction course for reactions (2) and (3), with the attendant complication of poor stability of the bromoethyl compound (not unexpected, by analogy with β-haloethyl carboxylic acid derivatives), making it impossible to isolate pure reaction products.

Summary

The reaction between triethyl phosphite, on one hand, and *n*-butyl bromide, *n*-hexyl bromide and ethylene bromide, on the other hand, was studied by following the rate of evolution of ethyl bromide. The latter reaction apparently follows the normally expected mono- and di-substitution courses, controllable by proportion of the reactants.

DAYTON, OHIO RECEIVED AUGUST 12, 1943

[CONTRIBUTION FROM THE IOWA AGRICULTURAL EXPERIMENT STATION]

The Relation of Starch–Iodine Absorption Spectra to the Structure of Starch and Starch Components[1]

BY R. R. BALDWIN, R. S. BEAR[2] AND R. E. RUNDLE

The activity of iodine in solution in the presence of starch has been shown to be a function of the nature of the starch, *i. e.*, of the proportion of amylose (or unbranched) component, the chain length of the amylose and the length of the free (or unbranched) portions of the amylopectin component.[3] Changes in starch-iodine color have long been known to accompany starch fractionation and starch degradation. It is to be expected that a more quantitative study of the absorption spectra of solutions of starch and its components should yield information, perhaps more detailed than that provided by the potentiometric study, concerning the structure of starch and its components.

Simerl and Browning made a spectrophotometric study of the iodine complex of a number of starches, dextrins, and starch components,[4] and Lampitt, Fuller and Goldenberg examined the absorption spectra of the starch–iodine complexes given by starch ground in a ball mill.[5] Both examinations were handicapped by the lack, at that time, of adequate methods of fractionating starch and characterizing the resultant fractions. Recent fractionation procedures and a rapid method of analysis of starch fractions[3] have overcome many of the previous difficulties.

Apparatus and Procedure.—Absorption spectra of the various solutions have been examined by means of a Coleman Model 10S double monochromator spectrophotometer, with an accompanying vacuum tube electrometer (Coleman pH meter) serving as an intensity measuring device. A slit selecting a 15 millimicron band of light was used for all transmission data. The solution to be examined was placed in a square cuvette, 13 mm. thick, and compared with a control solution in a matched square cuvette. The control solution contained a concentration of iodine equal to that used in preparing the starch–iodine solution. This procedure overcorrects for the iodine not involved in the complex, but the error is slight because of the negligible absorption of the very dilute iodine solutions used. For highly absorbing solutions a glass prism with optically parallel sides was placed in the cuvette to reduce the solution thickness from 13 to 1.63 mm. The temperature in all cases was kept at 23.0 ± 0.5°.

The perfectly clear solutions required for spectrophotometric work are possible only for very dilute starch solu-

(1) Journal Paper No. J-1150 of the Iowa Agricultural Experiment Station, Ames, Iowa. Project 660. Supported in part by a grant from the Corn Industries Research Foundation. This paper is based on a thesis submitted by R. R. Baldwin to the Iowa State College.

(2) Present address, Department of Biology and Biological Engineering, Massachusetts Institute of Technology, Cambridge, Mass.

(3) F. Bates, D. French and R. Rundle, THIS JOURNAL, 65, 142 (1943).

(4) L. Simerl and B. Browning, *Ind. Eng. Chem., Anal. Ed.*, 11, 125 (1939).

(5) L. Lampitt, C. Fuller and N. Goldenberg, *J. Soc. Chem. Ind.*, 60, 99 (1941).

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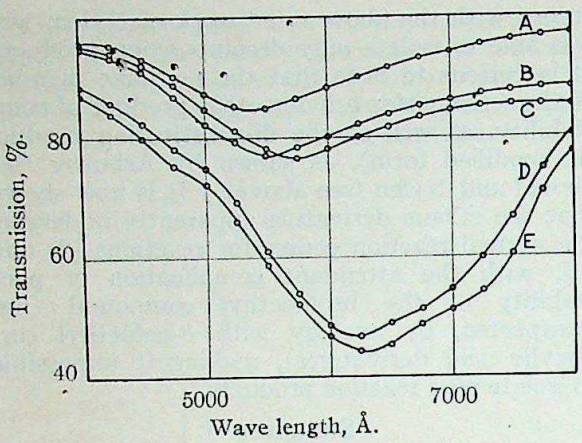

Fig. 1. Transmission curves of the iodine complex of amylose and amylopectin materials: A, waxy maize; B, potato amylopectin; C, corn amylopectin; D, corn amylose; E, potato amylose; cell depth, 1.63 mm.; iodine concn., 0.00005 *M*; starch concn., 0.01%.

tions. The starch or polysaccharide concentrations used in this investigation were generally 0.01%. In this concentration molecularly dispersed solutions can be approached, if not actually obtained, by the following procedures:

Pastes of native, granular starches were poured into boiling water, boiled for five minutes, and autoclaved for an hour at 18 lb. pressure. In strictly neutral solutions, degradation during this interval did not appear to be serious.

Amylose preparations are more difficult to disperse. A weighed amount of dried amylose was allowed to stand in dilute potassium hydroxide until a perfectly clear solution was obtained. It was found that 5 ml. of 0.5 *N* potassium hydroxide would readily disperse 50 mg. of amylose. The time required depended on the plant source of the amylose, but was generally less than an hour. The amylose solution was neutralized with aqueous hydriodic acid. If the solution was neutralized immediately before use retrogradation was not significant during the time required for the spectrophotometric observations.

Materials.—The whole starches used were generally milled in this Laboratory. The "crystalline amylose" was furnished by Kerr. Its preparation and properties have been described by Kerr and Severson,[6] and in papers from this Laboratory.[3,7] The term amylose is used to designate the unbranched component of starch. The amyloses discussed here were prepared by the fractionation procedure of Schoch.[8] Although this procedure proved the most successful of the methods tried for the separation of starch components, the amyloses thus prepared were generally contaminated by a small amount of amylopectin, or the branched component. Analyses of these fractions have been reported.[3] The amylopectins were likewise obtained by Schoch's fractionation, and the last traces of amylose were removed by cotton adsorption columns where necessary.

The amylodextrin used in this investigation was a Nageli dextrin[9] further fractionated by butanol–methanol precipitation, and is identical with the amylodextrin fraction examined by Foster and Hixon[10] and the fraction examined by Bates, French and Rundle.[3] It digests to 90% with β-amylose, retrogrades readily to give a crystalline diffraction diagram and in its change of viscosity with concentration it resembles the amyloses rather than the amylopectins.[10] All these properties indicate that it possesses unbranched chains. Its molecular weight is small, however, in the neighborhood of 44 glucose residues, or only about one-tenth as great as for the amyloses from whole starches.

Absorption Spectra of Amylose- and Amylopectin–Iodine Solutions.—The difference in ability of amylose and amylopectin to form complexes with iodine and the difference in color of the complexes[3] makes it necessary to regard starch as a complex substance in the study of iodine absorption spectra. These two components of starch were, therefore, studied separately. In Fig. 1 typical transmission curves of amylose and amylopectin are shown. The wave length of minimum transmission is greater for the amylose, and the % transmission under similar conditions is always far less. These factors make possible the colorimetric analysis of starch for amylose and amylopectin, and such an analysis has been described for potato starch.[11] It will be clear from what follows concerning specific amylose and amylopectin materials that such an analysis cannot be applied generally to starch without a preliminary investigation of the properties of the specific amylose and amylopectin making up the particular starch to be analyzed. This is, of course, a serious limitation on the method.

Outstanding is the difference in the behavior of amylose and amylopectin with different concentrations of iodine. In this respect the absorption curves are similar to the iodine titration curves, and are to be expected from that work.[3] In Fig. 2 are shown the spectrophotometric titrations characteristic of amylose and amylopectin materials. For both substances log *T* was chosen for the wave length of minimum transmission for that substance. The wave length of minimum transmission does not change materially with iodine concentration. The potentiometric titration of amylopectin with iodine indicates that not much of the iodine combines with the amylopec-

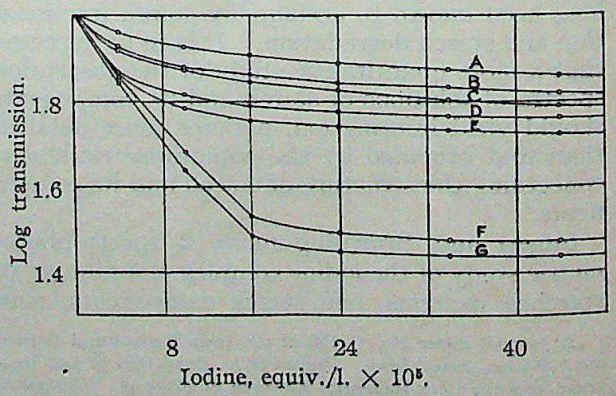

Fig. 2.—Spectrophotometric titration of various starchy materials: A, waxy maize; B, corn amylopectin; C, potato amylopectin; D, corn starch; E, potato starch; F, corn amylose; G, potato amylose; cell depth, 1.63 mm.; iodide concn., 0.005 *M*; starch concn., 0.01%.

(6) R. Kerr and G. Severson, THIS JOURNAL, **65**, 193 (1943).

(7) (a) R. Rundle and R. Baldwin, *ibid.*, **65**, 554 (1943); (b) R. Rundle and D. French, *ibid.*, **65**, 558 (1943); (c) R. Rundle and D. French, *ibid.*, **65**, 1707 (1943).

(8) T. Schoch, *ibid.*, **64**, 2957 (1942).

(9) C. Nageli, *Ann.*, **173**, 218 (1874).

(10) J. Foster and R. Hixon, THIS JOURNAL, **65**, 618 (1943).

(11) R. McCready and W. Hassid, *ibid.*, **65**, 1154 (1943).

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tin, and as indicated in Fig. 2, the transmission of the iodine solution is affected far less by the presence of amylopectin than by the presence of amylose. Both the potentiometric and spectrophotometric titrations indicate that a complex of a definite composition is formed between amylose and iodine. The spectrophotometric titration could be made the basis of an analysis of starch for amylose, but it appears to have no advantages over and is more laborious than the potentiometric titration. Apparently the spectrophotometric titration would not suffer from the limitations of the colorimetric analysis[11] if the end-point were determined by the break in the titration curve. Both the potentiometric and the spectrophotometric titrations indicate a discontinuous difference between amylose and amylopectin. Differences in degree of branching of amylose and amylopectin cannot then be continuous.

Iodine–Iodide Relationships in the Amylose–Iodine Complex.—In the potentiometric titration it was found that the % iodine in the amylose–iodine complex at the end-point decreased as the iodide concentration was increased.[3] This is confirmed by the spectrophotometric titration. In Fig. 3 are titration curves for "crystalline amylose" at various iodide concentrations. In Fig. 4 the number of glucose residues per iodine molecule is plotted against a function of the iodide concentration. It is seen that the curve extrapolates to approximately 6 glucose residues per iodine molecule in infinitely dilute iodide solutions.

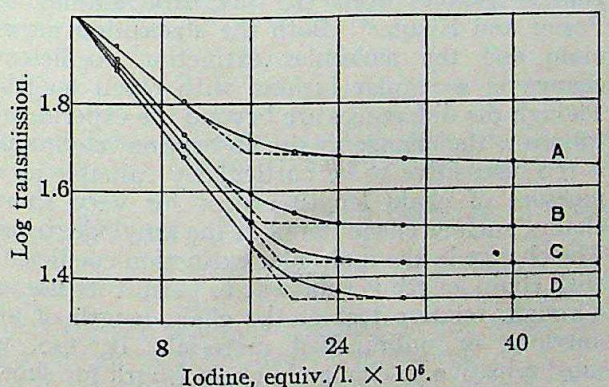

Fig. 3.—Spectrophotometric titration of crystalline amylose at various iodide concentrations: iodide concn. of A, 0.5 *M*; B, 0.05 *M*; C, 0.005 *M*; D, 0.001 *M*; cell depth, 1.63 mm.; amylose concn., 0.01%.

This value is, we feel, very significant. It has been found that the starch–iodine complex consists of helical starch chains with iodine molecules arranged along the helix axis.[7] The periodicity along the helix is probably 6 glucose residues. Apparently in the complex, free of iodide, one iodine molecule occupies one turn in the helix. It was found that dry amylose in the helical configuration takes up iodine vapor to the extent of one iodine molecule per 6 glucose residues.[7]

The reason for the decrease in iodine in the complex with increasing iodide concentration appears clear from the structure of the complex. With increasing iodide concentrations triiodide ions must enter the helix, probably accompanied by positive ions. A turn in the starch helix is 8 Å. long.[7] The space required for an iodine molecule is about 6.6 Å. along the helix, and the space required by a triiodide ion plus a positive ion must be considerably larger than 8 Å. For lack of space the amount of iodine in the helix must decrease as iodide enters. A more quantitative study based on the analysis of the complex for iodide is under way.

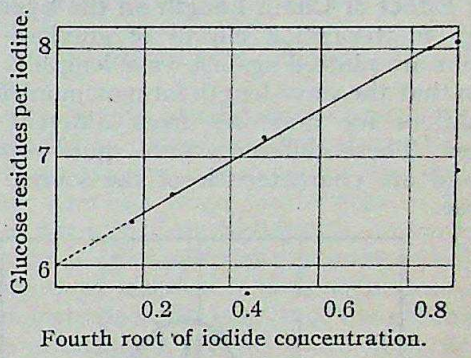

Fig. 4.—Glucose residues per iodine molecule at the end point of the spectrophotometric titration of "crystalline amylose" as a function of iodide concentration.

There is an interesting difference in the amount of iodine found to be bound in complex formation at the end-points of the spectrophotometric and potentiometric titrations (Table I). In all cases the spectrophotometric value is the higher. We believe that the difference can be explained in terms of the structure of the complex and the choice of the two end-points. The iodine activity of an amylose–iodine solution is fairly constant as long as the main body of the helices is being filled. From the ends of the helices, however, it would be expected that the iodine molecules could be removed more readily. An increase in the iodine activity then occurs before the last possible iodine molecules are put in the helices. The end-point of the potentiometric titration is taken at the first rapid increase in iodine activity and hence before complex formation is fully completed. In the spectrophotometric titration all iodine is counted as present in complex formation if it contributes to the increase in the absorption of the solution over that of an iodine–water solution.

TABLE I

GLUCOSE RESIDUES PER IODINE MOLECULE IN THE AMYLOSE–IODINE COMPLEX PRODUCED AT VARIOUS IODIDE CONCENTRATIONS AS DETERMINED BY SPECTROPHOTOMETRIC AND POTENTIOMETRIC METHODS

Iodide concn., moles/liter	Glucose residues per iodine molecule	
	Spectrophotometric	Potentiometric
0.5	8.0	9.9
.05	7.2	8.4
.005	6.7	7.8

Since amylopectin is quite different from amylose in its complex-forming ability with iodine, and

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since the % iodine in the complex varies with iodide concentration it is clear why previous attempts to determine a formula for the starch–iodine complex by using whole starch, or poorly fractionated starch, and various iodide concentrations have failed.[12]

In Fig. 3 it is seen that the transmission of amylose–iodine solutions increases with added iodide. This effect is probably due to a change in the nature of the complex; more triiodide and/or iodide ions enter the helices at higher iodide concentrations.

The Effect of Chain Length on the Spectra.—In Fig. 5 absorption curves of amylose–iodine solutions are plotted against wave length. It can be seen that the wave length for maximum absorption differs for amyloses from different plant sources. These differences are quite reproducible, and are characteristic of the source of the amylose.

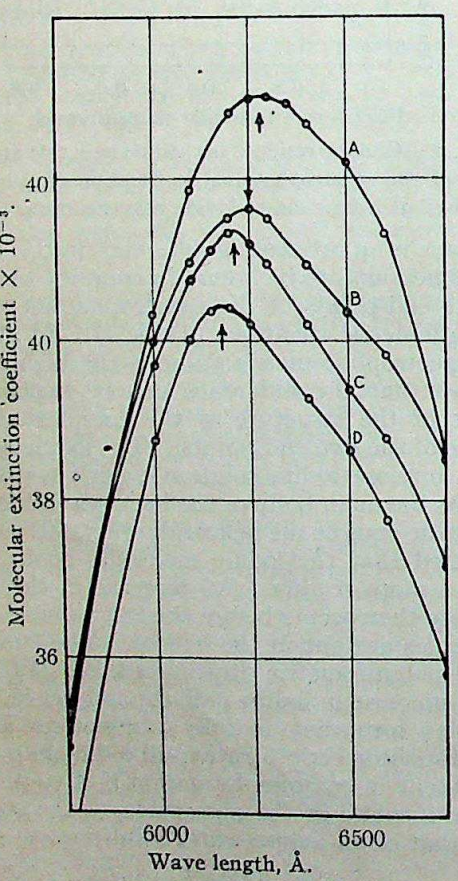

Fig. 5.—Molecular extinction curves of iodine in various amyloses: A, potato amylose; B, tapioca amylose; C, lily amylose; D, corn amylose; cell depth, 1.63 m.; iodine concn., 0.00005 *M*; amylose concn., 0.01%.

Even more variation is found in the molecular extinction coefficients of amylose–iodine solutions from different plant sources. For comparison purposes amylose must be kept in excess. The absorption is then a function of added iodine. In their spectrophotometric study of starch–iodine Lampitt, Fuller and Goldenberg found that an increased iodine concentration caused an increased value of the extinction coefficient.[5] If, however, the absorption is calculated as molecular extinction coefficient, the greater values are obtained with lower iodine concentrations. In Table II the molecular extinction coefficients are calculated for solutions 0.0001 *N* with respect to iodine and 0.01% with respect to starch.

It is to be noted that low iodine concentrations are particularly important in this comparison, for near the end-point of complex formation the molecular extinction coefficient is influenced profoundly by the per cent. amylopectin impurity which was never negligible in our work. At low iodine concentrations, however, the iodine first forms a complex with amylose, and the molecular extinction coefficient is nearly independent of the amylopectin impurity.

The amylose–iodine complexes listed have been found to differ in the activity of iodine in water solution of the complexes.[3] This difference was interpreted as due to the difference in chain lengths of the amyloses, and this point has been confirmed by the viscosity studies of Foster and Hixon.[10] In Table II are listed observed absorption maxima, molecular extinction coefficients, characteristic potentials for complex formation of an iodine half cell measured against a normal calomel half cell,[3] and estimates of chain length in glucose residues from the viscosity studies of Foster and Hixon.[10] Both the absorption maximum and the molecular extinction coefficient change in a regular fashion with chain length. Though the differences are beyond the experimental error, the change in the absorption maximum is too insensitive to be particularly valuable as a measure of chain length except for very short chains, such as encountered in the amylodextrins. The change in the molecular extinction coefficient with chain length is sufficient to permit its use as a rough, relative test of the chain length of an amylose, or unbranched material. It, too, is most sensitive to change in chain length for short chains. It is also a secondary method whose use depends upon the establishment of the molecular weights of a series of amyloses by other methods. It would appear advisable to await the further

TABLE II

Amylose	Molecular size	Wave length of absorption maximum	Molecular extinction coefficient	Characteristic potential
Potato	500	6280	43,000	0.197
Tapioca	450	6250	41,600	.200
Lily	310	6220	41,400	.202
Corn	250	6180	40,400	.203
Crystalline	175	6050	40,100	.205
Synthetic	85	5900	32,900	.204
Amylodextrin	44	5800	25,400	.218

(12) For a review of the literature on this point see G. Barger, "Some Applications of Organic Chemistry to Biology and Medicine," McGraw Hill Book Co., New York, N. Y., 1930.

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development of such standards before use of the molecular extinction coefficient for the determination of anything but the relative molecular weights of the amyloses.

The wave lengths of maximum absorption of the amylopectin–iodine solutions are all at much shorter wave lengths than those found for the amylose–iodine solutions. The wave lengths are again a reproducible function of the source of the amylopectin. There is a great deal of similarity in the wave length, molecular extinction coefficient, and general character of the absorption spectra of the amylopectins and the low molecular weight amylodextrin. The latter appears to have all the characteristics of an unbranched, but short chain material. The amylopectin, on the other hand, is of high molecular weight. The similarity in the absorption spectra seems to result from a similarity in the length of the free, unbranched portions of the chains in the amylopectin molecules and the length of the amylodextrin chains. It is believed that the wave length of maximum absorption and the molecular extinction coefficient of the amylopectin–iodine solutions are measures of the average length of the unbranched portions of the amylopectin chains. On this basis it appears that glycogen is most highly branched, and following in order, waxy rice, waxy maize, waxy barley, potato- and corn-amylopectin. Where tetramethyl end-group assay is known it is in agreement with this assignment. This order is also in agreement with the results of the potentiometric titration.[3]

Summary

Study of absorption spectra confirms the great difference in behavior of amylose and amylopectin with iodine found by the potentiometric iodine titration,[3] and provides another means of analyzing for the two components in whole starch. The differences in individual amyloses and amylopectins from different starches make a simple colorimetric analysis for the two components unreliable however.

The amount of iodine bound in complex formation with amylose increases as the concentration of iodide decreases, becoming one iodine molecule for six glucose residues for infinitely dilute iodide solutions.

The wave length of maximum absorption of an amylose solution shifts toward the red as the chain length of the amylose is increased. The shift is in the same direction when the lengths of the unbranched portions of an amylopectin are increased. An increase in the molecular extinction coefficient accompanies an increase in the length of an amylose or an increase in the lengths of the unbranched portions of an amylopectin. Both these properties permit the relative evaluation of molecular weight of an amylose and degree of branching of an amylopectin. The change in the molecular extinction coefficient is the more sensitive.

The relative molecular weights of a few amyloses and the degree of branching of some amylopectins have been examined. Results are in agreement with other determinations.

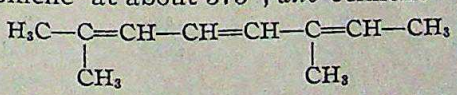
AMES, IOWA RECEIVED SEPTEMBER 28, 1943

[CONTRIBUTION FROM NAVAL STORES RESEARCH DIVISION, BUREAU OF AGRICULTURAL AND INDUSTRIAL CHEMISTRY, AGRICULTURAL RESEARCH ADMINISTRATION, U. S. DEPARTMENT OF AGRICULTURE]

Raman Spectra of Two Forms of *allo*-Ocimene

BY J. J. HOPFIELD,[1] S. A. HALL[2] AND L. A. GOLDBLATT

Among the products obtained in the pyrolysis of α-pinene[3] at about 375°, *allo*-ocimene



(2,6-dimethyl-2,4,6-octatriene), is of the greatest interest, both from a practical and theoretical viewpoint.

On careful re-fractionation of the portion of α-pinene pyrolysate boiling in the *allo*-ocimene range, two components were obtained, a major component boiling at 89.0° at 20 mm. pressure and a minor component boiling at 91°. Both components yield with maleic anhydride the same adduct (m. p. 83–84°) but the two components exhibit differences in their freezing points, densities and Raman spectra.

It may be reasonably assumed that these are two forms of *allo*-ocimene, of which there are four possible geometric isomers, arising from the double bonds at the 4 and 6 positions. Models (Fisher–Herschfelder) of the four geometrical isomers show that the *cis* form arising from the double bond at the C_4 carbon atom (regardless of whether the configuration at C_6 is *cis* or *trans*) is one of very limited rotation. The probability of its formation and continued existence during the high temperature pyrolysis of α-pinene would appear to be slight.[4] Such a configuration would be more likely to form a stable ring compound, such as one of the pyronenes which are also ob-

(1) Transferred to National Bureau of Standards, Washington, D. C., 10/18/42.

(2) Transferred to Bureau of Entomology and Plant Quarantine, 5/5/43.

(3) Goldblatt and Palkin, THIS JOURNAL, 63, 3517 (1941).

(4) In the case of pentadiene-1,3 (piperylene), however, Robey, *Science*, 96, 470 (1942), reports that the *cis* isomer, which is similarly more hindered than the *trans* isomer, is much more prominent in mixtures from high temperature processes.

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tained in the pyrolysis of α-pinene, or be "cracked" at the high temperature (375°) prevailing, thus accounting for the small percentage of very low-boiling substances always obtained during pyrolysis. On the other hand, the model of the *trans* form at C_4 shows relative freedom of rotation for all groups. Of the *cis* and *trans* configurations at the C_6 carbon atom, the model of the *cis* form appears to be slightly more compact, which should, of course, be reflected in a slightly greater density.

Although methods for the assignment of the *cis* or *trans* configuration to isomers of an olefin on the basis of their physical properties are admittedly of doubtful use,[5a] nevertheless, it is usually true that the *cis* isomer of an olefin has the lower melting point[5b] and the higher boiling point and higher density.[6]

If the two forms of *allo*-ocimene obtained are indeed the *trans*-(C_4)-*cis*-(C_6) and the *trans*-(C_4)-*trans*-(C_6) isomers, then we might expect from their physical properties to find as the *cis* isomer the hydrocarbon of higher boiling point, higher density, and lower melting point. The Raman spectra of these isomers tend to support this interpretation.

Materials.—125 grams of a fraction of *allo*-ocimene boiling at 89.0° at 20 mm. and melting at −24.3 to −22.6° was recrystallized twice from absolute alcohol; 125-cc. portions of the alcohol were used and crystallization was effected by cooling the solution in a bath of dry-ice in acetone. Filtration was accomplished in the usual manner, but in a refrigerated room (0°) using a Buchner funnel previously chilled in dry-ice. The occluded alcoholic mother liquor was readily removed by distillation and as a final purification the material was vacuum distilled. During and after distillation a blanket of nitrogen gas was used to avoid exposure to air for the *allo*-ocimene, after an induction period of about two hours, absorbs oxygen quite rapidly.

Approximately 50 g. of the isomer boiling at 91° at 20.0 mm. pressure and melting at −35.9 to −33.4° was subjected to the same procedure except that only one crystallization from alcohol was made.

The fractions thus purified have the following physical properties:

	B. p. at 20 mm.	M. p., °C.	d^{20}_4	$n^{20}D$
"A" form	89.0°	−21.0 to −20.6°	0.8060	1.5446
"B" form	91°	−35.4 to −34.0°	0.8118	1.5446

Procedure.—The Raman spectrograms were obtained with a Gaertner L-256 spectrograph having a dispersion of 39.5 A./mm. at 4500 Å. The Raman cell was specially constructed of a 12 mm. o. d. Pyrex tube enclosed by an outer tube to give a 30 mm. thickness of filter. A Hanovia fused quartz mercury arc lamp (Model 2444, 110 volt d. c., 4.5 amp.) was used for excitation. The filter solution for isolating the Hg 4358 A. line was the one recommended by Edsall and Wilson.[7] The slit opening was 100 μ and effective aperture F:4.5. Eastman II-J plates, developed at 20° for six minutes with developer DK-50, were used. The respective spectrograms of the "A" and "B" forms of *allo*-ocimene were taken on the same plate to obviate any differences in line densities arising from differences in plate gamma or in development time. Three different exposure times were used, namely, four, sixteen and thirty-two minutes. The spectrograms of the shorter exposures were used for the measurement of the strongest lines; but such measurements were checked with measurements of longer exposures. Also, doublets which were not well resolved were checked by examination of the spectra excited by the Hg 3650 Å. triplet. Because of the greater dispersion of the spectrograph at the lower wave lengths, a much better resolution of such doublets was effected. The lines were measured with a Gaertner comparator. The wave length shifts were calculated from these data by a three-constant quadratic equation[8] based on the measured positions and

TABLE 1[a]

RAMAN SPECTRA OF TWO FORMS OF *allo*-OCIMENE

Form "A"		Form "B"	
Δμ	*I*	Δμ	*I*
		151	1/4
196	2vb		
		227	1/2d
258	1/4		
		277	1/4
296	1/4		
		335	1/4d
361	1/4		
440	1/2		
		446	1/2d
518	1/8d	518	1/8d
790	1/2b		
		800	1/4bd
844	1/4b	844	1/2b
871	1	871	1
		961	3b
964	5		
1026	1/4	1026	2
		1054	1/2d
		1082	1
1091	1/2d		
1151	7	1151	7
1184	5	1184	7
		1231	3
1236	6		
		1272	4
1307	6	1308	1b
		1347	3
1365	3		
1383	3	1383	3
1448	2b	1448	2b
1532	1/2d	1532	1/2d
1590	6		
		1597	3d
		1627	10b
1631	10vb		
		1648	4
		2860	1d
2878	1vbd		
		2911	3b
2914	3b		
2971	1/2d		
		2977	1/4vbd
3012	1/4d		

[a] Δμ = Raman shift in cm.$^{-1}$; *I* = estimated intensity; v, b, d = very, broad, diffuse.

(5)(a) Gilman, "Organic Chemistry," Vol. I, John Wiley and Sons, New York, N. Y., 1938, p. 370; (b) *ibid.*, p. 372.

(6) Egloff, "Physical Constants of Hydrocarbons," Vol. I, A. C. S. Monograph No. 78, 1939, pp. 186, 200, 214, 216.

(7) Edsall and Wilson, *J. Chem. Phys.*, **6**, 124 (1938).

(8) Russel and Shenstone, *J. Opt. Soc.*, **16**, 298 (1928).

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wave numbers of three selected lines of the iron spectrum. Thus, instead of interpolating to the nearest iron line (which might not be well defined or, in some cases, might be an appreciable distance from a Raman line) the wave numbers were obtained from this equation and a correction curve based on some of the other iron lines in the region. For well-defined Raman lines an accuracy to 1 cm.$^{-1}$ was obtainable; but for broad or diffuse lines the accuracy was limited to about 3 cm.$^{-1}$.

Results

The results obtained for the two isomers are listed in Table I and shown graphically in Fig. 1. A photograph of the three exposures for each isomer is shown in Fig. 2. *allo*-Ocimene gives a very strong Raman spectrum in an unusually short exposure time.

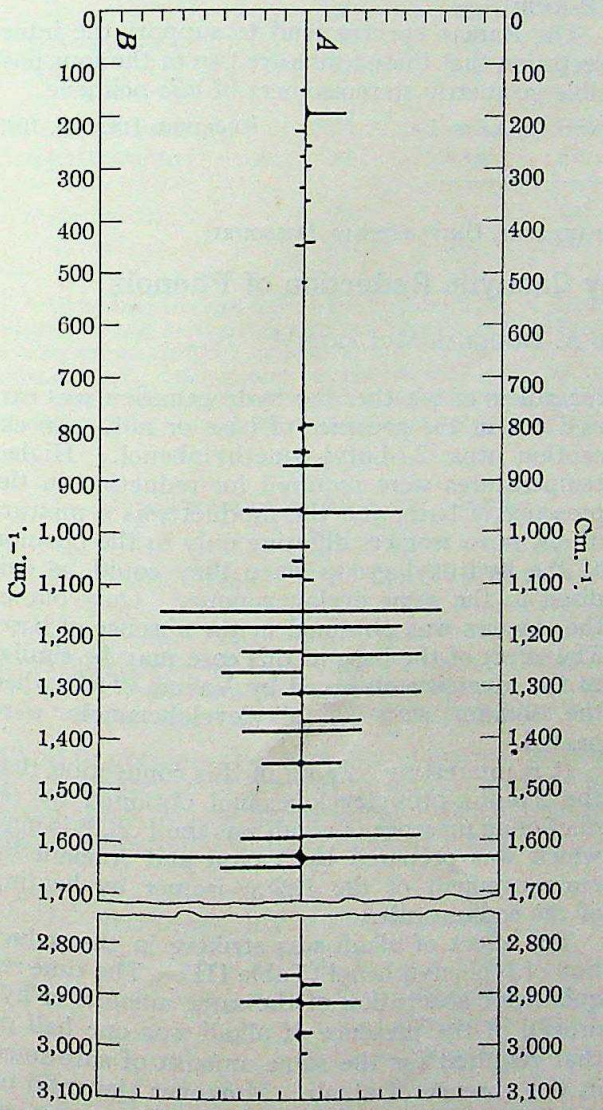

Fig. 1.

The strongest line at about 1631 cm.$^{-1}$, due to the double-bond vibration, is easily discernible after an exposure time of only twenty seconds. The isomeric triolefin, myrcene (2-methyl-6-methylene-2,7-octadiene), requires at least eight minutes exposure time under the same conditions to make visible its corresponding strong line at

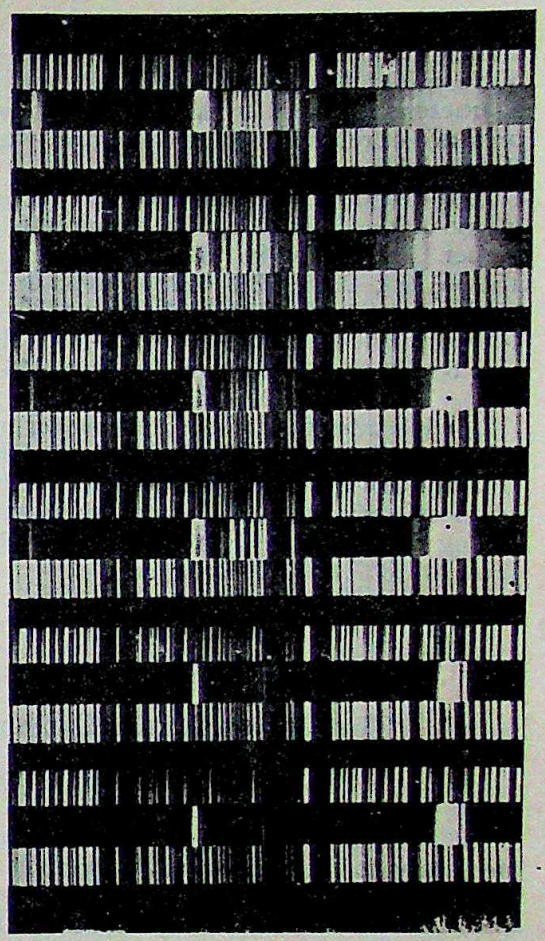

Fig. 2.

about 1636 cm.$^{-1}$. With *allo*-ocimene, four minutes exposure brings out 11 Raman lines; sixteen minutes brings out 26 lines; and thirty-two minutes brings out 28 lines. Longer exposures appear to be unprofitable, for the increasingly prominent background tends to obscure any additional weak lines.

Discussion

The line at 1307 cm.$^{-1}$, which is much more intense in the "A" than in the "B" isomer, is interpreted as due to a *trans* configuration.[9] The rather strong lines at 1272 cm.$^{-1}$ and at 1648 cm.$^{-1}$ in the "B" form, which have no counter parts in the "A" form, are attributed to a *cis* configuration.[10] A *trans* configuration should be reflected in a Raman line[11] at about 1673 cm.$^{-1}$, lowered somewhat by the influence of conjugation. Curiously this line is absent in both the "A" and the "B" isomers. Nor has it been reported by Dupont and co-workers in their work[12] on the Raman

(9) Gredy, *Compt. rend.*, **202**, 322 (1936); *Bull. soc. chim.*, **3**, 1101 (1936); **4**, 415 (1937).

(10) Bourgel, Gredy and Piaux, *Compt. rend.*, **195**, 129 (1933); Van Risseghem, Gredy and Piaux, *ibid.*, **196**, 938 (1933).

(11) Hibben, "The Raman Effect and its Chemical Applications," A. C. S. Monograph No. 80, 1939, pp. 170–171.

(12) Dupont, Dulou, Desreux and Picoux, *Bull. soc. chim.*, **5**, 322 (1938); Dupont and Dulou, *ibid.*, **3**, 1639 (1936).

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spectrum of *allo*-ocimene. These authors did not distinguish between the two forms of *allo*-ocimene but consideration of the Raman data and physical characteristics cited by them would indicate the presence of relatively large concentrations of both the A and B components.

It is also apparent that there is a tendency for many of the lines in the "A" isomer to shift to higher frequencies in the "B" isomer, namely, 151 → 196; 227 → 258; 277 → 296; 335 → 361; 961 → 964; 1082 → 1091; 1231 → 1236; 1347 → 1365; 1627 → 1631; 2911 → 2914. The opposite tendency is shown by the lines 446 → 440; 800 → 790 and 1597 → 1590.

For identification of the "A" isomer in a mixture, one could conveniently use the rather strong, well-defined 1365 line, while the "B" form could be most easily detected by its unique and rather strong line at 1272 cm.$^{-1}$, or alternatively by its lines at 1347 and 1648 cm.$^{-1}$.

Acknowledgment.—The continued interest and advice of the late Dr. S. Palkin, Chief of the Naval Stores Research Division, who originally proposed the project, is gratefully acknowledged.

Summary

Two forms of *allo*-ocimene, designated as A- and B- have been isolated.

Both forms yield with maleic anhydride the same adduct but they exhibit differences in boiling point, freezing point, density and Raman spectra.

Both forms give strong Raman spectra in an exceptionally short exposure time. Each may be detected in a mixture by the characteristic Raman lines at 1365 cm.$^{-1}$ (A-form) and 1272 cm.$^{-1}$ (B-form).

The Raman spectra tend to support the interpretation that these forms are two of the four possible geometric stereoisomers of *allo*-ocimene.

NEW ORLEANS, LA. RECEIVED JULY 30, 1943

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF MISSOURI]

The Preparation of Cyclohexanols by Catalytic Reduction of Phenols

BY HERBERT E. UNGNADE AND A. DOUGLAS MCLAREN[1,2]

In connection with another problem it became necessary to prepare alkylcyclohexanols in moderately large quantities. This has been accomplished by the catalytic reduction of alkyl-, alkenyl- and acylphenols with Raney nickel.

Since alkylphenols could be hydrogenated readily to the corresponding cyclohexanols, the chief limitation was the availability of the phenols. The ease of reduction was not greatly affected by substituents in the ring unless two ethyl or *n*-propyl groups occupied the ortho positions (Table I). In the latter cases no cyclohexanols were formed at temperatures above 300°. 2,6-Di-*n*-propylphenol was recovered unchanged but 2,6-diethyl-4-methylphenol underwent hydrogenolysis and reduction of the ring to give 1-methyl-3,5-diethylcyclohexane. The corresponding cyclohexanols could be obtained from the two phenols when the hydrogenation was carried out in the presence of a small amount of a 40% aqueous solution of sodium hydroxide. When the other phenols were reduced in the presence of alkali a slight promoting effect was evidenced in some cases by lower initial reduction temperatures. The promoting effect was lost when the phenolic hydroxyl was methylated (Table II). The formed cyclohexanols consisted predominantly of one of the possible geometric isomers. The same isomer was usually obtained regardless of whether the hydrogenation was carried out in the presence of base or not. An exception was 2-*t*-butyl-4-methylphenol. Higher temperatures were required for reduction in the presence of base, and the product was a mixture of *cis*, *trans* isomers differing only in the position of the hydroxyl group since they could be oxidized to the same cyclohexanone.[3] Only one of the isomers was obtained in the absence of base. The effect of the base in this case may be similar to the inversion observed by Vavon, *et al.*, when the sodium salts of alkylcyclohexanols were heated.[4]

It is interesting to note in this connection that the 2,6-di-*n*-propylcyclohexanol obtained by reduction in presence of alkali was the 1^t,2^c,6^c-isomer which was prepared by Vavon and Anziani by rearrangement of the 1^c,2^c,6^c-isomer by heating of the sodium salt.[5]

The effect of alkali was striking in the reduction of *p*-phenylphenol (Table III). The time required for absorption of the same amount of hydrogen in the presence of alkali was one half of that required for the same amount of substance in the absence of alkali. Moreover the ratio of the products was not the same. The percentage of *p*-cyclohexylphenol and *p*-cyclohexylcyclohexanol was smaller and the amount of *p*-phenylcyclohexanol larger when alkali was used as a promoter. It is therefore possible by means of

(1) An abstract of a dissertation submitted by A. Douglas McLaren in partial fulfilment of the requirements for the degree of Doctor of Philosophy, 1943.

(2) Presented before the Division of Organic Chemistry at the 105th meeting of the American Chemical Society, Detroit, Michigan, April 13, 1943.

(3) Unpublished data by the authors.

(4) Vavon, *et al.*, *Bull. soc. chim.*, (4) **39**, 1142 (1926); (4) **41**, 357 (1927); (4) **45**, 961 (1929).

(5) Vavon and Anziani, *ibid.*, (5) **4**, 1080 (1937).

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TABLE I

HYDROGENATION OF ALKYLPHENOLS[a]

Phenol	Moles	T_1,[i] °C.	T_2,[j] °C.	Time, hr.	Yield, %	Cyclohexanol[b]
4-Methyl	1.9	95	130	4	92	*trans*-4-Methyl
	0.88[c,d]	80	115	11	90	*trans*-4-Methyl
3-Ethyl	.66	90	145	7	94	3-Ethyl
4-Ethyl	.19	90	160	4.5	88	4-Ethyl
2-*n*-Propyl	.66	105	150	8	94	*cis*-2-*n*-Propyl
2,4-Dimethyl	.71	135	170	12	91	(1^t)2^c,4^t-Dimethyl
2,5-Dimethyl	.63	125	170	8	94	(1^t)2^c,5^t-Dimethyl
3,4-Dimethyl	.81	125	140	6	98	3,4-Dimethyl
	.41[c,e]	105	135	4	90	3,4-Dimethyl
3,5-Dimethyl	.84	90	125	6	91	(1^t)3^c,5^c-Dimethyl
2,6-Di-*n*-propyl	.1	...	360	1	0	
	.1[c,f]	260	280	3.5	90	(1^t)2^c,6^c-Di-*n*-propyl
4-Methyl-2-*t*-butyl	.36	160	190	7	91	4-Methyl-2-*t*-butyl (liq.)
	.17[c,g]	195	220	5.5	64	4-Methyl-2-*t*-butyl (liq.)
					27	4-Methyl-2-*t*-butyl (sol.)
2,3,5-Trimethyl	.74	95	155	13	90	2,3,5-Trimethyl
2,4,6-Trimethyl	.18	145	200	4.3	30	2,4,6-Trimethyl (solid)[k]
					60	2,4,6-Trimethyl (liquid)
4-Methyl-2,6-diethyl	.08	...	340	1		1-Methyl-3,5-diethylcyclohexane
	.08[c,h]	205	235	1.5	14	4-Methyl-2,6-diethyl (sol.)[k]
					76	4-Methyl-2,6-diethyl (liq.)

[a] All hydrogenations were carried out with 3 g. of Raney nickel. [b] The *cis–trans* isomers were assigned on the basis of properties and derivatives wherever these were described in the literature. [c] Hydrogenation in the presence of the following amounts of 40% aqueous alkali: [d] 1.6 cc., [e] 1.5 cc., [f] 1.0 cc., [g] 1.3 cc., [h] 1.2 cc. [i] T_1, temperature of initial hydrogen uptake. [j] T_2, temperature maintained during the hydrogenation. [k] The solid isomer was separated by freezing out. The separation is not considered to be quantitative. The two isomers give the same cyclohexanone on oxidation and therefore differ only in the configuration around Carbon 1.

TABLE II

HYDROGENATION OF 4-METHYLANISOLE

Moles	T_1,[b] °C.	T_2,[c] °C.	Time, hr.	Yield, %	Product
0.29	155	180	3.7	98	1-Methyl-4-methoxycylohexane
.26[a]	185	220	6.7	85	

[a] Hydrogenation in the presence of 1.6 cc. of 40% aqueous alkali. [b] T_1, temperature of initial hydrogen uptake. [c] T_2, temperature maintained during the hydrogenation.

alkali to promote the reduction of a phenolic ring in the presence of another aromatic nucleus or presumably in the presence of other functions whose reduction is not activated by alkali.

TABLE III

HYDROGENATION OF 4-PHENYLPHENOL

Moles	T_1,[b] °C.	T_2,[c] °C.	Time, hr.	Yield, %	Product
0.295	110	125	6	25.7	4-Cyclohexylphenol
				7.4	4-Phenylcyclohexanol
				59.2	4-Cyclohexylcyclohexanol
.295[a]	95	115	3	16.6	4-Cyclohexylphenol
				30.3	4-Phenylcyclohexanol
				43.2	4-Cyclohexylcyclohexanol

[a] Hydrogenation in the presence of 2 cc. of 40% aqueous alkali. [b] T_1, temperature of initial hydrogen uptake. [c] T_2, temperature maintained during the hydrogenation.

Allyl or propenylphenols which are readily available through the Claisen allyl ether rearrangement have been converted in good yields to alkylcyclohexanols. The reduction was found to take place in two steps. Isolation of the alkylphenol was not necessary. The addition of alkali shortened the time required for the saturation of the side-chain, lowered the initial temperature for the reduction of the ring and reduced the time required for the saturation of the ring. The experimental data are summarized in Table IV.

TABLE IV

HYDROGENATION OF ALKENYLPHENOLS

Phenol	Moles	T_1,[c] °C.	T_2,[d] °C.	Time, hr.	Yield, %	Product
2-Allyl	0.77	30	50	0.4	95	2-*n*-Propylphenol
2-Allyl	.37	30	50	0.4		
		100	140	11.0	91	*cis*-2-*n*-Propylcyclohexanol[a]
2-Allyl	.37[b]	30	50	0.3		
		85	130	5.6	90	*cis*-2-*n*-Propylcyclohexanol[a]
2-Propenyl	.53	30	50	6.5		
		105	160	2.5	95	*cis*-2-*n*-Propylcyclohexanol[a]
2,6-Diallyl	.39	30	50	2.75	99	2,6-Di-*n*-propylphenol

[a] The hydrogenation was continued until no more hydrogen was absorbed, then the temperature was raised to the next reduction stage. [b] Hydrogenation in the presence of 1.5 cc. of 40% aqueous alkali. [c] T_1, temperature of initial hydrogen uptake. [d] T_2, temperature maintained during the hydrogenation.

It was shown some years ago[6] that *p*-propionylphenol can be converted to 4-propylcyclohexanol

(6) Harris, D'Ianni and Adkins, THIS JOURNAL, 60, 1467 (1938).

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TABLE V

HYDROGENATION OF ACYLPHENOLS[a]

Phenol	Moles[a]	T_1,[c] °C.	T_2,[d] °C.	Time, hr.	Yield, %	Products
2-Acetyl	0.37	70	180	5.8	87	*cis*-2-Ethylcyclohexanol
4-Acetyl	.018	65	90	5.0	86	4-Ethylphenol
4-Acetyl	.34[e]	45	50	11.0	31	4-Ethylphenol
					48	4-(1-Hydroxyethyl)-cyclohexanol[b]
4-Acetyl	.23[e]	65	160	3.0	67	4-Ethylcyclohexanol
					21	4-(1-Hydroxyethyl)-cyclohexanol
2-Acetyl-4-methyl	.73	85	115	12.0	87	2-Ethyl-4-methylphenol
2-Acetyl-4-methyl-6-ethyl	.21	85	135	9.5	83	2,6-Diethyl-4-methylphenol
2-Propionyl	.39	105	180	6.5	81	*cis*-2-*n*-Propylcyclohexanol
2-Propionyl	.33	60	110	3.0	83	2-*n*-Propylphenol
2-Propionyl	.34[e]	55	65	10.3	34	2-*n*-Propylphenol
					46	2-(1-Hydroxypropyl)-cyclohexanol
2-Propionyl	.31[e]	60	140	2.25	72	*cis*-2-*n*-Propylcyclohexanol
					23	2-(1-Hydroxypropyl)-cyclohexanol
2-Propionyl	.32[e]	55	220	5.2	67	*cis*-2-*n*-Propylcyclohexanol
					23	2-(1-Hydroxypropyl)-cyclohexanol

[a] All hydrogenations with 3 g. of Raney nickel and 100 cc. of ethanol. [b] The authors are indebted to Dr. Austin Patterson for his advice in naming these compounds. [c] T_1, temperature of first hydrogen uptake. [d] T_2, temperature maintained during the hydrogenation. [e] Hydrogenation in the presence of 2 cc. of 40% aqueous alkali.

by reduction with Raney nickel at 200°. More recently Smith and Rouault[7] were able to hydrogenate 2-(2′,6′-dimethylheptanoyl)-4-methylphenol and 2-lauroyl-4-methylphenol in practically quantitative yields by a two stage reduction. In our hands both ortho and para acylphenols gave excellent yields of alkylphenols at about 110° when the hydrogenation was carried out in alcoholic solution. When the temperature was raised to 180° the ring could be saturated without previous isolation of the alkylphenol. Attempts to stop the hydrogenation at the first reduction stage, the (1-hydroxylalkyl)-phenols, were unsuccessful. The products were mixtures of alkyl and acylphenols. In the presence of alkali ortho and para acylphenols absorbed hydrogen rapidly between 45 and 65°. The products consisted of mixtures of alkylphenols and hydroxyalkylcyclohexanols. The second reduction stage (110°) gave a mixture of alkylcyclohexanols and hydroxyalkylcyclohexanols. Further increase in temperature up to 220° did not change the products or their ratio (Table V).

The experimental data allow the conclusion that the hydrogenation of the phenolic ring as well as that of the carbonyl group is activated by alkali. The latter case has been studied previously by Delépine and Horeau.[8]

The results cannot be entirely accounted for unless it is assumed that the hydrogenation of one function is affected by the presence of the other. Thus, the hydrogenation of the phenolic ring during the first reduction stage takes place at temperatures appreciably below those required for alkylphenols even in the presence of base. This effect is ascribed to the acyl group.

During the second stage the hydroxylalkylcyclohexanols are partially converted to alkylcyclohexanols by hydrogenolysis of the side-chain hydroxyl group. Simultaneously the alkylphenols formed in the first stage undergo complete saturation. Since heating to higher temperatures does not bring about further hydrogenolysis (after all phenolic rings have been reduced), it is proposed that this reaction is catalyzed by the sodium phenolate still present during the second stage. The resistance of the dihydric alcohol to further hydrogenation is not surprising since the side-chain hydroxyl group is no longer on a carbon directly connected to an aromatic nucleus[9] and is, therefore, not expected to undergo hydrogenolysis below 200°.[10] Further aspects of these reactions are now under investigation.

Acknowledgment.—The authors wish to express their thanks to the University Research Council for funds to purchase apparatus and chemicals necessary for this investigation.

Experimental[10a]

The hydrogenations reported in the tables were carried out in general at 100–300 atm. with Raney nickel in a steel chamber equipped with a copper liner having a total capacity of 500 cc.[11] The temperature of initial hydrogen absorption was determined by plotting temperature against pressure. The data chosen for the tables were for catalysts with as near the same age as possible since Raney nickel was found to lose some of its activity upon aging, as evidenced by higher initial hydrogenation temperatures required with some older catalysts for the same sample of starting-material.

Hydrogenation of Alkyl and Alkenylphenols.—Most of the phenols were obtained from commercial sources and were purified in addition to the usual methods by distillation from Raney nickel. *o*-*n*-Propylphenol and 2,6-di-*n*-

(7) Smith and Rouault, THIS JOURNAL, 65, 745 (1943).

(8) Delépine and Horeau, *Bull. soc. chim.*, (5) 4, 34 (1937).

(9) Gilman, "Organic Chemistry," 2nd ed., John Wiley and Sons, New York, N. Y., 1943, Vol. I, p. 805.

(10) Schröter, *Angew. Chem.*, 54, 252 (1941).

(10a) All melting points are uncorrected.

(11) American Instrument Company, Silver Springs, Maryland.

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TABLE VI

Cyclohexanol	B. p., °C.	M. p., °C.	Phenyl urethan, m. p., °C.	α-Naphthyl urethan, m. p., °C.	Nitrogen, % Found	Calcd.
trans-4-Methyl[a]	167–170		124–124.5	156.5–157.5	4.81	4.95
cis-2-Ethyl[14]	180–182		99–99.8	151–153.5	4.92	4.72
3-Ethyl[b]	191.5–192			98.5–99.5	4.70	4.72
4-Ethyl[15]	191–192		114–115	139.5–140.5	4.92	4.72
cis-2-*n*-Propyl[16]	201.5–202		94–95	103–104	4.39	4.5
(1*t*)2*c*,4*t*-Dimethyl[c]	176.5–177.5		95–96	152.5–153.5	4.72	4.72
(1*t*)2*c*,5*t*-Dimethyl[18]	179–180.5		116–117	172–173.5	4.64	4.72
3,4-Dimethyl	188–189.5		96–97[d,19]	162–163	4.90	4.72
(1*t*)3*c*,5*c*-Dimethyl[20]	181–183	8–9.8	106–107.5	141–143	4.67	4.72
2-*t*-Butyl-4-methyl[e]	215–216			130–131[g]	4.06	4.15
2-*t*-Butyl-4-methyl[f]		112–113		130.5–131.5[g]	4.07	4.15
(1*t*)2*c*,6*c*-Di-*n*-propyl[5]	241–242	109–110	145.5–146.5	137–138	4.01	3.97
2,3,5-Trimethyl[h]	196–197			148–149[i]	4.3	4.5
2,4,6-Trimethyl[j]	182–184	70.5–71		197.5–198	4.35	4.5
2,6-Diethyl-4-methyl[k]	219–220	86–87		143.5–144	3.91	4.15

[a] 3,5-Dinitrobenzoate, m. p. 137.2–138.7°.[13] [b] $n^{25}D$ 1.4600, d^{25} 0.9094, M_D (calcd.) 38.47, M_D (found) 38.56. *Anal.* Calcd. for $C_{18}H_{16}O$: C, 75.00; H, 12.50. Found: C, 74.69; H, 12.52. [c] The exact configuration of this compound is uncertain since the literature data are conflicting.[17] [d] *Anal.* Calcd. for $C_{15}H_{21}NO_2$: N, 5.68. Found: N, 5.74. [e] *Anal.* Calcd. for $C_{11}H_{22}O$: C, 77.65; H, 13.06. Found: C, 77.79; H, 13.00. $n^{25}D$ 1.4661; d^{25}_4 0.9002; M_D(calcd.) 52.32; M_D(found) 52.30. [f] *Anal.* Calcd. for $C_{11}H_{22}O$: C, 77.65; H, 13.06. Found: C, 77.35; H, 12.94. [g] Mixed melting point 111–113.5°. [h] *Anal.* Calcd. for $C_9H_{18}O$: C, 76.06; H, 12.7. Found: C, 75.7; H, 12.9. $n^{25}D$ 1.4572; d^{25} 0.9002; M_D(calcd.) 43.09; M_D(found) 42.97. [i] *Anal.* Calcd. for $C_{20}H_{25}ON_2$: C, 77.1; H, 8.03. Found: C, 76.8; H, 7.54. [j] *Anal.* Calcd. for $C_9H_{18}O$: C, 76.05; H, 12.65. Found: C, 75.73; H, 12.99. [k] *Anal.* Calcd. for $C_{11}H_{22}O$: C, 77.65; H, 12.94. Found: C, 77.54; H, 12.78.

TABLE VII

ALKYLPHENOLS OBTAINED BY HYDROGENATION OF ALKENYL AND ACYLPHENOLS

Phenol	B. p., °C.	Mm.	Derivative	M. p., °C.
4-Ethyl	213–216	739	Aryloxyacetic acid	94–94.5[24]
2-*n*-Propyl	214–216	740	Phenylurethan	109–110[25]
2,6-Di-*n*-propyl	247.5–249	740	Phenlyurethan	126.5–127[26]
2-Ethyl-4-methyl	131–133	135	Aryloxyacetic acid	130.5–131.5[27]
2,6-Diethyl-4-methyl	133–134	23	Benzoate	100.5–101.5[28]

propylphenol were obtained by hydrogenation of the corresponding allyl compounds, and 2-*t*-butyl-4-methylphenol by alkylation of *p*-cresol with *t*-butyl alcohol.[12] Mesitol was prepared by hydrolysis of bromomesitylene, 4-ethyl- and 2,6-diethyl-4-methylphenol by hydrogenation of the corresponding acylphenols.

All phenols were hydrogenated in the absence of solvents. The pertinent data for the cyclohexanols are given in Table VI.

1-Methyl-3,5-diethylcyclohexane.—B. p. 175–176.5°, $n^{25}D$ 1.4345, d^{25}_4 0.7841; M_D (calcd.) 50.80; M_D (found) 51.21. *Anal.* Calcd. for $C_{11}H_{22}$: C, 85.71; H, 14.28. Found: C, 85.55; H, 14.49.

1-Methyl-4-methoxycyclohexane.—B. p. 146–148.5°, $n^{20}D$ 1.4333.[21]

Hydrogenation of *p*-Phenylphenol.—A solution of 50 g. of *p*-phenylphenol (Eastman Kodak Co.) in 50 cc. of ethanol was hydrogenated in the presence of 3 g. of Raney nickel until a total of 1200 lb. of hydrogen had been absorbed at 115°. A subsequent run with addition of 2 cc. of 40% aqueous alkali was made under identical conditions. After removal of the solvent the mixture of products was taken up in benzene and petroleum ether and extracted with 10% aqueous alkali. Acidification of the alkaline extract gave *p*-cyclohexylphenol which melted at 129.2–130.5° after crystallization from benzene–petroleum ether.[22] Fractional crystallization of the remaining benzene–petroleum ether solution gave *p*-phenylcyclohexanol, m. p. 116–117°, and *p*-cyclohexyl-cyclohexanol, m. p, 98–99°.[22] *p*-Phenylcyclohexanol was converted to the corresponding ketone, m. p. 77–78°, by oxidation with sodium dichromate and sulfuric acid.[23]

Hydrogenation of Acylphenols.—The acylphenols used in this investigation were prepared by the Fries rearrangement of the phenol esters. No special purification was necessary even though carbon disulfide was used in the procedure. The hydrogenations were carried out in 100 cc. of ethanol with 3 g. of Raney nickel catalyst. The products were separated by fractional distillation under reduced pressure. The constants of the phenols are listed in Table VII.

4-(1-Hydroxyethyl)-cyclohexanol.—B. p. 129–133° (2 mm.), m. p. 91–92.2°. *Anal.* Calcd. for $C_8H_{16}O_2$: C, 66.66; H, 11.01. Found: C, 66.32; H, 10.87. 3,5-

(12) Chichibabin, *Compt. rend.*, **198**, 1239 (1934).
(13) Skita and Faust, *Ber.*, **64**, 2878 (1931).
(14) Vavon and Mitchovitch, *Bull. soc. chim.*, (4) **45**, 961 (1939).
(15) v. Braun, Mannes and Reuter, *Ber.*, **66**, 1499 (1933).
(16) Vavon and Anziani, *Bull. soc. chim.*, (4) **41**, 1638 (1927).
(17) Skita, *Ann.*, **427**, 275 (1922); Godchot and Bedos, *Compt. rend.*, **180**, 751 (1925).
(18) Skita, *Ber.*, **56B**, 2234 (1923).
(19) Sabatier and Mailhe, *Ann. chim.*, (8) **10**, 527 (1907).
(20) Skita and Faust, *Ber.*, **72B**, 1127 (1939); v. Braun and Anton, *ibid.*, **60B**, 2442 (1927).
(21) Cornubert and Le Bihan, *Bull. soc. chim.*, **43**, 74 (1928); Musser and Adkins, THIS JOURNAL, **60**, 664 (1938).
(22) Musser and Adkins, THIS JOURNAL, **60**, 666 (1938).
(23) Braun and Weissbach, *Ber.*, **64B**, 1785 (1931).
(24) Kruber and Schmitt, *Ber.*, **64**, 2272 (1931).
(25) Claisen, *Ann.*, **418**, 89 (1919).
(26) Claisen, *ibid.*, **418**, 93 (1919).
(27) Niederl, *et al.*, THIS JOURNAL, **59**, 1113 (1937).
(28) v. Auwers and W. Mauss, *Ann.*, **460**, 240 (1928).

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Dinitrobenzoate, m. p. 210–212°. *Anal.* Calcd. for $C_{22}H_{20}N_4O_{12}$: C, 49.62; H, 3.95. Found: C, 49.94; H, 4.11.

2-(1-Hydroxypropyl)-cyclohexanol.—B. p. 256–259°, $n^{25}D$ 1.4788, d^{25}_4 1.0060; MD (calcd.) 44.61; MD (found) 44.65. *Anal.* Calcd. for $C_9H_{18}O_2$: C, 68.35; H, 11.39. Found: C, 67.96; H, 11.42. 3,5-Dinitrobenzoate, m. p. 162.5–164°. *Anal.* Calcd. for $C_{23}H_{22}O_{12}N_4$: C, 50.54; H, 4.04. Found: C, 50.71; H, 4.48.

Summary

1. Alkylcyclohexanols are readily obtained by the hydrogenation of alkyl-, alkenyl- and acylphenols in the presence of Raney nickel.

2. The hydrogenation of di-ortho substituted phenols is promoted by small amounts of alkali.

3. The hydrogenation of alkenyl and acylphenols may be conducted at low temperatures to give good yields of alkylphenols.

4. The hydrogenation of acylphenols gives alkylphenols or alkylcyclohexanols depending upon the temperature. In the presence of alkali a mixture of alkylphenol and hydroxyalkylcyclohexanol is obtained at low temperatures and a mixture of alkylcyclohexanol and hydroxylalkylcyclohexanol at high temperatures.

COLUMBIA, MISSOURI RECEIVED SEPTEMBER 9, 1943

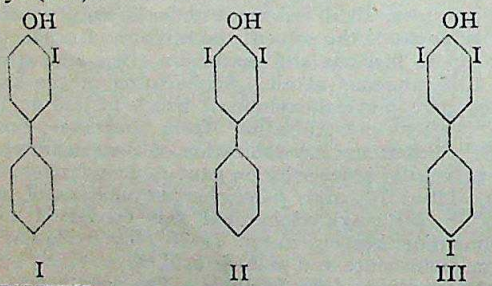
[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE UNIVERSITY OF TEXAS AND THE UNIVERSITY OF OKLAHOMA]

The Iodination of 4-Hydroxybiphenyl[1a]

BY J. C. COLBERT,[1b] H. W. HOUGHTON,[1b] H. R. SCHMIDT[2] AND J. L. ABERNETHY[2]

Although the chlorination[3] and bromination[4,5] of 4-hydroxybiphenyl have been investigated, the only iodine derivative of this phenol mentioned in the literature appears to be 4′-iodo-4-hydroxybiphenyl[6] obtained by use of the Sandmeyer reaction.

On the basis of the results of chlorination and bromination, it was anticipated that iodination of 4-hydroxybiphenyl would cause the first iodine atom to enter the 3-position, thereby yielding 3-iodo-4-hydroxybiphenyl (I); the second atom would enter the 5-position, with the resultant formation of 3,5-diiodo-4-hydroxybiphenyl (II); and, finally, the third atom would enter the 4′-position, giving rise to 3,5,4′-triiodo-4-hydroxybiphenyl (III).



I II III

Introduction of a solution of iodine dissolved in potassium iodide into a solution of 4-hydroxybiphenyl in sodium hydroxide[7] gave rise to I. However, when an attempt was made to diiodinate 4-hydroxybiphenyl using the same procedure, II could not be isolated from the reaction products. Instead, a compound which gave an analysis very close to a monoiodinated derivative was obtained. This substance decomposed at temperatures above 170°. Since it is known that on heating diiodinated phenols[8] with sodium hydroxide, two molecules undergo condensation with loss of hydrogen, *i. e.*, aristol formation takes place, it seemed plausible that a similar reaction had taken place during the attempted diiodination of 4-hydroxybiphenyl. Consequently a Rast molecular weight of this product was determined. This indicated that the molecular weight was approximately double that of a monoiodo-4-hydroxybiphenyl and suggested that aristol formation had taken place. No further attempt was made to prove its structure.

Iodination of 4-hydroxybiphenyl in an ammonium hydroxide solution gave rise to I. Further iodination introduced iodine in the 5-position, hence yielding II. This procedure is known to be more satisfactory than the procedure in which sodium hydroxide is used, in that in most instances very little aristol formation takes place with iodinated phenols.

Iodination with iodine monochloride gave rise to I, and further iodination gave rise to II. Attempts to triiodinate 4-hydroxybiphenyl were unsuccessful.

The benzoates of I and II were prepared by benzoylation of these substances with benzoyl chloride in pyridine. It was found that benzoylation of I took place readily, whereas benzoylation of II was somewhat more difficult. This latter

(1a) In 1938 at the University of Oklahoma an attempt was made to apply the detailed method of iodination of a phenol used by Harington in the synthesis of thyroxin to the iodination of 4-hydroxybiphenyl. This method made use of a solution of iodine in potassium iodide which was added to the ammoniacal solution of the phenol. In work initiated independently at the University of Texas in 1942 an attempt was made to iodinate this substance in a sodium hydroxide solution. This was abandoned, however, in favor of iodination with iodine monochloride. Shortly after this latter work was under way it was learned through correspondence that the iodination had been accomplished at the University of Oklahoma. The present paper presents the results of the investigations conducted independently at both institutions.

(1b) University of Oklahoma, Norman, Oklahoma.

(2) University of Texas, Austin, Texas.

(3) Colbert, Meigs and Mackin, THIS JOURNAL, **56**, 202 (1934).

(4) Raiford and Colbert, *ibid.*, **47**, 1456 (1925).

(5) Bell and Robinson, *J. Chem. Soc.*, 1128 (1927).

(6) Angelletti and Gatti, *Gazz. chim. ital.*, **58**, 630–635 (1929).

(7) Harington and Barger, *Biochem.*, **21**, 169 (1927); **22**, 1429 (1928).

(8) Bordeianu, *Chem. Abs.*, **30**, 1760 (1936).

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finding is in accord with earlier investigations[9] involving diortho substituted phenols.

The introduction of one nitro group into 3-iodo-4-hydroxybiphenyl was accomplished by a method[4] previously used in the mononitration of 4-hydroxybiphenyl.

Acknowledgment.—The writers are indebted to Professor G. W. Watt of the University of Texas for a supply of liquid ammonia used in the analysis, and to the Research Institute of the University of Texas for a grant permitting the continuance of this work.

Experimental

3-Iodo-4-hydroxybiphenyl.—(a) 2.0 g. of 4-hydroxybiphenyl was dissolved in warm ammonium hydroxide and cooled as low as possible without causing the phenol to separate. The molecular equivalent (*i. e.*, three grams) of iodine was dissolved in a potassium iodide solution and diluted to the basis of 3.0 g. of iodine per 500 cc. of solution. The reagent was added at the surface of the solution with as rapid stirring as possible, the addition requiring one hour. Best results were obtained using only diffused light. Following filtration, which should be rapid, the filtrate was cooled in an ice-bath and the phenol precipitated by addition of a 10% solution of sulfuric acid. During addition of acid decomposition occurred unless the temperature were held below 35°. The white needle-like precipitate was filtered rapidly, care being taken to avoid drawing air through the residue, *i. e.*, the last of the filtrate was obtained by gravity filtration. The crystals were washed with water and air dried in a dark place. Final drying was completed *in vacuo*. The yield of crude material was 91.1% and the melting point 108–109°. Analysis for iodine was made by sodium peroxide fusion followed by titration with silver nitrate. Recrystallization from chloroform by addition of petroleum ether raised the melting point to 115–116°.

Anal. Calcd. for $C_{12}H_9OI$: I, 42.86. Found: I, 43.16.

(b) 4-Hydroxybiphenyl (17 g.) was dissolved in a solution of 35 g. of sodium hydroxide in 600 ml. of water. This solution was heated in order to dissolve the 4-hydroxybiphenyl completely and was subsequently cooled until the 4-hydroxybiphenyl began to precipitate. Iodine (25.4 g.) dissolved in 200 ml. of an aqueous solution of potassium iodide (25.4 g.) was then added over a period of two hours. At the end of this time the mixture was acidified with dilute hydrochloric acid, causing 27 g. of a white precipitate to separate. After several recrystallizations a small amount of pure 3-iodo-4-hydroxybiphenyl was obtained.

(c) Seventeen grams of 4-hydroxybiphenyl was dissolved in 40 ml. of glacial acetic acid upon being heated on a steam-bath. Iodine monochloride (20.4 g.), Eastman Kodak Co. grade, dissolved in glacial acetic acid (14 ml.) was added dropwise to the above solution over a period of twenty minutes. The reaction proceeded readily with the liberation of hydrogen chloride. Heat was also liberated as the reaction proceeded. After complete addition of the iodine monochloride solution the mixture was heated gently on a steam-bath with constant stirring for an additional two hours. At the end of this time the resultant solution was cooled to room temperature and poured into ice-water. The precipitate which separated was filtered and dissolved in chloroform. The chloroform solution was then washed with an aqueous solution of sodium bisulfite to remove the excess iodine. It was washed with water and dried over anhydrous sodium sulfate. The solution was filtered and approximately three-fourths of the chloroform was removed under reduced pressure. A white precipitate separated on cooling the solution in an ice-bath. After two recrystallizations from a mixed solvent of one-third chloroform and two-thirds petroleum ether (b. p. 30–35°), 18 g. of white needles was obtained which melted at 115–116°; yield of recrystallized material, 60.8%.

A more direct procedure for removal of the excess iodine from the iodinated product involved addition of an aqueous solution of sodium bisulfite directly to the acetic acid solution after iodination had taken place. Removal of the impure 3-iodo-4-hydroxybiphenyl by filtration followed by recrystallization from the mixed solvent named above yielded the pure substance in approximately the same quantity as by the other method.

Anal. Calcd. for $C_{12}H_9OI$: I, 42.86. Found: I, 42.75.

Benzoylation of 3-Iodo-4-hydroxybiphenyl.—To a cooled solution of 2 g. of 3-iodo-4-hydroxybiphenyl in 20 ml. of pyridine, 2 ml. of benzoyl chloride was added slowly, with shaking. The mixture was heated for one hour on a steam-bath. On cooling to room temperature, following which the mixture was poured into a large volume of ice-water, a precipitate separated. The precipitate was filtered and washed successively with 10% sodium hydroxide solution, a dilute hydrochloric acid solution and water. The product was recrystallized from ethanol. The white crystals were obtained in a yield of 1.2 g., or 44.4% and melted at 99.5–100°. The Schotten–Baumann method gave a 68.2% yield of the benzoate melting at 91–92°.

Anal. Calcd. for $C_{19}H_{13}O_2I$: I, 31.71. Found: I, 31.35.

Nitration of 3-Iodo-4-hydroxybiphenyl.—Two grams of 3-iodo-4-hydroxybiphenyl was dissolved in 20 cc. of glacial acetic acid and 0.43 cc. of concd. nitric acid dissolved in 5.0 cc. of glacial acetic acid added slowly to the cooled solution. Nitration occurred slowly and the product was recovered by pouring the solution into ice-water. Recrystallization from 50% alcohol gave a 62.4% yield of 3-iodo-5-nitro-4-hydroxybiphenyl; m. p. 95–100° with decomposition.

Anal. Calcd. for $C_{12}H_8O_3NI$: I, 37.21. Found: I, 37.24.

Attempted Diiodination of 4-Hydroxybiphenyl.—4-Hydroxybiphenyl (8.5 g.) was dissolved in 600 ml. of an aqueous solution containing 36 g. of sodium hydroxide. To this solution was added, dropwise, over a period of two hours, 200 ml. of an aqueous solution containing 25.4 g. of potassium iodide and 25.4 g. of iodine. At the end of the addition dilute hydrochloric acid was added to the resultant mixture until the solution was acid to litmus. A yellow precipitate (17.6 g.) separated which was thought to be 3,5-diiodo-4-hydroxybiphenyl. This material, upon recrystallization from an alcohol–water mixture, melted with decomposition at 170–171°.

An analysis of the above compound indicated that apparently a mono iodinated product was formed. It was assumed then that a second reaction had taken place with the formation of an aristol. A Rast molecular weight determination was then made on the compound. It was found that 0.0132 g. of the compound dissolved in 0.091 g. of camphor lowered the melting point of camphor 9°. This indicated a molecular weight of 637. The theoretical molecular weight of the aristol is 590.

Anal. Calcd. for $C_{24}H_{16}O_2I_2$: I, 43.01. Found: I, 42.08.

No further investigation was made on this compound.

3,5-Diiodo-4-hydroxybiphenyl.—(a) The ammonium salt of this phenol was obtained by dissolving 2.0 g. of 4-hydroxybiphenyl in 350 cc. of warm ammonium hydroxide followed by cooling as low as possible without precipitation. Six grams of iodine in one liter of potassium iodide solution was added with rapid stirring over a period of one hour. Upon the first appearance of a dark residue the dropwise titration was discontinued since otherwise the solution became dark. This appearance which is also mentioned by Harington appears after the addition of about 95% of the iodine. The white precipitate was filtered by gravity, light being excluded. Upon drying in a cool, dark place, a 79.5% yield of the ammonium salt of 3,5-diiodo-4-hydroxybiphenyl was obtained; m. p. for the white crystals, 95–97°. Upon standing the precipitate

(9) Brazier and McCombie, *J. Chem. Soc.*, **101**, 970 (1912).

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slowly turned yellow, the melting point falling to 92–93°. The yellow samples upon analysis appeared to have lost iodine.

Anal. Calcd. for $C_{12}H_8OI_2$: I, 57.86. Found: I, 55.10.

The 3,5-diiodo-4-hydroxybiphenyl set free from a sample of this ammonium salt gave white needles which readily decomposed.

(b) Seventeen grams of 4-hydroxybiphenyl was dissolved in 40 ml. of glacial acetic acid. To this mixture, 45 g. of iodine monochloride dissolved in 25 ml. of glacial acetic acid was added dropwise over a period of one-half hour. The mixture was then refluxed on a steam-bath for two hours. Hydrogen chloride gas was liberated freely during the reaction. After this treatment the mixture was cooled to room temperature and poured into a large volume of ice-water. A pale yellow solid and an oily, brown substance separated. Solid sodium bisulfite was added to the mixture in order to remove the iodine to some extent. The water soluble constituents of the mixture were decanted and the remaining portion extracted with carbon tetrachloride. The carbon tetrachloride solution was washed with sodium bisulfite solution which removed the remaining iodine and was then washed with water and dried over anhydrous sodium sulfate.

After the solution had dried, its volume was reduced to one-fourth the original volume by distillation under reduced pressure. Addition of petroleum ether to the remaining solution caused 21 g. of a white precipitate to separate. After dissolving the precipitate in chloroform and precipitating it from solution by the addition of petroleum ether several times and finally recrystallization from the mixed solvent of one-third chloroform and two-thirds petroleum ether (b. p. 30–35°), the yield was reduced to 4.8 g. The pure white solid melted at 86–87°.

Anal. Calcd. for $C_{12}H_8OI_2$: I, 60.15. Found: I, 60.07.

Benzoylation of 3,5-Diiodo-4-hydroxybiphenyl.—The procedure used to prepare 3,5-diiodo-4-benzoxybiphenyl was the same as given above for the preparation of 3-iodo-4-benzoxydiphenyl. The product was recrystallized from ethanol. The resulting white needles melted at 159–160°.

Anal. Calcd. for $C_{19}H_{12}O_2I_2$: I, 48.24. Found: I, 47.80.

Attempted Triiodination of 4-Hydroxybiphenyl.—Several attempts were made to prepare this compound in the manner described above for the mono- and diiodination of 4-hydroxybiphenyl by varying the solvent, the time of reaction and external heat applied. In each attempt, however, isolation of the desired product was unsuccessful.

Summary

4-Hydroxybiphenyl has been mono- and diiodinated forming 3-iodo-4-hydroxybiphenyl and 3,5-diiodo-4-hydroxybiphenyl, respectively. They were identified by analysis and analogy to the chlorination and bromination products of 4-hydroxybiphenyl.

Attempts to triiodinate 4-hydroxybiphenyl were unsuccessful.

The benzoate derivatives of the above mono- and diiodo-hydroxybiphenyls have been prepared. The mononitro derivative of 3-iodo-4-hydroxybiphenyl also has been obtained.

NORMAN, OKLAHOMA
AUSTIN, TEXAS
RECEIVED OCTOBER 1, 1943

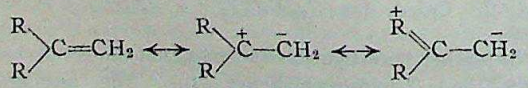
[CONTRIBUTION FROM THE MARIAN EDWARDS PARK LABORATORY OF BRYN MAWR COLLEGE]

The Condensation of Naphthoquinones with Polar Ethylenes

BY MARSHALL GATES

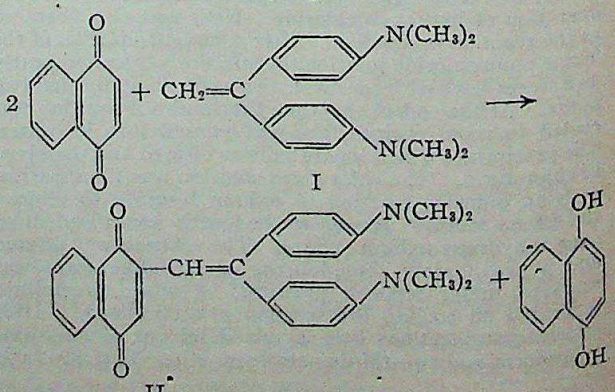
In 1939 Wizinger and Coenen[1] showed that a carbon–carbon bond could be established by displacement of chlorine from polynitro aromatic chlorides using as displacing agents certain unsymmetrically substituted ethylenes.

The ethylenes involved were of the type whose members readily form halochromic salts and show reactions with other types of electron acceptors.[2] Their reactions indicate large contributions from forms in which the ethylenic link is polarized



Since many of the reactions of quinones involve the addition of a molecule with an unshared electron pair to the conjugated system of the quinone, it might be expected that a carbon–carbon bond could be established by the action of a polar ethylene of the above-mentioned type acting as an electron donor on a quinone acting as an electron accepting center. This expectation was fully realized and a number of condensations of this type were found to take place with ease.

To provide a trial free from the complicating side reactions which might be expected of benzoquinone, the action of 1,1-bis-(*p*-dimethylaminophenyl)-ethylene (I) on α-naphthoquinone was studied. On mixing these two reagents in benzene, acetone or dioxane, an intense deep purple color is produced immediately even at room temperature, and on standing the solution deposits beautiful fine purple needles of 2-(1′,4′-



I

II

(1) Wizinger and Coenen, *J. prakt. Chem.*, **153**, 127 (1939).
(2) Pfeiffer and Wizinger, *Ann.*, **461**, 132 (1928).

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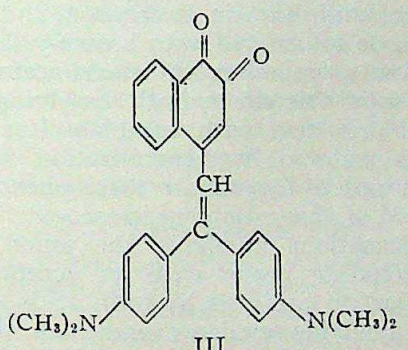
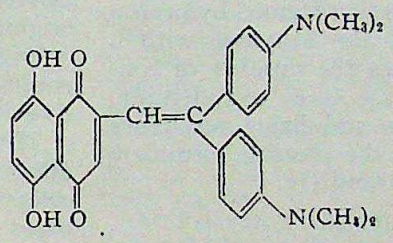
naphthoquinonyl-2′)-1,1-bis-(*p*-dimethylaminophenyl)-ethylene (II). The best preparative procedure for this condensation product involves heating two molecular equivalents of quinone with one of ethylene to 70° for twenty-four hours in dioxane. Under these conditions II separates in a directly pure condition in 59% yield, m. p. 271–272.5° (cor.). From the filtrate α-naphthohydroquinone, characterized as its diacetate and by oxidation to the starting quinone, was obtained in 95% yield (crude). The expected reaction course, in which the intermediate hydroquinone of II is oxidized to the quinone at the expense of a molecule of starting quinone, is followed. The sparingly soluble condensation product II was characterized by analysis and by reductive acetylation to a greenish-yellow leucodiacetate.

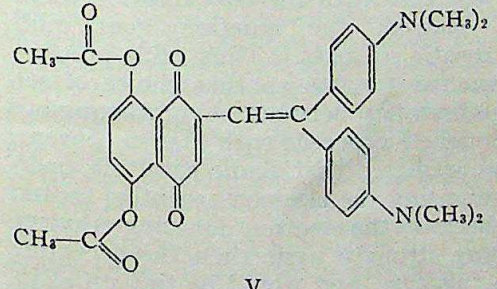
Using freshly prepared β-naphthoquinone, an even more facile condensation afforded 2-(1′,2′-



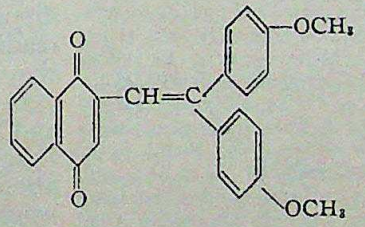
III



IV



V



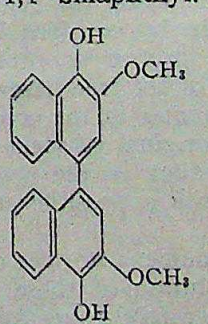
VI

naphthoquinonyl-4′)-1,1-bis-(*p*-dimethylaminophenyl)-ethylene (III) as deep blue-black needles (indigo blue in solution) in 83.7% yield. It was characterized as its deep red azine and as its canary-yellow leucodiacetate. Other successful condensations using the same ethylene include those with naphthazarin and naphthazarin diacetate, leading to the related condensation products IV and V, respectively.

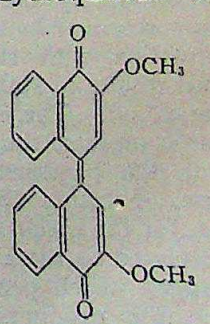
Although poor yields were obtained in the case of the naphthazarin derivatives, purification losses were high and it is believed that the yields of pure material do not reflect the extent of condensation. The condensation product from naphthazarin crystallizes from benzene in beautiful black needles which exhibit a faint deep green surface luster, m. p. 306–308° (uncor.). Naphthazarin diacetate gives V as an amorphous indigo-blue solid, m. p. 261–264°, which can be hydrolyzed to IV with acid. The sparingly soluble 5,8-diacetoxy-1,4-naphthohydroquinone was isolated in 58% yield as the expected by-product.

Condensation of the desired type was not obtained using 2-methyl-1,4-naphthoquinone and I. A compound apparently derived from two moles of quinone and one of ethylene was obtained in low yield but its structure has not been established. The failure of 2-methyl-1,4-naphthoquinone to undergo easy condensation was not entirely unexpected since Fieser and Seligman[3] showed that the presence of a methyl group in the quinonoid ring of 1,4-naphthoquinone materially reduces its ability to undergo 1,4-additions.

Extension of this reaction to the preparation of condensation products of 1,1-dianisylethylene was successful at least in the case of α-naphthoquinone. In keeping with the less highly polar nature of this ethylene, as exhibited by its weaker proton affinity,[1] condensation took place only slowly to give 2-(1′,4′-naphthoquinonyl-2′)-1,1-dianisylethylene (VI) as fine deep orange-red needles. An attempt to condense 1,1-dianisylethylene with β-naphthoquinone in methanol failed to yield a condensation product containing the ethylene, but in addition to 8% of 2-methoxy-1,4-naphthoquinone, gave rise to 43% of a high melting (275°) hydroquinone, $C_{22}H_{14}O_4$, containing two methoxyl groups. On methylation with dimethyl sulfate this gave the known[4] 3,4,3′,4′-tetramethoxy-1,1′-binaphthyl. The hydroquinone can



VII



VIII

(3) Fieser and Seligman, THIS JOURNAL, 56, 2690 (1934).
(4) Straus, Bernoully and Mautner, *Ann.*, 444, 165 (1925).

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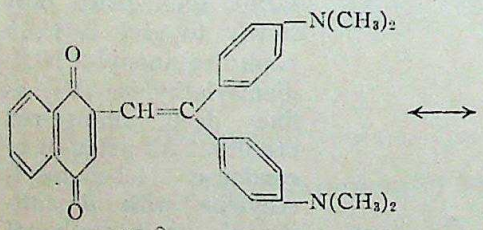
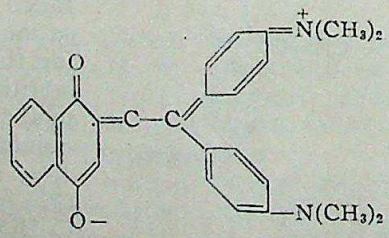
probably be assigned the structure VII, since oxidation with silver oxide gave the hitherto unknown dimethyl ether of Stenhouse and Groves's[5] "dinaphthyl diquinhydrone" as a deep magenta-colored quinone, m. p. 260–262° (VIII).

The deep purple-black condensation product II derived from α-naphthoquinone and 1,1-bis-(*p*-dimethylaminophenyl)-ethylene dissolves readily in 3 *N* hydrochloric acid to give a bright yellow solution. Dilution of this hydrochloric acid solution with a large volume of water causes the original quinone to separate as a purple-black solid. The bright scarlet 3 *N* hydrochloric acid solution of IV likewise precipitates the original blue-black solid on strong dilution. These observations indicate that condensation of 1,1-bis-(*p*-dimethylaminophenyl)ethylene with α-naphthoquinones results in a considerable decrease in basicity. An explanation of this is provided by a comparison of the structure of the free base with that of the cation formed by proton addition. Conjugation of the ethylene with a quinonoid nucleus increases the number of contributing forms of the free base considerably, and thereby increases the stabilizing resonance of the free base. Two of the possible forms are represented by formulas II and IIa.



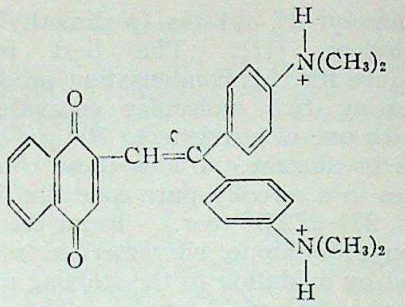
II



II a

On the other hand, this increased resonance is not shown by the cation, in which the electron pairs responsible are tied up by covalent bond formation with the added proton or protons. This results in stabilization of the free base over the cation. The effect is greater in the condensation product than in the original ethylene and thus the condensation product is the weaker base. Formula IX represents a possible structure for the cation.

Related to the above phenomena are the color changes which occur on solution of these condensation products in moderately concentrated solutions of strong acids. Thus the deep purple-black II gives a bright yellow solution, IV gives



IX

a brilliant scarlet-red solution, and III (deep indigo blue) gives an orange-brown solution in 3 *N* hydrochloric acid. Since deep color is associated with the high electronic mobility of extensively conjugated systems to which many forms contribute,[6] elimination of part of these contributing forms as shown above should lighten the color.[7] Qualitatively, at least, elimination of this resonance restores the color attributable to the original quinones alone, since α-naphthoquinone is bright yellow, naphthazarin is crimson, and β-naphthoquinone is golden-yellow to brown-yellow. Even the yellow to yellow-green leucodiacetates of II and III show this effect, both dissolving in dilute hydrochloric acid with complete loss of color which is restored by neutralization with bases. It is hoped to investigate these phenomena with the aid of absorption spectroscopy.

Many condensations involving the union of an electron donating group with an accepting center are subject to catalysis by both acids and bases.[8] The available evidence indicates that this is not the case with the condensation under discussion. Indeed, the reaction goes quite readily in aprotic solvents. Thus while preparative convenience dictates another choice of solvent the condensation between α-naphthoquinone and the ethylene I proceeds with ease in benzene. It might be predicted that acidic catalysis, operating by activating the electron accepting center, would fail because the electron donating ethylene is much more strongly basic than the accepting quinone in this case, and would be tied up as its inactive salt. This prediction is verified by the complete failure of the reaction to proceed when glacial acetic acid is used as solvent.

Somewhat similar considerations indicate that basic catalysis is also unlikely. This type of catalysis, ordinarily effective because of proton capture from the electron donating component, cannot activate the donor in this case, since the donor is already basic and tends to gain rather than lose a proton. Experimentally it is found that even with the least basic ethylene examined (1,1-dianisylethylene), condensation with α-naphthoquinone goes with optimum yields when

(5) Stenhouse and Groves, *J. Chem. Soc.*, **33**, 418 (1878).

(6) Lewis and Calvin, *Chem. Rev.*, **25**, 273 (1939).

(7) Compare the cases of "reverse halochromism" described by Brooker, Sprague, Smyth and Lewis, THIS JOURNAL, **62**, 1116 (1940).

(8) For examples, see Hauser and co-workers, Abstracts, Ninth National Organic Chemistry Symposium, 1941, p. 84.

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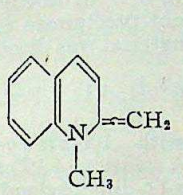
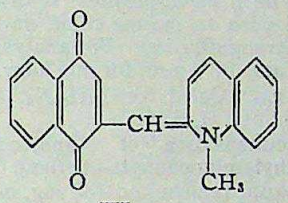
no added basic catalyst (dimethylaniline) is present.

It is planned to extend this work to other series of quinones and polar ethylenes, and at least a start has been made in this direction. Thus with the expectation of obtaining XI, α-naphthoquinone has been condensed with N-methyl-2-methylene-1,2-dihydroquinoline (X), although the condensation product has not been fully characterized



X



XI

The relationship of this condensation product to the cyanine dyes is apparent. Other members of this series should be available by this condensation.

An examination of the oxidation–reduction potentials of these condensed quinones should provide interesting data, and such determinations are to be made at the earliest opportunity.

The interruption of this work for the duration of the national emergency has prompted publication of the present incomplete report.

Experimental Part[9,10]

2-(1′,4′-Naphthoquinonyl-2′)-1,1-bis-(*p*-dimethylaminophenyl)-ethylene (II).—A solution of 1.16 g. of α-naphthoquinone in 15 ml. of warm dioxane was added to 0.973 g. of 1,1-bis-(*p*-dimethylaminophenyl)-ethylene[11] dissolved in 15 ml. of the same solvent. A dark purple-red color appeared immediately. The mixture, protected from light, was heated to 70° for twenty-three hours in a flask closed with a rubber stopper, then allowed to cool for four hours. The beautiful blue-black needles which had separated were collected and washed with cold dioxane; yield 906 mg. (59%), of directly pure material, m.p. 270.5–272°. The condensation product is very sparingly soluble in alcohol, acetone and glacial acetic acid, moderately soluble in boiling dioxane with a deep purple-blue color. Its solution in concentrated sulfuric acid is deep red-brown in color. It dissolves in 3 *N* hydrochloric acid to give a bright yellow solution, which on strong dilution with water gives first a greenish-yellow solution which then deposits the original material as a blue–black solid. A small portion was recrystallized twice from dioxane and dried at 78° and 0.1 mm. for analysis, m.p. 272–273.5°.

Anal. Calcd. for $C_{28}H_{26}O_2N_2$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.45; H, 6.04; N, 6.72.[12]

The original dioxane filtrate was diluted with somewhat more than an equal volume of water, then strongly acidified with dilute hydrochloric acid. The dirty brown solution thus obtained was extracted twice with ether, the ether layers washed with dilute hydrochloric acid, saturated brine, decolorized with norite, filtered through anhydrous sodium sulfate, concentrated and diluted with 30–60° petroleum ether to incipient crystallization. On cooling, 437 mg. of impure material, m. p. 175–179° with decomposition, was obtained. A second crop of 119 mg. was obtained from the filtrate; yield 95% (crude). Attempts to recrystallize this material from dilute alcohol in the presence of a little stannous chloride and hydrochloric acid were unsuccessful. Accordingly, 177 mg. was dissolved in 1 ml. of pyridine and treated with 0.5 ml. of acetic anhydride. After standing two hours, the mixture was heated to boiling and poured into water. The precipitated material was taken into ether, washed with dilute alkali several times, then with brine, filtered through anhydrous sulfate, and concentrated nearly to dryness. The residue on crystallization from alcohol afforded 127 mg. of light tan blades, m. p. 128–130°. Recrystallization gave 92 mg., m. p. 129–130°. Korn[13] records 128–130° for the m. p. of 1,4-diacetoxynaphthalene.

The remainder of the material, dissolved in alcohol–acetone, was treated with 1 g. of ferric chloride dissolved in dilute hydrochloric acid. A crop of orange-brown needles separated. These were collected, taken into ether, the ethereal solution treated with norite, filtered, concentrated, and diluted with petroleum ether. A crop of acicular blades separated, 86 mg., m. p. 121.5–125°. After recrystallization from ether, the material melted at 123.5–125.5° and did not depress the melting point of an authentic sample of α-naphthoquinone.

The original orienting experiments on this condensation were carried out using benzene as a solvent. The condensation takes place readily under these conditions but the by-product α-naphthohydroquinone is sparingly soluble in this solvent and contaminates the product. It can also be carried out in refluxing acetone to give good yields. However, the procedure given above yields the best product and is preferred.

The following describes an unsuccessful attempt to carry out the condensation using glacial acetic acid as a solvent. To the brilliant deep blue-green solution of 976 mg. of 1,1-bis-(*p*-dimethylaminophenyl)-ethylene in 6 ml. of glacial acetic acid was added a warm solution of 1.16 g. of α-naphthoquinone in 4 ml. of glacial acetic acid. Another 2 ml. of acid was used to wash in the quinone. The mixture was heated to 70° for sixty-seven hours, then allowed to cool. No crystalline material had deposited after standing for twenty-four hours. The desired product is very sparingly soluble in glacial acetic acid (74 mg. in 100 ml. at room temperature).

2-(1′,4′-Diacetoxynaphthyl-2′)-1,1-bis-(*p*-dimethylaminophenyl)-ethylene.—The condensation product II was reductively acetylated as follows: 502 mg. of II dissolved in 10 ml. of hot pyridine was treated with 0.4 g. of zinc dust and 5 ml. of acetic anhydride. On addition of the acetic anhydride the deep purple-black color changed to a light yellow-tan marked by an intense greenish fluorescence.

After standing ten minutes, the zinc was filtered off and washed with ether, the filtrate diluted with ether, washed three times with water, then three times with dilute alkali, once with water, finally with brine, and filtered through anhydrous sodium sulfate. The yellow solution thus obtained had the same intense greenish fluoresence observed in the reaction mixture. After removal of the ether the residual deep brown viscous oil on triturating under hexane solidified to a brown-yellow solid, 628 mg. (605 theoretical) m. p. 201–211°. In contrast to the starting quinone, this leucodiacetate crystallizes only with difficulty and purification was costly. The crude material (550 mg.), dissolved in the minimal quantity of hot dioxane was treated with a little hot water and allowed to cool. The first crop separated as a glassy crust, 205 mg., m. p. 227–230°, with decomposition. Dilution of the filtrate with alcohol gave 97 mg., m. p. 225–226°, dec. These two crops were combined, dissolved in the minimal quantity of hot dioxane, diluted with an equal volume of hot alcohol and allowed to crystallize. The solution still showed an intense fluorescence. Small compact prisms adhering to the walls of the flask were obtained, 181 mg., m. p. 228–230° with decom-

(9) All melting points are corrected except those specifically described as uncorrected.

(10) A preliminary condensation was carried out in collaboration with Mrs. Ray Longley.

(11) Pfeiffer and Wizinger, *loc. cit.* One crystallization from alcohol containing a trace of alkali yields an excellent product if the crude ethylene is subjected to preliminary vacuum distillation.

(12) Semimicro Dumas analysis by Miss Gladys Whitridge.

(13) Korn, *Ber.*, **17**, 3025 (1884).

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position. Two further crystallizations gave small yellow-tan prisms, m. p. 230–231° with decomposition. The m. p. depends somewhat on the rate of heating. For analysis the material was dried for three hours at 78° and 0.1 mm. It is sparingly soluble in alcohol, fairly soluble in acetone, and readily soluble in dioxane. Its solution in concentrated sulfuric acid is orange-red appearing canary-yellow to greenish-yellow in thin layers. It is soluble with complete loss of color in 3 *N* hydrochloric acid. Neutralization with dilute alkali gives a bright yellow precipitate of the unchanged leucodiacetate.

Anal. Calcd. for $C_{32}H_{32}O_4N_2$: C, 75.56; H, 6.34. Found: C, 75.20; H, 6.23.

2-(1′,2′-Naphthoquinonyl-4′)-1,1-bis-(*p*-dimethylaminophenyl)-ethylene (III).—To 2.32 g. of β-naphthoquinone[14] in 30 ml. of warm methanol was added a solution of 1.95 g. of 1,1-bis-(*p*-dimethylaminophenyl)-ethylene in 50 ml. of warm methanol. An immediate deep blue-green color was produced which on heating to boiling rapidly gave way to a deep indigo blue. At the end of a few minutes the product began to separate as fine violet-black prismatic blades. The reaction mixture was allowed to stand overnight at room temperature, then the product was collected and washed with cold methanol until the filtrate was clear blue with no reddish-purple tinge. After air drying, 2.58 g. (83.7%) of material, m. p. 194–196° was obtained. It is rather sparingly soluble in methanol, fairly soluble in hot acetone and dioxane to give deep indigo blue solutions. Its solution in concentrated sulfuric acid is a deep ultramarine color. It dissolves in 3 *N* hydrochloric acid with a brown color. Dilution has no effect on this color, nor does it cause precipitation of the free base. A small sample was recrystallized twice from acetone–methanol, then dried at 100° and 10^{-4} mm. for one hour, m. p. 199–201°, with gas evolution.

Anal. Calcd. for $C_{23}H_{26}O_2N_2$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.40; H, 6.10; N, 6.81.[15]

2-(1′,2′-Diacetoxynaphthyl-4′)-1,1-bis-(*p*-dimethylaminophenyl)-ethylene.—To 630 mg. of the condensation product III suspended in 5 ml. of acetic anhydride was added 0.4 g. of zinc dust, then 10 ml. of pyridine. The deep blue suspension rapidly gave way to a greenish-yellow fluorescent solution. After standing for fifteen minutes, the zinc dust was filtered off, washed with ether, then twice with hot pyridine, then again with ether. The light yellow filtrate was diluted with water, the yellow ethereal layer was separated, washed three times with water and then extracted twice with dilute hydrochloric acid. The nearly colorless acid layer on neutralization with solid sodium bicarbonate yielded a canary-yellow solid. A third acid extract gave no precipitate on neutralization. After air drying, this precipitate amounted to 738 mg. (97.4%), m.p. 95–102°. The material is sparingly soluble in cold methanol, readily soluble in benzene and chloroform. Its solution in hot acetone on cooling deposits the material as beautiful canary yellow needles, m. p. 92.5–94.5°, but the yield on crystallization is poor. Successive crops afforded a total of 541 mg. (71.5%), m. p. 93–94°. To avoid prohibitive crystallization losses, a mixture of acetone–hexane was used for subsequent purification of an analytical sample. The material is obtained in partially solvated form from mixtures containing acetone. Thus a sample of the above material after two further crystallizations melted at 96–96.8°, but after drying one hour at 78° and 10^{-4} mm., the m. p. was raised to 105.6–106.8°. It is soluble in concentrated sulfuric acid with a deep orange-red color which changes to red-purple on standing. Its solution in 3 *N* hydrochloric acid is colorless. Neutralization precipitates the bright yellow solid.

Anal. Calcd. for $C_{32}H_{32}O_4N_2$: C, 75.56; H, 6.34. Found: C, 75.59; H, 6.64.

Azine of Condensation Product III.—A solution of 619 mg. of III and 168 mg. of *o*-phenylenediamine in 10 ml. of benzene was treated with 1 ml. of glacial acetic acid. On addition of the acetic acid and slight warming, the color changed from the original blue to a deep red-brown. The mixture was heated under reflux for ten minutes, then diluted with an equal volume of hexane and set aside. Collection of the crystallizate afforded 645 mg. (89%) of deep red prismatic needles, m.p. 244–246°, softening from 241°. Three further crystallizations of a small sample from benzene–hexane gave ruby-red blades, m. p. 246–247.5°. The azine is rather sparingly soluble in alcohol and acetone, readily soluble in hot acetic acid, hot dioxane or hot benzene. Its solution in concentrated sulfuric acid is a deep black-purple. It dissolves in 3 *N* hydrochloric acid with an orange color, and does not precipitate even on strong dilution. For analysis the material was dried at 78° and 10^{-4} mm. for one hour.

Anal. Calcd. for $C_{34}H_{30}N_4$: C, 82.56; H, 6.11. Found: C, 82.94; H, 6.15.

Condensation of Naphthazarin with 1,1-Bis-(*p*-dimethylaminophenyl)-ethylene (IV).—A solution of 190 mg. of naphthazarin and 133 mg. of 1,1-bis-(*p*-dimethylaminophenyl)-ethylene in 15 ml. of benzene was brought to boiling, then heated for twenty-four hours at 74° in the dark. The resulting deep red-purple solution was concentrated somewhat and set aside to crystallize. The crude material which separated was collected and recrystallized from benzene to give 54 mg. of black needles, m. p. 303–305° (uncor.). Recrystallization from hot benzene (deep blue-purple solution) gave 37 mg. of beautiful black needles with a faint deep green surface reflex, m. p. 306–308° (uncor.). Its solution in concentrated sulfuric acid is a beautiful intense deep purple color. It dissolves in 3 *N* hydrochloric acid with a deep crimson color, and on strong dilution separates out as a blue-black solid. A small amount suspended in alcohol (very sparingly soluble) gives a deep cornflower blue color on treatment with a drop of dilute alkali. The cornflower blue alkali salt thus formed is rather insoluble in water, but has some solubility in alcoholic solutions. The color produced is very similar to that produced when naphthazarin itself is treated with alkali. For analysis the material was dried at 78° and 10^{-4} mm. for one hour.

Anal. Calcd. for $C_{28}H_{26}O_4N_2$: C, 73.99; H, 5.77. Found: C, 74.27; H, 5.40.

A larger run using dioxane as a solvent gave 233 mg. of crude material, m. p. 290–296° (uncor.), starting from 500 mg. of naphthazarin, but attempts to purify this by solution first in dilute alcoholic alkali, then in dilute hydrochloric acid resulted in prohibitive losses, although a small amount of excellent material was obtained.

Condensation of Naphthazarin Diacetate with 1,1-Bis-(*p*-dimethylaminophenyl)-ethylene (V).—A solution of 402 mg. of naphthazarin diacetate[16] in 8 ml. of hot dioxane was treated with 192 mg. of 1,1-bis-(*p*-dimethylaminophenyl)-ethylene in 2 ml. of dioxane and heated to 78° for ninety hours protected from light. The reaction mixture became brown immediately, then gradually darkened to purple-red. Some very small well-formed colorless prisms separated along with some dark purple-red solid. The mixture of solids was filtered off (air dried, 286 mg.) and recrystallized once from dioxane and once from ethyl alcohol to give 133 mg. of colorless prismatic plates of 5,8-diacetoxy-1,4-naphtholhydroquinone,[17] m. p. 249–250°. The filtrate was diluted with water and the blue-black solid which precipitated was filtered off. In contrast to the other condensation products described, this material was not easily obtained in crystalline form. From its strongly concentrated dioxane solution only amorphous material separated (88 mg., m. p. 253–257°). Very slow recrystallization of this material yielded amorphous material along with some needles. A further crystallization gave 60 mg. of blue-black amorphous material, m. p. 261–264°. It is very sparingly soluble in alcohol, soluble in acetone, dioxane or benzene. Its solution in sulfuric acid is a beautiful deep purple color. It dissolves in 3 *N* hydrochloric acid to give a bright yellow solution which acquires a

(14) "Organic Syntheses," **17**, 68 (1937).

(15) Semimicro Dumas analysis by Miss Mathilde Beal.

(16) Thiele and Winter, *Ann.*, **311**, 348 (1900).

(17) Wheeler and Edwards, THIS JOURNAL, **39**, 2465 (1917).

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greenish tinge on dilution but fails to precipitate. For analysis the material was dried at 78° and 10^{-4} mm. for two hours.

Anal. Calcd. for $C_{32}H_{30}O_6N_2$: C, 71.36; H, 5.61. Found: C, 71.25; H, 5.23.

The material is readily hydrolyzed to the parent naphthazarin derivative as the following experiment shows.

A solution of 42 mg. of crude condensation product (m. p. 250–255°) in 3 ml. of dilute hydrochloric acid was heated to boiling for five minutes. As the solution was heated, the color changed from yellow-green to deep crimson. The hydrolytic mixture was diluted with water, neutralized with solid sodium bicarbonate, the precipitated blue-black solid was taken into benzene, filtered, concentrated and set aside to crystallize. Beautiful black needles of IV (20 mg.), m. p. 307–308° (uncor.), were obtained.

Condensation of 2-Methyl-1,4-naphthoquinone with 1,1-Bis-(*p*-dimethylaminophenyl)-ethylene.—The reddish purple methanol solution of 645 mg. of 2-methyl-1,4-naphthoquinone and 500 mg. of 1,1-bis-(*p*-dimethylaminophenyl)-ethylene was heated to boiling, then allowed to stand at room temperature. A considerable portion of the ethylene separated on cooling. After standing in the dark without attention for one month, the original color had changed to a deep green and small nodules of dark crystalline material had separated. These were quite insoluble even in the boiling solvent, and on collection appeared greenish gray. The material was taken into dioxane to give a deep purple solution which on crystallization yielded 311 mg. of light tan platelets, m. p. 285–295° (uncor.). Two further crystallizations from dioxane gave 105 mg. of yellow plates which when introduced into a copper melting point block at 290° melted at 298–300° (uncor.) after drying at 78° and 10^{-4} mm. for two hours. The melting point depends on the rate of heating. This material is soluble in dilute hydrochloric acid but is insoluble in alkali even on boiling. Its solution in concentrated sulfuric acid is a bright purple-blue which fades to a paler green-blue on standing. Analytical figures indicate that it is derived from two moles of quinone and one of ethylene. It has not been further characterized.

Anal. Calcd. for $C_{40}H_{40}O_4N_2$: C, 78.40; H, 6.58. Calcd. for $C_{40}H_{38}O_4N_2$: C, 78.66; H, 6.27. Found: C, 78.47; H, 6.57.

2-(1′,4′-Naphthoquinonyl-2′)-1,1-dianisylethylene (VI).—A solution of 500 mg. of α-naphthoquinone and 38 mg. of 1,1-dianisylethylene[2] in 10 ml. of methanol was refluxed for six days, when a small amount of the ethylene remained undissolved. After a day, the mixture had turned a dirty gray-green color and small amounts of bright orange fluffy solid could be discerned. At the end of the refluxing period the reaction mixture was filtered hot, the insoluble material washed thoroughly with hot methanol, then taken into hot benzene. After filtration to remove a small amount of dark green-brown material insoluble in benzene, the filtrate was diluted with hot methanol and allowed to crystallize. Fluffy balls of very fine orange needles separated, 139 mg. (35% based on ethylene utilized), m. p. 209–210°. A second crop of 18 mg., m. p. 208–210° was obtained from the filtrate; total yield 39.4%. Two further crystallizations from benzene–methanol gave 105 mg. of fluffy balls of very fine orange needles, m. p. 211.8–212.3°. The substance is very sparingly soluble in methanol, readily soluble in hot benzene. Its solution in concentrated sulfuric acid is a deep blue to blue-green color. It is not soluble in dilute acids. The sample was dried at 78° and 10^{-5} mm. for two hours for analysis.

Anal. Calcd. for $C_{26}H_{20}O_4$: C, 78.77; H, 5.09; 2 OCH_3, 15.66. Found: C, 78.85; H, 4.76; OCH_3, 15.59.

The original methanol filtrate on concentration and crystallization yielded 138 mg. of recovered ethylene as tan plates, m. p. 140–141.5°.

Earlier attempts to carry out this preparation in dioxane using anhydrous zinc chloride as a catalyst were unsuccessful, although the reaction was not heated so long as in the example given above.

An effort to speed up the condensation and improve the yield by use of dimethylaniline as a catalyst was likewise unsuccessful, although a small amount of the desired product was obtained. A description of this experiment follows:

A mixture of 500 mg. of α-naphthoquinone, 380 mg. of 1,1-dianisylethylene, 4 drops of dimethylaniline and 25 ml. of methanol was heated in a closed pressure bottle at 78–80° for forty-eight hours. After cooling, the precipitated solid was filtered off and washed with methanol. The insoluble residue amounted to 257 mg. and contained particles of the characteristic orange condensation product. It was taken into boiling benzene, filtered from some dark gray-brown insoluble material (49 mg.) and diluted with an equal volume of hot methanol. The desired condensation product was obtained in poor condition as orange brown fluffs, 37 mg., m. p. 206.5–208°, mixed m. p. with material obtained as above, 207–208.5°.

The filtrate from this crop on concentration and crystallization afforded 100 mg. of felty, fine gray-tan needles, m. p. 136–139°, which after two crystallizations from pure methanol formed nearly colorless plates, m. p. 141–141.5°. A mixed m. p. with the starting ethylene was not depressed.

The original methanol filtrate on concentration and crystallization yielded 226 mg. of nearly black very impure material, m. p. 123–128°, probably largely unchanged ethylene.

Attempted Condensation of β-Naphthoquinone and 1,1-Dianisylethylene.—A solution of 1.00 g. of β-naphthoquinone and 760 mg. of 1,1-dianisylethylene in 30 ml. of methanol was heated to boiling and set aside in the dark. A part of the ethylene separated on cooling. After standing for one month, the solution was again heated to boiling. The ethylene dissolved, but considerable insoluble material remained. This was filtered off, dissolved in boiling dioxane to give a wine-red solution, and crystallized. Compact, red-brown prisms were obtained, 469 mg. (43% crude), m. p. 273–276°. While this material dissolved in boiling dioxane to give a deep wine-red solution, it was noticed that the refluxing solvent washed crystalline material adhering to the flask walls almost colorless. Therefore a small amount of stannous chloride dissolved in hydrochloric acid was added. This caused complete removal of the wine-red color, and after two crystallizations, 355 mg. of very pale pink prisms was obtained, m. p. 277.5–278.8°, becoming brown a degree or so below the melting point. One further recrystallization from dioxane containing stannous chloride and hydrochloric acid gave 313 mg. of nearly colorless material of the same melting point. Its solution in concentrated sulfuric acid was a very deep black to black green color. For analysis one sample was dried two hours at 100° and 10^{-3} mm., and another sample was sublimed at 200° and 10^{-3} mm.

Anal. Calcd. for $C_{22}H_{18}O_4$: C, 76.27; H, 5.24; 2 OCH_3, 17.92. Found: (crystallized sample) C, 76.18; H, 5.41. Found: (sublimed sample) C, 76.37; H, 5.24; OCH_3, 17.41.

Eighty-three mg. of this material was suspended in a small amount of potassium hydroxide solution containing some sodium hydrosulfite. Complete solution did not occur even after further dilution with water, but the hard prisms gave way to a very fine suspension. This suspension was treated with 0.2 ml. of dimethyl sulfate, stoppered, and vigorously shaken. The methylation was repeated, using additional dimethyl sulfate and more alkali. The agglomerated solid material was filtered off, washed with water, then with methanol, and crystallized from methanol. A considerable portion was lost accidentally, but the remainder afforded 27 mg. of small plates, m. p. 145–147°. One further crystallization gave material melting at 146.5–148.5° which showed no depression in melting point when mixed with an authentic sample of 3,4,3′,4′-tetramethoxy-1,1′-binaphthyl[4] prepared by methylating a vatted sample of dinaphthyldiquinhydrone[5] with dimethyl sulfate.

The original methanol filtrate on concentration yielded 428 mg. of unchanged ethylene, m. p. 139–141°, mixed m. p. 140.5–142°. The filtrate from this crystallization on

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standing deposited 147 mg. (8%) of brick-red material, m. p. 177–180.5°. Recrystallization from methanol with the aid of charcoal gave 109 mg. light yellow needles, m. p. 180.5–181.5° whose mixed m. p. with an authentic sample of 2-methoxy-1,4-naphthoquinone of m. p. 181.2–182° was 180.5–181.7°.

Oxidation of VII.—A suspension of 40 mg. of VII, 200 mg. of silver oxide and some anhydrous magnesium sulfate in dioxane was warmed to facilitate solution. A brilliant deep magenta-purple was produced almost at once. After shaking for thirty minutes the suspension was heated to boiling and filtered. The deep magenta filtrate was concentrated to a small volume and set aside. An amorphous dark precipitate separated which was collected and washed with cold dioxane, yield 17 mg., m. p. 260–262°. When held above its melting point for a few minutes, the beautiful deep red melt fades to a yellow-brown. The material when dry possesses a deep greenish-bronze surface reflex. Its magenta-purple solution in dioxane on standing fades to a brown solution. A small amount in dioxane on treatment with dilute aqueous alkali fades through a tan to a light green-yellow solution. It dissolves in concentrated sulfuric acid with a deep green-black color. For analysis, the material was dried at 78° and 10^{-4} mm. for one hour.

Anal. Calcd. for $C_{22}H_{16}O_4$: C 76.73; H, 4.68; 2 OCH_3, 18.02. Found: C, 76.26; H, 4.79; OCH_3, 16.33.

Summary

1. Condensation reactions between 1,1-bis-(*p*-dimethylaminophenyl)-ethylene and α-naphthoquinone, β-naphthoquinone, naphthazarin, and naphthazarin diacetate as well as a similar condensation between 1,1-dianisylethylene and α-naphthoquinone have been described.

2. These condensations are those expected from a consideration of the electron donating capacity of the ethylene and the electron accepting capacity of the quinones involved. Present evidence indicates that the condensation is not catalyzed by acids or bases.

3. A discussion of certain points of interest in connection with the color and basicity of the condensation products is given.

BRYN MAWR, PENNSYLVANIA
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[CONTRIBUTION FROM THE IOWA AGRICULTURAL EXPERIMENT STATION]

The Structure of the "B" Modification of Starch from Film and Fiber Diffraction Diagrams[1]

BY R. E. RUNDLE, LESTER DAASCH AND DEXTER FRENCH

Introduction.—Of the unit cells proposed for the "A" (cereal) and "B" (tuber) modifications of a starch, those of Bear and French[2] are supported by the best diffraction data, and are altogether the most reasonable thus far proposed. Yet even their data, as they point out, were necessarily confined to those available from powder diagrams. Such data are not wholly adequate for the support of large unit cells for crystals of low symmetry, so that their results are left open to question.

Though the desirability of obtaining film and fiber diffraction diagrams for starch is obvious, attempts to prepare suitable films and fibers have been unsuccessful because whole starch was employed. The chief constituent of whole starch[3] is a highly branched component, amylopectin in Meyer's nomenclature,[4] where interruptions in the starch chains occur approximately every 20 glucose residues. The resulting unbranched portions of the chains are too short to produce satisfactory films or fibers.

Fortunately, it is now possible to isolate the unbranched (amylose) component present in most starches.[5] The unbranched chains in this component are probably in excess of 200 glucose units long,[6] and upon suitable treatment form both films and fibers. The production of these films and fibers and mention of the importance of their optical properties have been reported previously.[7] Recently Whistler and Hilbert have confirmed this property of amylose, finding that the acetate of this component of starch forms films with properties to be expected only for films of long, linear molecules.[8]

The diffraction diagrams from amylose retrograded at room temperature are quite like those from tuber starch granules and retrograded whole starch, so that the amylose component of starch can be used for the study of the crystalline portions of whole starch.

Preparation of the Samples.—A hot solution containing about 5% amylose is allowed to evaporate slowly, and the surface skins are removed carefully from time to time. The skins are allowed to dry on an aluminum sheet or ferrotype. Dry films thus prepared are only a few hundredths of a millimeter thick. The thicker films usually tend to curl or become distorted, but this can be overcome to some extent by doubling them while they are still wet.

Fibers which produce a "B" diffraction diagram are very difficult to prepare, and none that we have produced is of particularly high quality. The chief difficulty lies in the fact that plasticizers which can be used to aid in stretching produce fibers corresponding to new crystalline modifications of starch. These, of course, are of interest in

(1) Journal Paper No. J-1129 of the Iowa Agricultural Experiment Station, Ames, Iowa. Project 639. Supported in part by a grant from the Corn Industries Research Foundation.

(2) R. S. Bear and D. French, THIS JOURNAL, **63**, 2298 (1941).

(3) F. Bates, D. French and R. Rundle, *ibid.*, **65**, 142 (1943).

(4) K. Meyer, "Advances in Colloid Science," Interscience Publishers, Inc., New York, N. Y., 1942, pp. 142–162.

(5) T. J. Schoch, THIS JOURNAL, **64**, 2957 (1942). For an analysis of the component isolated by Schoch, and a discussion of structure, see (3).

(6) J. Foster and R. Hixon, *ibid.*, **65**, 618 (1943).

(7) R. Rundle and D. French, *ibid.*, **65**, 559 (1943).

(8) R. Whistler and G. Hilbert, "The Film-Forming Properties of the Acetates of Fractionated Starch," read before the Division of Sugar Chemistry, Am. Chem. Soc. convention, Detroit, 1943.

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themselves, and are reported in another paper.[9] Without plasticizers, amylose films are brittle and cannot be stretched enough to produce a high degree of orientation. So far we have been able to use only water with the starch if a "B" diffraction diagram is to be obtained.

The following method is effective for the preparation of "B" type fibers. A 3% amylose solution is allowed to evaporate near the boiling point until it becomes quite viscous. At this point a wire frame with one side movable is dipped into the solution, and a film is prepared by extending the area of the film as much as possible without breaking the film. The film is then allowed to dry in the frame. Though very thin, the dry film can be removed from the frame and narrow strips cut from it. The strips can be stretched when moistened with water. Those which have been extended 50% or more show definite fiber orientation by X-ray diffraction. Similar techniques can be used with plasticizers added to the solution. Better orientation can then be produced in the fibers, but the plasticizers thus far employed alter the diffraction diagram of the amylose.[9]

Optical Properties.—The amylose films are highly birefringent, both wet and dry, and in convergent polarized light they show a typically uniaxial, optically negative, interference pattern. Fibers produced from the strips of amylose film retard light most if its electric vector is along the fiber axis. Optically the fibers are quite like cellulose and protein fibers in this respect. It is now certain that in the "B" modification the direction of greatest polarizability of the starch molecule is along its greatest length.[10]

X-Ray Diffraction Diagrams.—Diffraction diagrams of both films and fibers were made using Cu K radiation, Ni filtered. The amylose films were mounted with the normal to the film at right angles to the X-ray beam. Patterns of the fibers were made with the fiber axis normal to the beam. The patterns are not so sharp as those obtained from wet starch granules, probably because the samples were too dry to produce the best diffraction patterns. Both films and fibers become rather weak and gummy and hard to handle when moist, and wet fibers could not be kept under tension.

Indexing of the Diffraction Diagrams.—The layer line separation of the fiber diagram gives a fiber spacing of about 10.6 Å. This corresponds to none of the dimensions of the unit suggested by Bear and French.[2] Indeed the fiber spacing is not at all explained by any previous cells suggested for starch, yet the maxima are clearly those of the "B" modification of starch (Table I). In indexing the fiber and film patterns, and in the determination of the unit cell for the "B" modification, reference was made to the powder patterns of "B" starch, since on it diffuse maxima could be located with much greater accuracy than on the oriented patterns.

In Table I, column 3, values of $(2 \sin \theta/\lambda)^2 \times 10^4$ were obtained by measurement of patterns from wet potato starch, taken according to the technique suggested by Bear and French.[2] Cu Kα radiation was used. At angles greater than those which they list $[(2 \sin \theta/\lambda)^2 \times 10^4 = 860]$ the maxima are rather diffuse and many are quite weak in intensity. It is probable, therefore, that not all maxima have been observed to the largest spacing given in Table I. However, the more intense maxima in this region can be measured with considerable accuracy on good powder diagrams and are included in the table.

Examination of the equatorial reflections of the fiber pattern indicated that they could be indexed by the equation

$$\sin^2 \theta_{(h0l)} = 0.00230h^2 + 0.00705l^2 \quad (1)$$

This corresponds well with the equation for reflection $(hk0)$ of the Bear and French unit.[2] It was observed that differences in the $\sin^2 \theta$ values of the powder diagram frequently involved 0.00525 and 0.02100, corresponding to $\lambda^2/4b_0^2$ and λ^2/b_0^2, where b_0 is the fiber axis determined by layer line measurement. The equation

$$\sin^2 \theta_{(hkl)} = 0.00230h^2 + 0.00525k^2 + 0.00705l^2 \quad (2)$$

was then tested, both against the measurable reflections of the powder diagrams and the intensifications noted on film and fiber diagrams. The results are recorded in Table I.

The film and fiber diagrams provide the severest test of the indexing. From the fiber diagram the middle index can be determined beyond question, since $k = 0$ in the equator, $k = 1$ in the first layer line, etc.

A film corresponds to rotation of a fiber about a normal to the fiber axis. If b_0 is again taken as the fiber axis the type of intensification of the various planes (hkl) about what would be the powder arcs permits the evaluation of k. On the film diagrams it was possible to note the intensification only for the low order reflections, where $k = 0$ or 1. For reflections $(h0l)$, the intensification is greatest in the equator (Fig. 1). Doublets, with a plane (hkl) and a plane $(h0l)$, showed no

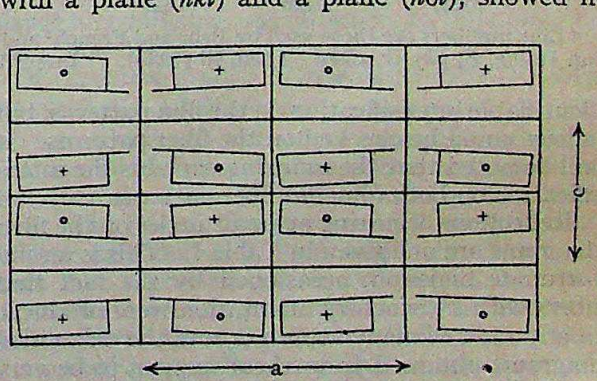

Fig. 1.—Symmetry requirements of space groups D_2^1 and D_2^2: Small circle indicates a chain running in one direction, across the other. For space group D_2^1 all chains running in the same direction are superimposable by translation along a_0 and c_0, together with rotation about b_0. D_2^2 differs only in that alternate chains running in the same direction are also transposed $^1/_2$ along b_0.

(9) R. E. Rundle and L. Daasch, *ibid.*, **65**, 2261 (1943).

(10) This statement has to be limited to certain modifications of starch, for in the "V" or helical configuration the greatest polarizability of the starch molecule is normal to its greatest length. See (7) and R. Rundle and R. Baldwin, *ibid.*, **65**, 554 (1943).

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TABLE I

X-RAY DATA FROM POWDER, FILM AND FIBER DIAGRAMS

No.[a]	Indices	$\left(\frac{2 \sin \theta}{\lambda}\right)^2 \times 10^4$ (Calcd.)	(Powder)	(Film)	(Fiber)	k-Obsd.	Intensity[b] (Powder)	(Film or fiber)
1	(100)	38.8	38.2	38.8	..	0-(film)	s	vs
	(010)	..		...	..	....	...	...
2a	(001)	119	123	...	..	....	...	...
	(110)	128		129	..	1-(film)	f	f
2b	(200)	155	157	159	..	0-(film)	vf	vf
	(101)	158						
	(011)	207	(196)	...	..	....	vvf	...
3a	(210)	244	244	244	244	1	m	m
	(111)	247						
3b	(201)	274	282	281	274	0	ms	ms
	(300)	350		345	345	0		s
4a	(020)	355	358	...	..	....	s	...
	(211)	363		361	358	1		vs
	(120)	393	..	...	..	....	...	...
	(310)	438	..	...	..	....	...	...
5a	(301)	469	478	462	473	0	f	f
	(002)	476						
	(220)	510						
5b	(121)	513	517	...	..	....	vvf	...
	(102)	515						
	(311)	557	..	...	..	....	...	...
	(012)	565						
					591	1-(fiber)		m
6a	(112)	604	598	(591)	621	0-(fiber)	ms	f
	(400)	621						
	(320)	704		...	701	2-(fiber)	ms	m
6b	(410)	710	713	...	?	?	ms	...
	(212)	720		...			ms	...
	(321)	823		...	..	....		...
7	(302)	826	832	...	..	....	m	...
	(411)	829		...	..	....		...
	(022)	831		...	..	....		...
	(420)	976	978	...	..	....	f	...
	(422)	986						
	(003)	1072	1067	...	..	....	f	...
	(322)	1180	1184	..	1182	2-(fiber)	m	f
	(132)	1320	1319	...	..	....	vf	...
	(023)	1426	1429	...	..	....	m	...

[a] Line numbers are those used by Bear and French[2] and correspond to the original numbering of the lines by Katz and van Itallie, *Z. physik. Chem.*, A150, 90 (1930). [b] Intensity notation—s, strong; m, moderate; f, faint and v, very.

identifiable intensification on the film patterns, but indices could be checked on the fiber patterns. It will be noted that the indexing explains the intensification on both film and fiber patterns.

Reflections occurring at small angles on the fiber diagrams are not given in Table I. This is an unfortunate omission, occasioned by the fact that fibers with satisfactory orientation were produced in but a few of many attempts, and the diffraction diagrams obtained from them happen to be very intense, with reflections at low angles obscured by the heavy background. Fortunately, the film patterns obtained are quite satisfactory for settling the middle index of these reflections.

The Unit Cell.—The unit cell dimensions, determined from the coefficients in equation (2), are

$a_0 = 16.0$ Å. $b_0 = 10.6$ Å. $c_0 = 9.2$ Å.

The cell is, within the limits of our observation, orthorhombic. The possibility cannot be excluded that the unit is monoclinic or triclinic with the angles between the axes very nearly 90°.

Two of the above dimensions, a_0 and c_0, are just those of the unit suggested by Bear and French.[2] Here, however, they are more unambiguously determined by the equatorial reflections on the fiber diagram. The fiber spacing, b_0, results directly from measurement of the layer-line spacings on the fiber diagram.

The volume of the unit cell of "B" starch is 1566×10^{-24} cc. If the density and water content assumed by Bear and French[2] are adopted, the carbohydrate density for starch is 1.23 g./cc. There are then 7.25 glucose residues per unit. The density, 1.50 g./cc., assumed by Bear and

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French, corresponds to the bulk density of starch. It seems far more likely that the X-ray density of a substance as porous as starch should materially exceed its bulk density. If it be assumed that there are eight glucose residues per unit cell, the X-ray carbohydrate density is 1.36 g./cc., and if it be assumed that tuber starches contain about 15% water, the X-ray density for starch is about 1.60 g./cc., as contrasted with 1.50 g./cc. for bulk starch. It appears entirely reasonable that the X-ray density should exceed the bulk density of starch by this amount.

It is worthy of note, too, that granular starch is by no means 100% crystalline material. Whole starch, from whatever source, contains a branched component, the branch points of which cannot be within the starch crystallites. Preliminary experiments indicate that the crystalline portions of most ordinary, granular starches constitute about 50–60% of the total granule. One would expect the amorphous parts of the starch granule to be less dense than the crystalline regions, so for this reason too the average starch density should be less than the X-ray density reported here.

The Structure of the "B" Modification.—The present fiber patterns from starch are not yet of a quality to be compared with those obtained from cellulose and other naturally occurring fibers, so that any structure proposed for the "B" modification of starch must remain more tentative in nature than those proposed for chitin, cellulose, etc. Nevertheless, the dimensions of the unit cell and the apparent symmetry of the cell suggest the gross aspects of the structure.

Most important is the fiber spacing. It is very surprising to find this spacing perhaps even larger than that for cellulose.[11] Space models of starch using the usual strainless configurations of the pyranose ring or the semiplanar Cox model[12] would make it appear that the starch chains should be far more crumpled than those of cellulose, resulting in a much shorter fiber spacing. Regardless of the validity of the rest of the unit cell, however, the fiber spacing of the "B" modification can no longer be in doubt by more than a few tenths of an Å., and must be very closely equal to that of cellulose. It would appear that closer attention to the special arrangement of the ring than that afforded by building space-filling models is deserved.

The dimensions of the unit cell are quite similar to those of the chitin unit cell,[13] except that the 16 Å. spacing is increased to 19 Å. in chitin. In chitin the glucose residues are arranged with the planes of the glucose rings nearly parallel to the 19 Å. axis, the normals to the rings approximately parallel to the 9 Å. spacing. The width of the chitin unit is about 9.5 Å. It is interesting to note that it decreases to about 8.5 Å. when half the acetyl groups are removed from the residues, as in chitosan.[14] A width of 8 Å., or just half the 16 Å. spacing, would be expected for the glucose unit in starch. It is noteworthy that the periodicity of the starch helix in the starch–iodine complex is 8 Å.[15] It is presumed that this corresponds to the width of the glucose residue.

The thickness of the glucose residue appears to be about 4.5 Å. in both chitin and starch and in the carbohydrates in general; this is half the 9 Å. spacing reported here. The gross structure of starch in the "B" modification probably resembles the chitin structure, in that the planes of the glucose residues are probably parallel to the largest spacing of the cell (Fig. 2).

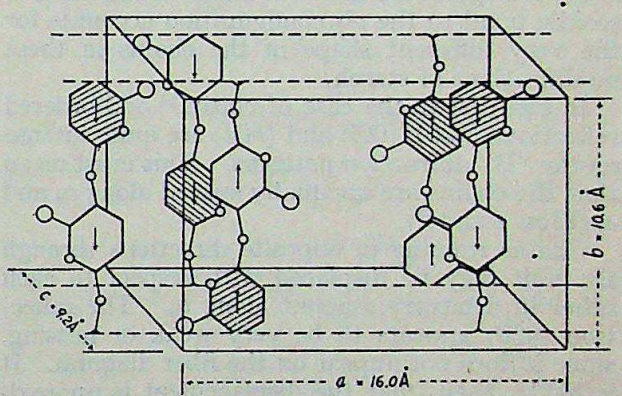

Fig. 2.—Structure of the "B" modification of starch: This structure is based on the space group D_2^1. An equally likely structure based on D_2^2 would differ only in having chains running the same direction in the unit-cell translated with respect to each other $^1/_2$ along b_0.

If the starch structure is orthorhombic, as appears likely, then the space group must be isomorphous with the point group D_2, since all other point groups of the orthorhombic system contain planes of symmetry, not allowable to the optically active starch chains.

Of the space groups isomorphous with D_2, only D_2^1–P222 and D_2^2–$P22_12$ are permitted by the observed reflections. The first requires that there be a two-fold axis parallel to the chains, the second that there be a two-fold screw axis in this direction. The failure to observe reflections (010) and (030) is not sufficient to establish the latter as more than a possibility. In either case the two-fold axes normal to the chains must run between the chains, and in either case half the chains will be running in one direction, half in the other, as indicated in Figs. 1 and 2. The only difference is that for the space group D_2^2 a translation $^1/_2$ along b_0 is also required. In cellulose fibers,[16] chitin fibers,[13] etc., it has been found that half the

(11) O. Sponsler and W. Dore, "Fourth Colloid Symposium Monograph," Chem. Catalog Co., Reinhold Publ. Corp., New York, N. Y., pp. 174–202.

(12) E. Cox, T. Goodwin and A. Wagstaff, *J. Chem. Soc.*, 1495 (1935).

(13) K. Meyer and G. Pankow, *Helv. Chim. Acta*, **18**, 589 (1935).

(14) G. Clark and A. Smith, *J. Chem. Phys.*, **40**, 863 (1936).

(15) R. Rundle and D. French, THIS JOURNAL, **65**, 1707 (1943).

(16) K. Meyer and L. Misch, *Helv. Chim. Acta*, **20**, 232 (1937).

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chains run in one direction, half in the other direction. This is most probably the case with starch too, and one of the above arrangements of the chains is probably approximately correct even if the starch structure is only pseudo-orthorhombic.

If adjacent glucose residues along the starch chain are identical in their configurations, the periodicity along the chain requires that adjacent glucose residues be rotated about b_0, so that the (CH_2OH) groups on adjacent glucose residues are *trans* to each other (Fig. 2). (This is also found to be the case in cellulose[16] and chitin,[13] where the glucosidic link is β.) The *trans* arrangement for starch in the "B" modification does not necessitate this arrangement in the "V" modification, where the chains assume a helical configuration.[15] Indeed, it is probable that a rotation about the glucosidic bond to the *cis* configuration accounts for the very different shape of the chains in these modifications of starch.

In contrast to the case of chitin,[14] odd-ordered reflections ($h00$), ($00l$) and ($h0l$) are quite intense on the "B" diffraction patterns. This must mean that the chains are unequally spaced along a_0 and c_0 (Figs. 1 and 2).

Chains running in opposite directions through the unit may be displaced with respect to each other in arbitrary amount along b_0. The reflection (020) appears to be very weak or missing, since it does not appear on the fiber diagram. It is likely, then, that the displacement is approximately $^1/_4\ b_0$.

The structure shown in Fig. 2 is in accord with these qualitative observations of intensities. It is based on the space group D_2^1, but a similar structure, based on D_2^2, with every other chain translated $^1/_2$ along b_0 is equally likely. Even if the structure is not truly orthorhombic the spacing and orientation of the chains should approximate, in its gross aspects, the structure shown in Fig. 2.

Bear and French[2] have established a close relationship between the "A," "B" and "C" modifications of starch. This relationship is independent of the validity of their unit cells, so that it should be found that the "A" and "C" unit cells resemble closely that reported here for the "B" modification.

It seems well to point out that in contrast to cellulose, the configuration of the starch chain depends upon how the starch is treated. The chains, fully extended in the "B" modification, become helices in the "V" modification and the starch–iodine complex, and assume an intermediate, crumpled form in the fibers prepared by the use of certain plasticizers.[9]

Summary

1. Methods for preparing films and fibers of the "B" modification of starch are outlined.

2. Film and fiber diffraction patterns of the "B" modification of starch have been prepared. The fiber axis is 10.6 Å.

3. A new unit cell for the "B" modification has been found, with $a_0 = 16.0$, $b_0 = 10.6$, $c_0 = 9.2$ Å. The structure is probably orthorhombic. There are 8 glucose residues per unit; the density of the crystalline portion of starch is about 1.6 g./cc.

4. A rough structure of the "B" modification of starch has been proposed on the basis of the unit cell dimensions and qualitative consideration of the intensities (Fig. 2).

5. It is pointed out that plasticizers useful in producing starch fibers generally alter the starch structure materially, and unlike the case of cellulose, the fiber spacing of starch is easily altered by treatment of the starch.

AMES, IA. RECEIVED JUNE 18, 1943

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

α,β-Diamino Ketones. I. Reactions of Heterocyclic Secondary Amines with α-Bromo-β-aminoketones[1]

BY NORMAN H. CROMWELL, CHARLES E. HARRIS AND DONALD J. CRAM

The reactions of α-bromo-α,β-unsaturated ketones with primary and secondary amines have been the subjects of several investigations in this Laboratory.[2] The development of an excellent method of preparing mixed α,β-diamino ketones from α-bromo-α,β-unsaturated ketones is one of the results of these investigations. From a knowledge of the mechanisms[2f] of these reactions it is possible to arrange the conditions in such a manner as to allow the preparation of many specific mixed diamino ketones of possible chemotherapeutic interest.

α-Bromo-β-morpholinobenzylacetone[2c] reacted readily with tetrahydroquinoline (which is a weaker base than morpholine) to give good yields of the expected α-morpholino-β-tetrahydroquinolinobenzylacetone (I). The structure of (I) was established by hydrolysis to give α-morpholinoacetone, isolated as its oxime. This same bromo amino ketone reacted in dry ether with piperidine (which is a stronger base than morpholine) to give very poor yields of α-morpholino-β-piperidino-

(1) Presented before the Division of Organic Chemistry, American Chemical Society, Pittsburgh, Pa., September 6, 1943.

(2) (a) Cromwell, *et al.*, THIS JOURNAL, **62**, 1672 (1940); (b) **62**, 2897 (1940); (c) **62**, 3470 (1940); (d) **63**, 837 (1941); (e) **63**, 2984 (1941); (f) **65**, 301 (1943); (g) **65**, 308 (1943); (h) **65**, 312 (1943).

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benzylacetone (II). In alcohol solution the product from this reaction seemed to be a mixture of all of the possible diamino ketones.[2d]

α-Bromo-β-piperidinobenzylacetone[2g] reacted readily either in dry ether or absolute alcohol with morpholine to give fair yields of the expected α-piperidino-β-morpholinobenzylacetone (III). Compound (III) was obtained in a high and a low melting form, probably the two possible racemates. Either of these two forms of (III) lowered the melting point of (II) considerably, when mixed with it. The diamino ketone (III) was hydrolyzed by acid solution to give the known α-piperidinoacetone, isolated as its oxime.[2f]

In the benzylacetophenone series it was found that tetrahydroisoquinoline added readily to α-bromobenzalacetophenone to give α-bromo-β-tetrahydroisoquinolinobenzylacetophenone (IV). This bromo amino ketone (IV) was found to be more stable in the presence of absolute alcohol than the analogous α-bromo-β-tetrahydroisoquinolinobenzylacetone which has been studied in a previous investigation.[2f] However, on long standing, alcoholic suspensions of (IV) did form small amounts of α,β-ditetrahydroisoquinolinobenzylacetophenone (V), indicating a decomposition of the bromo amino ketone, and the subsequent reaction of the tetrahydroisoquinoline, so formed, with unchanged (IV). The diamino ketone (V) was also prepared in good yields in the usual way from tetrahydroisoquinoline and α,β-dibromobenzylacetophenone.

(IV) reacted with morpholine (a base that seems to be weaker than tetrahydroisoquinoline), giving a fair yield of the expected α-tetrahydroisoquinolino-β-morpholinobenzylacetophenone (VI). Acid hydrolysis of this diamino ketone (VI) gave a good yield of the known ω-tetrahydroisoquinolinoacetophenone.[3] This bromo amino ketone (IV) also reacted readily with a weaker base, tetrahydroquinoline, to give a good yield of α-tetrahydroisoquinolino-β-tetrahydroquinolinobenzylacetophenone (VII).

When α-bromo-β-morpholinobenzylacetophenone[2b] reacted with tetrahydroisoquinoline, a mixed product was obtained as expected. From this mixed product a small amount of not quite pure α-morpholino-β-tetrahydroisoquinolinobenzylacetophenone (VIII) was separated.

α-Bromo-β-piperidinobenzylacetophenone[4] reacted with tetrahydroisoquinoline (which is a weaker base than piperidine) to give good yields of α-piperidino-β-tetrahydroisoquinolinobenzylacetophenone (IX). The structure of (IX) was established by acid hydrolysis. When this same bromo amino ketone reacted with cyclohexylamine (a weaker base than piperidine) a fair yield of α-piperidino-β-cyclohexylaminobenzylacetophenone (X) was obtained. This is the first mixed diamino ketone containing a primary amino group that has been prepared in these investigations.

Certain theoretical studies as well as several further practical applications of these reactions to prepare specific compounds are the subjects of other investigations in these Laboratories.

(3) Allewelt and Day, *J. Org. Chem.*, 6, 384 (1941).
(4) Dufraisse and Moureu, *Bull. soc. chim.*, (4°) 41, 457 (1927).

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TABLE I

PHYSICAL AND ANALYTICAL DATA

Diamino ketones	No.	M. p., °C., dec.	Yield, %	Formula	Percentage composition Calcd. C	Calcd. H	Found C	Found H
			Benzylacetones					
α-Morpholino-β-tetrahydroquinolino-[a]	(I)	173	51	$C_{23}H_{28}N_2O_2$	75.79	7.74	75.68	7.58
α-Morpholino-β-piperidino-[b]	(II)	123	10	$C_{19}H_{28}N_2O_2$	72.12	8.92	72.30	8.86
							71.75	8.87
α-Piperidino-β-morpholino-	(III)	117[c]						
		101[d]	32	$C_{19}H_{28}N_2O_2$	72.12	8.92	72.11	8.94
			Benzylacetophenones					
α,β-Ditetrahydroisoquinolino-	(V)	187	51	$C_{33}H_{32}N_2O$	83.86	6.83	83.67	6.88
α-Tetrahydroisoquinolino-β-morpholino-	(VI)	177	30	$C_{23}H_{30}N_2O_2$	78.84	7.09	78.76	7.10
α-Tetrahydroisoquinolino-β-tetrahydroquinolino-	(VII)	164	47	$C_{33}H_{32}N_2O$	83.86	6.83	83.69	6.90
α-Morpholino-β-tetrahydroisoquinolino-	(VIII)	163	15	$C_{23}H_{30}N_2O_2$	78.84	7.09	79.23	7.20
α-Piperidino-β-tetrahydroisoquinolino-	(IX)	165	37	$C_{29}H_{32}N_2O$	82.03	7.60	82.15	7.62
α-Piperidino-β-cyclohexylamino-	(X)	155	20	$C_{26}H_{33}N_2O$	80.16	8.54	79.98	8.62

[a] N, Calcd., 7.69. Found, 7.68. [b] N, Calcd., 8.86. Found, 9.06. [c] N, Calcd., 8.86. Found, 8.90. [d] N, Calcd., 8.86. Found, 8.92.

Experimental[5]

Derivatives of Benzylacetone

α-Morpholino-β-tetrahydroquinolinobenzylacetone (I).—To 114 ml. of absolute alcohol were added 57 g. (0.183 mole) of α-bromo-β-morpholinobenzylacetone[2c] and 49 g. (0.371 mole) of tetrahydroquinoline and the mixture allowed to stand at room temperature for two days. At the end of this time the precipitate was filtered, washed and recrystallized from chloroform and alcohol giving 34.3 g. (0.0943 mole) of a white crystalline product. This compound was soluble in benzene and chloroform, slightly soluble in ether, very slightly soluble in alcohol and in dilute hydrochloric acid, and 0.1 g. was soluble in 10 ml. of absolute alcohol containing 0.95 g. of dry hydrogen chloride gas. This preparation was repeated using ether as a solvent. A white crystalline product was obtained, in 20.4% yield, which was identical with (I).

Hydrolysis.—Acid hydrolysis of the diamino ketone (I) in the usual way[2f] gave benzaldehyde, tetrahydroquinoline (isolated as the benzene sulfonamide) and the water soluble α-morpholinoacetone (isolated as its water soluble oxime, recrystallized from petroleum ether and benzene, m. p. 104–106°).

Anal. Calcd. for $C_7H_{14}N_2O_2$: C, 53.14; H, 8.92. Found: C, 53.42; H, 8.98.

α-Morpholino-β-piperidinobenzylacetone (II).—In 10 ml. of dry ether were placed 5 g. (0.0160 mole) of α-bromo-β-morpholinobenzylacetone[2c] and 2.8 g. (0.0320 mole) of piperidine and the mixture allowed to stand in the icebox for two days. At the end of this time the precipitate was filtered but it all proved to be water soluble. The filtrate was evaporated and the resulting oil taken up in alcohol and a white solid obtained which after four recrystallizations from alcohol and water gave 0.5 g. (0.00158 mole) of a white crystalline product m. p. 118–123°. A mixed melting point with α,β-dimorpholinobenzylacetone[2c] gave m. p. 108–132°, and with α,β-dipiperidinobenzylacetone[2g] gave m. p. 100–110°. This reaction was also carried out in alcohol but a mixture impossible to separate was obtained.

α-Piperidino-β-morpholinobenzylacetone (III).—To 25 ml. of absolute alcohol were added 12 g. (0.0387 mole) of α-bromo-β-piperidinobenzylacetone[2g] and 6.74 g. (0.0775 mole) of morpholine and the mixture allowed to stand at room temperature. The reaction took place with evolution of heat and was complete in about three hours. At the end of this time the precipitate was filtered and the product recrystallized three times from alcohol and water giving 2.4 g. of white needles, m. p. 115–117°. A mixed melting point experiment with this compound and α-morpholino-β-piperidinobenzylacetone (II) gave m. p. 90–111°; with α,β-dipiperidinobenzylacetone,[2g] m. p. 95–116°; and with α,β-dimorpholinobenzylacetone,[2c] m. p. 95–140°.

The reaction mixture filtrate was concentrated and cooled and a second crop of crystals came out, which, after recrystallization from alcohol and water, gave 1.5 g. of white crystalline compound, m. p. 100–101°. A mixed melting point of the two racemates gave m. p. 102–114°; a mixed melting point of the lower melting racemate with α,β-dipiperidinobenzylacetone[2g] gave m. p. 92–116°; with α,β-dimorpholinobenzylacetone,[2c] m. p. 93–140°; and with α-morpholino-β-piperidinobenzylacetone (II), m. p. 90–110°.

This reaction was also carried out in ether solution and a 40.2% yield of product was obtained, m. p. 102–114°, which when mixed with a mixture of the two racemates gave m. p. 103–114°. An analysis of this product also agreed with the formula, $C_{19}H_{28}N_2O_2$.

Hydrolysis.—Acid hydrolysis of the mixed racemates of (III) in the usual way gave α-piperidinoacetone, isolated as its oxime, m. p. 122–123°.[2f] No α-morpholinoacetone was detected.

Derivatives of Benzylacetophenone

α-Bromo-β-tetrahydroisoquinolinobenzylacetophenone (IV).—In 20 ml. of a 50% ether–petroleum ether (b. p. 37°) solution was dissolved 10 g. (0.035 mole) of α-bromobenzalacetophenone[2b] and the solution cooled to −10° in an ice–salt mixture. Previously cooled tetrahydroisoquinoline (0.035 mole (4.65 g.)) was added to the cold mixture with shaking. The resulting solution was allowed to stand well-corked for two hours at −10°. The white product (12.5 g.) was filtered off, washed with 50% ether-petroleum ether, and dried *in vacuo*, m. p. 117°, yield 85%.

(5) All m. p. are corrected and determined by placing sample in bath 10° below m. p. and heating at the rate of 3° per minute. Micro Dumas analyses for nitrogen and semimicro carbon–hydrogen analyses by the Analytical Laboratory, Department of Chemistry, University of Nebraska, under the supervision of H. Armin Pagel.

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Anal. Calcd. for $C_{24}H_{22}NOBr$: C, 68.57; H, 5.28. Found: C, 68.80, 68.52; H, 5.36, 5.42.

This bromo amino ketone reacted with sodium ethoxide in the usual way to give a red oily product which was probably the α-tetrahydroisoquinolinobenzalacetophenone. All attempts to crystallize this oil failed.

When a sample of (IV) was allowed to stand in absolute alcohol at room temperature for one week a small amount (about 20%) of the addition product decomposed[2f] to give α-bromobenzalacetophenone and tetrahydroisoquinoline. This was shown by the isolation of a 10% yield of α,β-ditetrahydroisoquinolinobenzylacetophenone (V), m. p. 184–186°, identical with that prepared from α,β-dibromobenzylacetophenone as described below.

α,β-Ditetrahydroisoquinolinobenzylacetophenone (V).—In 20 ml. of absolute alcohol was suspended 5 g. (0.0136 mole) of α,β-dibromobenzylacetophenone and the mixture cooled to 0°. Tetrahydroisoquinoline (8 g. (0.060 mole)) was added rapidly while shaking. The solution at first remained white, but then changed to an orange color. After allowing it to stand for two days at room temperature, during which time the mixture was shaken and worked with a spatula, the white precipitate was filtered off and washed well with petroleum ether and then with water. The crude product was recrystallized twice from benzene–petroleum ether (b. p. 80°) mixtures to give 4.4 g. of a white product.

α-Tetrahydroisoquinolino-β-morpholinobenzylacetophenone (VI).—In 15 ml. of dry ether and 5 ml. of absolute alcohol, were suspended 5 g. (0.012 mole) of (IV) and 3.6 g. (0.024 mole) of morpholine added. After standing overnight at room temperature the red-colored solution was filtered, the precipitate washed with petroleum ether and then with water. After three recrystallizations from a chloroform–alcohol mixture and two from a benzene–petroleum ether mixture, 1.7 g. of pale yellow crystals was obtained.

Hydrolysis.—Acid hydrolysis (40 ml., 15% sulfuric acid) of the diamino ketone (VI) (4.0 g.) in the ordinary manner[2e] gave 1.65 g. of ω-tetrahydroisoquinolinoacetophenone, identical with a sample prepared from ω-bromoacetophenone.[3]

Other mixed diamino ketones prepared by essentially[6] this same procedure were: (VII) from (IV) and two equivalents of tetrahydroquinoline; (VIII) from α-bromo-β-morpholinobenzylacetophenone[2b] and tetrahydroisoquinoline (mixed m. p. of (VI) with (VIII), 150–163°; hydrolysis of (VIII) gave mainly ω-morpholinoacetophenone[2b] and traces of ω-tetrahydroisoquinolinoacetophenone[3] along with tetrahydroisoquinoline and benzaldehyde); (IX) from α-bromo-β-piperidinobenzylacetophenone[4] and tetrahydroisoquinoline (hydrolysis of (IX) gave ω-piperidinoacetophenone, isolated as its hydrochloride[2d]); (X) from α-bromo-β-piperidinobenzylacetophenone[4] and cyclohexylamine.

Summary

1. The preparation of one new α-bromo-β-amino ketone and nine new diamino ketones has been described.

(6) The amount of absolute alcohol in the reaction medium and the time for reaction varied slightly in each individual case.

LINCOLN, NEBRASKA RECEIVED JUNE 7, 1943

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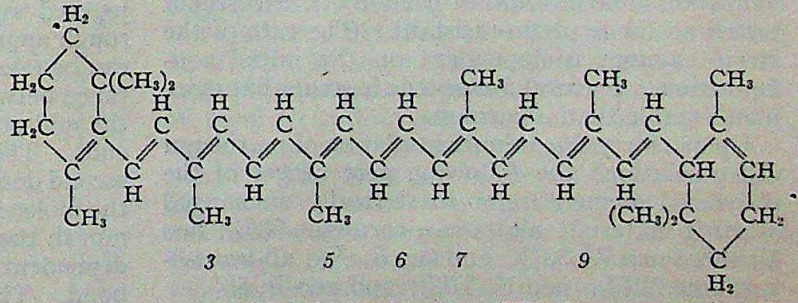
cis–trans Isomerization and *cis*-Peak Effect in the α-Carotene Set and in Some Other Stereoisomeric Sets

BY L. ZECHMEISTER AND A. POLGÁR

As far as we know, no up-to-date study of the stereoisomerization of α-carotene[1] is available while a more detailed investigation has been presented for β-carotene.[2] The α-carotene molecule includes five double bonds which are available for *trans*→*cis* rotations (see the formula), the number of stereoisomers being thirty-two.[3]

It was first assumed[4] that the all-*trans* member of a stereoisomeric hydrocarbon set possesses greater adsorption affinity than any other member of the set but this postulate must now be abandoned for both carotene sets mentioned.

A re-investigation of α-carotene showed the presence of the eleven isomers listed in Table I of which neo-α-carotene U and W have been crystallized.



All-*trans*-α-carotene. (The double bonds available for a *trans*→*cis* shift are numbered.)[5]

The ratio of stereoisomers is dependent on the method of isomerization (Table II).

(1) A. E. Gillam, M. S. El Ridi and S. K. Kon, *Biochem. J.*, **31**, 1605 (1937).

(2) A. Polgár and L. Zechmeister, THIS JOURNAL, **64**, 1856 (1942).

(3) L. Pauling, *Fortschr. Chem. organ. Naturstoffe*, **3**, 203 (1939); *cf.* L. Zechmeister, A. L. LeRosen, F. W. Went and L. Pauling, *Proc. Natl. Acad. Sci.*, **27**, 468 (1941).

(4) L. Zechmeister and P. Tuzson, *Ber.*, **72**, 1340 (1939); L. Zechmeister, L. Cholnoky and A. Polgár, *ibid.*, **72**, 1678 (1939).

(5) The following *nomenclature* is proposed. Each double bond of the *conjugated system* will be assigned an *italicized* number in order to avoid confusion with the numbering of carbon atoms: *e. g.*, *3,6*-di-*cis*-β-carotene. The lowest number will be given to the double bond in the β-ionone ring or, if the double bond of this ring is not part of the chromophore, to the conjugated double bond nearest the β-ionone ring. In the absence of such a system an α-ionone ring receives preference over an aliphatic terminal group.

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TABLE I

VISUALLY DETERMINED SPECTRAL MAXIMA OF OBSERVED MEMBERS OF THE STEREOISOMERIC α-CAROTENE SET IN THE SEQUENCE OF DECREASING ADSORPTION AFFINITY

Name	Maxima in petroleum ether (b. p. 60–70°), mμ	
Neo-α-carotene U	471.5	441.5
Neo-α-carotene V	465.5	437
Neo-α-carotene W	470.5	441
Neo-α-carotene X	463.5	435
Neo-α-carotene Y	467.5	437
All-*trans*-α-carotene	477	446.5
Neo-α-carotene A	468.5	439
Neo-α-carotene B	466.5	437
Neo-α-carotene C	472.5	442.5
Neo-α-carotene D	460	432
Neo-α-carotene E	461.5	433.5

TABLE II

RELATIVE COLORIMETRIC VALUES OF THE MAIN PRODUCTS OF STEROISOMERIZATION OF ALL-*trans*-α-CAROTENE BY VARIOUS METHODS

Method	All-*trans*	Neo U	Neo W	Neo B	Other isomers
Refluxing	92	4	—	4	—
Iodine catalysis (in light)	65	8.5	8	13	5.5
Acid catalysis (10% HI)	64.5	5	24	4.5	2
Acid catalysis (37% HCl)	50	13	15	9	13
Melting crystals	35	12	19	14	20

For effective iodine catalysis diffuse daylight or illumination is required.

Exposure to sunshine ("insolation") in the absence of catalysts is a recent addition to isomerization methods. Even when gradual destruction takes place, this irreversible change does not hinder the chromatographic study of the stereoisomerization. We wish to emphasize that the configuration of no all-*trans* or partially *cis* carotenoid tested so far is photo-resistant. The rate of the steric changes is dependent on the initial configuration. Natural β-carotene is somewhat more photo-stable than α-carotene.

Upon a forty-five minute insolation of petroleum ether solutions the following percentages of the recovered pigment refer to sterically unchanged starting material: all-*trans*-α-carotene, 93%; neo V, 43%; neo W, 33%; and neo B, 8%; all-*trans*-β-carotene, 98%; neo U, 37%; and neo B, 5%.

A study of the "*cis*-peak" effect has been of aid in establishing the most probable configuration of some stereoisomers. While it had been found by several authors that the extinction maxima of the ordinary carotenoids in the visible region decrease upon isomerization,[6] we observed that a new marked maximum develops simultaneously at some wave length between 320 and 380 mμ ("*cis*-peak").[7] The contribution of individual stereoisomers to the height of the *cis*-peak observed in equilibrium mixtures is very unequal in the β-carotene set. The greatest contribution is made by those neo-compounds which are adsorbed below the all-*trans* pigment while the U isomer contributes much less. We have now carried out a more detailed differentiation of individual *cis*-peak effects in the β-carotene, α-carotene, lutein, and lycopene sets as shown in Figs. 1 to 4.

If an all-*trans* carotenoid undergoes spatial changes, the bending of the molecule causes two different, easily observable optical effects which may be helpful in the assignment of a definite configuration to each isomer formed: (a) the visible maxima shift toward shorter wave lengths and (b) a *cis*-peak with characteristic height appears in the ultraviolet region. In possession of a sound theoretical basis, effect (a) would give us the number of *cis* double bonds and (b) would determine the general shape of the molecule, *i. e.*, the position of the *cis* bonds in the conjugated system. The main difficulty at present lies in the lack of precise information concerning the possible dependence of (a) on the position of the double bonds which have completed a *trans*→*cis* rotation. On the basis of the experimental material available it seems that the *trans*→*cis* rotation of one double bond displaces the longest wave length maximum in petroleum ether about 5 mμ toward shorter wave lengths. If this spectral shift equals approximately 10 mμ the presence of two *cis* double bonds is probable, etc.

It has been reported by Pauling, LeRosen, Schroeder and the authors[8] that a stereoisomer showing a very high *cis*-peak must possess a *cis* double bond at (or near) the center of the conjugated system. It was pointed out that as a rough approximation the intensity of the *cis*-peak can be taken proportional to the square of the distance between the center of the chromophore and the mid-point of the straight line between its two ends. The models show that the rotation of a second double bond into *cis* position will straighten the molecule considerably and accordingly will diminish the *cis*-peak. This effect is essentially independent of the position of the second double bond. The conditions are more complicated in the case of a chromophore containing an even number of conjugated double bonds (α-carotene) than in that of, for example, β-carotene. The center of the α-carotene chromophore is a single bond; two "central" double bonds, *5* and *6*, are present, each of which has four other conjugated double bonds on one side and five on the other. These "central" double bonds, while structurally different in α-carotene, are equivalent from the

(6) *Cf. e. g.*, some curves of original and isomerized pigments in the visible region: H. H. Strain, "Leaf Xanthophylls," Carnegie Inst. of Washington (1938); *J. Biol. Chem.*, **127**, 191 (1939); B. W. Beadle and F. P. Zscheile, *ibid.*, **144**, 21 (1942); J. W. White, F. P. Zscheile and A. M. Brunson, THIS JOURNAL, **64**, 2603 (1942); J. W. White, A. M. Brunson and F. P. Zscheile, *Ind. Eng. Chem., Anal. Ed.*, **14**, 798 (1942).

(7) L. Zechmeister and A. Polgár, THIS JOURNAL, **65**, 1522 (1943).

(8) L. Zechmeister, A. L. LeRosen, W. A. Schroeder, A. Polgár and L. Pauling, *ibid.*, **65**, 1940 (1943).

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stereochemical viewpoint. Therefore, two of the mono-*cis*-α-carotenes can be expected to have much higher *cis*-peaks than any other isomer. Models show that the molecule of *5,6*-di-*cis*-α-carotene, the isomer which contains both "central" double bonds in *cis* position, is considerably straighter than either *5*- or *6*-mono-*cis*-α-carotene.

The following discussion in which some stereoisomers are tentatively given spatial structures is based on the foregoing considerations and on the optical data summarized in Table III. (Should stereoisomers be detected in the future which possess higher *cis*-peaks than any of the members of the set known at the present, a revision of our assignments of spatial structures in that particular set would become necessary.)

TABLE III

TYPICAL SPECTROSCOPIC DATA FOR SOME MEMBERS OF THE STEREOISOMERIC β-CAROTENE, α-CAROTENE, LUTEIN, AND LYCOPENE SETS

Stereoisomeric set	Member of the set	Difference of the visually established longest wave length maximum from that of the all-*trans* form, in petroleum ether (mμ)	Molecular extinction coefficient, in hexane, at the respective *cis*-peaks, $E^{mol.}_{1cm.} \times 10^{-4}$	Difference of $E^{mol.}_{1cm.}$ for member of the set and the all-*trans* form
β-Carotene	neo U	5	1.3	0.5
	neo V	13.5	0.8	0
	all-*trans*	0	0.8	0
	neo B	10.5	3.4	2.6
	neo E	8.5	3.4	2.6
α-Carotene	neo U	5.5	1.2	0.4
	neo V	11.5	1.1	0.3
	neo W	6.5	1.6	0.8
	neo X	13.5	2.7	1.9
	all-*trans*	0	0.8	0
	neo A	8.5	3.8	3.0
	neo B	10.5	3.8	3.0
	neo C	4.5	4.5	3.7
Lutein	neo A	6	4.9	4.1
	neo B	7	2.1	1.3
	all-*trans*	0	0.8	0
Lycopene	all-*trans*	0	1.4	0
	neo A	5	6.8	5.4
	neo B	8	3.7	2.3
	unnamed cryst. isomer	28	1.3	−0.1
	prolycopene	34	1.6	0.2
	all-*cis*	38.5	2.2	0.8

β-Carotene Set (Fig. 1).—The visual maxima of neo-β-carotene U differ by 5 mμ and those of neo-β-carotene V by 13.5 mμ from the positions of the maxima of all-*trans*-β-carotene and indicate thereby that neo U is a mono-*cis* and neo V a di-*cis* compound. Neither of them can contain a *6*-*cis* double bond because of their low *cis*-peaks and relatively high thermostability. We suggest as the most probable configurations:[9] *3*-mono-*cis*-β-carotene for neo U, and *3,9*-di-*cis*-β-carotene for neo V; however, for neo V the configuration *5,7*-di-*cis* cannot be excluded.

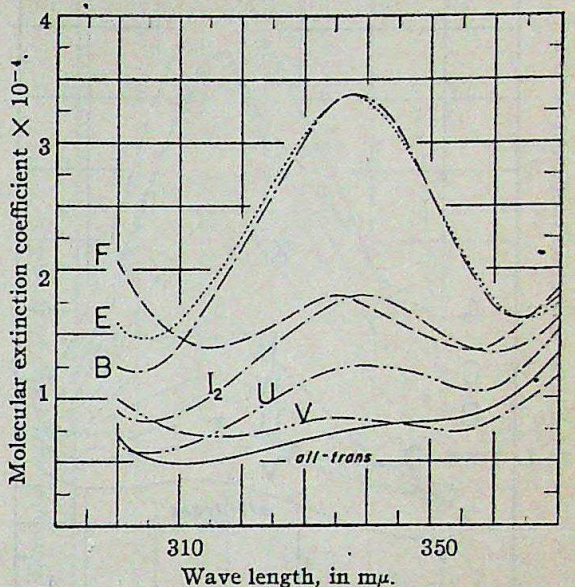

Fig. 1.—Molecular extinction curves of some β-carotene stereoisomers in the *cis*-peak region (in hexane). I_2 indicates the equilibrium mixture obtained upon iodine catalysis.

Neo-β-carotene B, a main isomer, is interpreted as a di-*cis* compound which has one of its *cis* bonds in the *6*-position; this is substantiated by the high *cis*-peak and the relatively slight thermostability. The most probable configuration for neo B is *3,6*-di-*cis*-β-carotene because *5,6* must be definitely eliminated after a consideration of the *cis*-peak and models. The minor isomer, neo-β-carotene E, belongs to the same type as neo B but because of its lability we do not wish to make suggestions concerning its configuration.

α-Carotene Set (Fig. 2).—The neo-α-carotenes U, V, and W show considerable thermostability and very moderate *cis*-peaks. The isomers U and W seem to contain one *cis* double bond while V must reasonably be interpreted as a di-*cis* compound. The most probable configurations are: neo U = *9*-mono-*cis*-α-carotene, neo W = *3*-mono-*cis*-α-carotene, and neo V = *3,9*-di-*cis*-α-carotene. Neo-α-carotene X, a di-*cis* compound, was preponderantly formed upon mild heating of a neo U solution. Therefore, we suggest that one of its *cis* double bonds, *viz.*, *9*, is identical with that in neo U. Since, as will be shown, the configurations *5,9* and *6,9* must be allocated to other isomers, neo-α-carotene X possessing a medium *cis*-peak is probably *7,9*-di-*cis*-α-carotene. Neo-α-carotene C, a labile minor isomer, seems to be *6*-mono-*cis*- or *5*-mono-*cis*-α-carotene.

One of the main observed isomers, neo B, has

(9) Before the *cis*-peak was found we stated that neo-β-carotene U possibly contains a *6*-*cis* double bond (footnote 2). This assumption must be abandoned.

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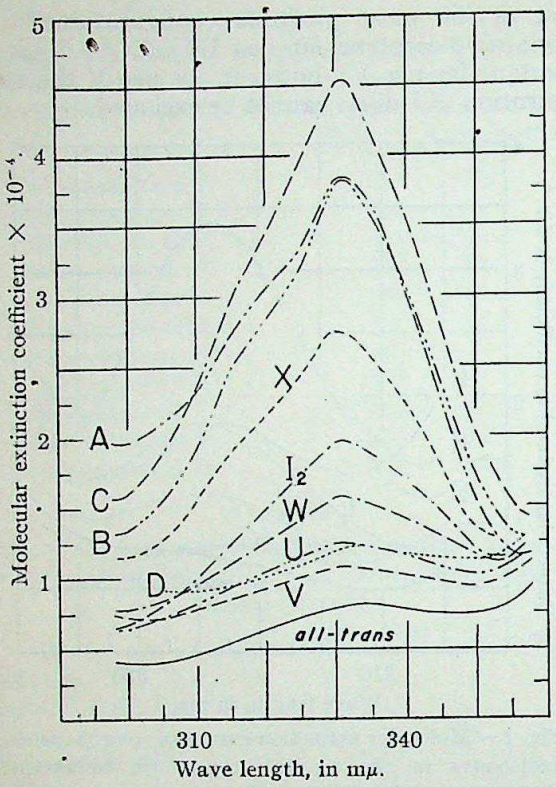

Fig. 2.—Molecular extinction curves of some α-carotene stereoisomers in the *cis*-peak region (in hexane). I_2 indicates the equilibrium mixture obtained upon iodine catalysis.

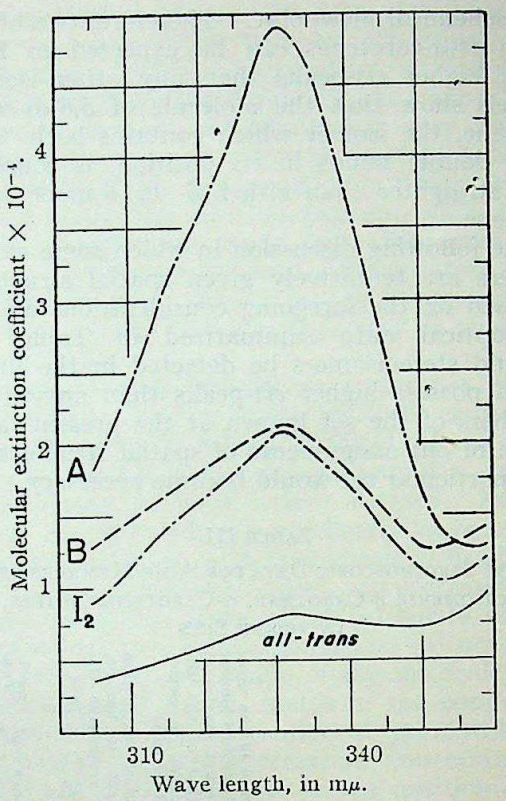

Fig. 3.—Molecular extinction curves of some lutein stereoisomers in the *cis*-peak region (in hexane). I_2 indicates the equilibrium mixture obtained upon iodine catalysis.

approximately the same *cis*-peak and in the visible region, the same spectral difference from the all-*trans* maxima as neo-β-carotene B. The great height of its *cis*-peak strongly suggests that one of its *cis* positions is central, the other peripheral, since neither two peripheral nor two central *cis* double bonds would explain the height of the peak observed. The very fact, however, that in α-carotene we find two stereochemically equivalent but structurally different central double bonds, leaves for neo-α-carotene B two spatial possibilities open which are, according to the models, *5,9*- and *6,9*-di-*cis*-α-carotene. Since the neo-α-carotenes A and B have practically identical *cis*-peaks, it is reasonable to say that for these two isomers the following four configurations are possible: *5,9*, *6,9*, *3,5*, and *3,6*.

Lutein Set (Fig. 3).—Only the two main isomers, neo A and B, have been investigated. On the basis of Table III neo-lutein A is very probably *6*- or *5*-mono-*cis*-lutein. The extinction at the *cis*-peak of neo-lutein B is less than half that of neo A. Neo B is probably *3*- or *9*-mono-*cis*-lutein.

Lycopene Set (Fig. 4).—As previously mentioned,[8] neo-lycopene A, which possesses the highest *cis*-peak so far observed, must be interpreted as *6*-mono-*cis*-lycopene. The isomer B is evidently a di-*cis* compound which could well be *1,6*- or *3,6*-di-*cis*-lycopene.

It will be an important task for the future to establish the precise nature of the dependence of adsorption affinity on the configuration of polyenes. At present only the following remarks can be made with reference to the adsorbability of stereoisomeric α- and β-carotenes (on calcium hydroxide). If the tentatively proposed spatial structures are correct, it follows that, when the position of the *cis* double bonds is *3* or *9*, the mono-*cis* compounds observed possess greater adsorption affinity than the all-*trans* form. In contrast, mono-*cis* isomers with one centrally located *cis* double bond show a decreased adsorbability. The chromatographic behavior of *3,9*-di-*cis* compounds is like that of the *3*- or *9*-mono-*cis* isomers. No simple rule is available for the case in which one peripheral and one central double bond are present. Isomers with two centrally located *cis* double bonds or with three *cis* double bonds in any combination observed so far possess definitely weaker adsorption affinity than the all-*trans* member of the α- and β-carotene sets.

Experimental

Methods.—The pigment solutions were chromatographed on calcium hydroxide[10] (Shell brand lime, chemical

(10) Since calcium hydroxides from various sources show a great difference in the rate of solvent flow, the following test, suggested by Dr. A. L. LeRosen, is used in our laboratory for standardization: a 7 × 2 cm. column is prepared, petroleum ether is sucked into it, and the time needed for the solvent to travel 50 mm. down the column is measured. A result of 35 to 70 seconds is adequate (pressure 25 mm. Hg).

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hydrate; 98% through 325 mesh). For development petroleum ether (Skellysolve B, b. p. 60–70°) containing 0.5% acetone was used. The figures on the left side of the chromatograms described below denote width of the zones in mm. Petroleum ether–alcohol mixtures are suitable eluents. The visual spectral maxima were determined with an Evaluating Grating Spectroscope (Zeiss, light filter BG-7, 2 mm. thick) in petroleum ether unless otherwise indicated. For colorimetric estimations a Pulfrich Gradation Photometer was used (petroleum ether, filter S47). The extinction coefficients were determined in a Beckman Photoelectric Spectrophotometer.[11] For these experiments "Hexane" (Eastman Kodak Co. from petroleum, "practical") was purified by shaking with fuming sulfuric acid and then with alkaline permanganate, and by fractionating; b. p. 62–65°.

The treatment of isomers which were available as solutions was described earlier.[7,8] The curves in Figs. 1 to 4 may be in error to the extent of ±1 to 5% at the maxima.

All pigments listed in the chromatograms as members of the α-carotene set shifted their visually observed spectral maxima to 473.5, 443.5 mμ (±0.5 mμ) after addition of iodine.

(a) ***cis–trans* Isomerization of α-Carotene Solutions on Standing or Refluxing.**—A solution of 3 mg. of pure α-carotene in 30 ml. of petroleum ether was found chromatographically to be nearly unchanged after remaining two hours in diffuse light. Even upon longer standing the extent of isomerization is very moderate. The neo-compounds formed were adsorbed partially above and partially below the unchanged portion. In petroleum ether solution the colorimetric ratio, unchanged all-*trans:* neo-forms was 98:2 after a day. At 5° and in the dark 1% of the α-carotene isomerized within three days.

A 50-ml. petroleum ether solution containing 5 mg. of α-carotene was refluxed in carbon dioxide for thirty minutes in an all-glass apparatus. The cooled solution was developed on a 24 × 5.8 cm. column.

35 colorless
45 pale orange, neo U: 470.5, 440.5 mμ
17 colorless
45 orange, unchanged all-*trans:* 476, 445 mμ
2 colorless
20 pale orange, neo B . . .:[12] 469.5, 440.5 mμ

The colorimetric ratio was, unchanged all-*trans* : neo U:neo B . . . = 92:4:4.

(b) ***cis–trans* Isomerization of α-Carotene by Iodine Catalysis at Room Temperature.**—To the solution of 6 mg. of homogeneous α-carotene in 50 ml. of petroleum ether a solution of 0.1 mg. of iodine was added and the mixture chromatographed thirty minutes later (24 × 4.8 cm.).

10 colorless
40 pale orange, neo U: 471, 442 mμ
7 colorless
10 light yellow, neo V: 466, 437 mμ
7 colorless
40 yellow, neo W: 470, 440.5 mμ
2 colorless
36 light orange, unchanged all-*trans:* 476, 447 mμ
5 colorless
25 yellow, neo B: 467.5, 438 mμ
2 colorless
2 pale yellow, neo C: 472.5, 442.5 mμ
2 colorless
5 pale yellow, neo D: 460, 432 mμ
2 colorless
5 pale yellow, neo E: 461.5, 433.5 mμ

The colorimetric ratio was, unchanged all-*trans*:neo U:neo V:neo W:neo B:neo C:neo D:neo E = 51.5:14.5:3:15.5:13:0.5:1:1.

(11) H. H. Cary and A. O. Beckman, *J. Optical Soc. Am.*, **31**, 683 (1942).

(12) The dots . . . indicate that the zone of the neo-compound designated by the letter included minor isomers, whose separation was unsatisfactory. In this case the neo-forms C, D, and perhaps E, were present.

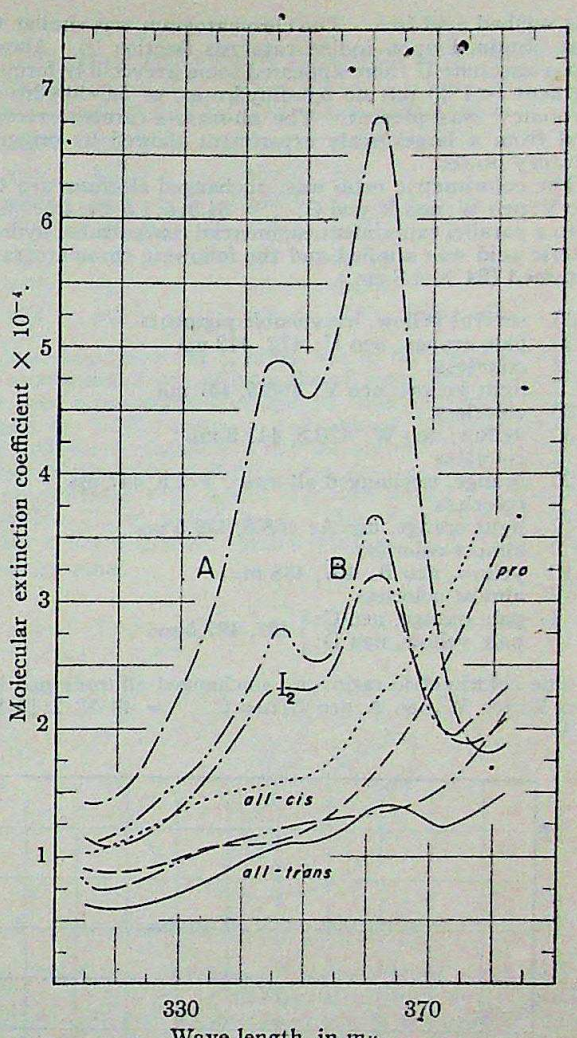

Fig. 4.—Molecular extinction curves of some lycopene stereoisomers in the *cis*-peak region (in hexane). I_2 indicates the equilibrium mixture obtained upon iodine catalysis, and . . – – . . an unnamed crystallizable stereoisomer (first absorption band at 476 mμ).

Similar isomerization experiments were carried out with the respective neo pigments (Table IV).

TABLE IV

RELATIVE COLORIMETRIC VALUES OF α-CAROTENE AND OF SOME OF ITS STEREOISOMERS FORMED BY IODINE CATALYSIS AT 25°

Starting material	Relative colorimetric values (% of the recovered pigment) neo U	neo V	neo W	all-*trans*	neo B	neo C . . .
Neo U	11	3.5	21	49.5	12	3
Neo V	11.5	4	19.5	50	13	2
Neo W	15.5	3.5	18.5	43.5	17	2
All-*trans*	14.5	3	15.5	51.5	13	2.5
Neo B	10.5	3	15	57	12.5	2
Neo C + D + E	10	2.5	21	51.5	9.5	5.5

(c) ***cis–trans* Isomerization of α-Carotene with Hydriodic Acid and Hydrochloric Acid.**—A homogeneous solution containing 7.5 mg. of pigment in 30 ml. of petroleum ether was shaken for thirty minutes with 15 ml. of hydriodic acid (Merck Reagent, 55–58% HI, diluted 1:1) in a carbon dioxide atmosphere. The pigment solution

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was washed acid-free. The chromatogram was similar to that obtained upon iodine catalysis (section b). Above neo-α-carotene U there appeared some irreversibly formed pigment (<1%) but no 5,6-dihydro-α-, or 5,6-dihydro-β-carotene[13] was present. The all-*trans*-α-carotene recovered from a larger scale experiment showed its original rotatory power.

The colorimetric ratio was, unchanged all-*trans*:neo U:neo V:neo W:neo B:neo C... = 64.5:5:1.5:24:4.5:0.5.

In a parallel experiment commercial concentrated hydrochloric acid was applied and the following chromatogram obtained (24 × 4.8 cm.).

35	several yellow, irreversible pigments
25	pale orange, neo U: 472, 442 mμ
2	colorless
3	light yellow, neo V: 465.5, 437 mμ
25	colorless
30	yellow, neo W: 470.5, 441.5 mμ
3	colorless
25	orange, unchanged all-*trans:* 477.5, 447 mμ
5	colorless
12	light orange, neo A: 468.5, 439.5 mμ
2	almost colorless
10	yellow, neo B: 467, 438 mμ
2	almost colorless
4	pale orange, neo C: } 467, 437.5 mμ
5	pale yellow, neo D: }

The colorimetric ratio was, unchanged all-*trans*:neo U:neo V:neo W:neo A:neo B:neo C... = 49:13:2:15:8:9:4.

The quantity of the *irreversibly formed pigments* amounted to about 3% of the total. Longer shaking with the acid promotes their formation (79% after 3 hours). Chromatography on calcium carbonate and subsequent crystallization from benzene-methanol yielded a few milligrams of long orange needles, m. p. 170° (cor.). In the partition test this pigment behaved like cryptoxanthin. The visual maxima follow: in carbon disulfide, 507, 473 mμ (with iodine, 504, 471.5 mμ); in benzene, 488, 456.5 mμ (486, 454.5 mμ); in petroleum ether (b. p. 60–70°), 477, 446.5 mμ (474, 443.5 mμ); and in ethanol, 477.5, 448 mμ (477.5, 448 mμ).

(d) *cis–trans* **Isomerization of α-Carotene by Melting.**—Three milligrams of pigment was melted in a sealed tube filled with carbon dioxide and kept in a bath at 195–200° for fifteen minutes. After cooling in ice water the petroleum ether solution was chromatographed (23 × 4.8 cm.).

20	colorless
12	pale orange, neo U: 472.5, 442.5 mμ
22	colorless
5	yellow, neo V: 466.5, 437.5 mμ
6	colorless
10	pale orange, neo W: 470.5, 440.5 mμ
2	colorless
3	yellow, neo X: 463.5, 434 mμ
5	colorless
17	light orange, unchanged all-*trans:* 476.5, 447 mμ
5	colorless
10	yellow, neo B: 466, 437 mμ
5	almost colorless
15	pale yellow, neo D...: 462, 433.5 mμ

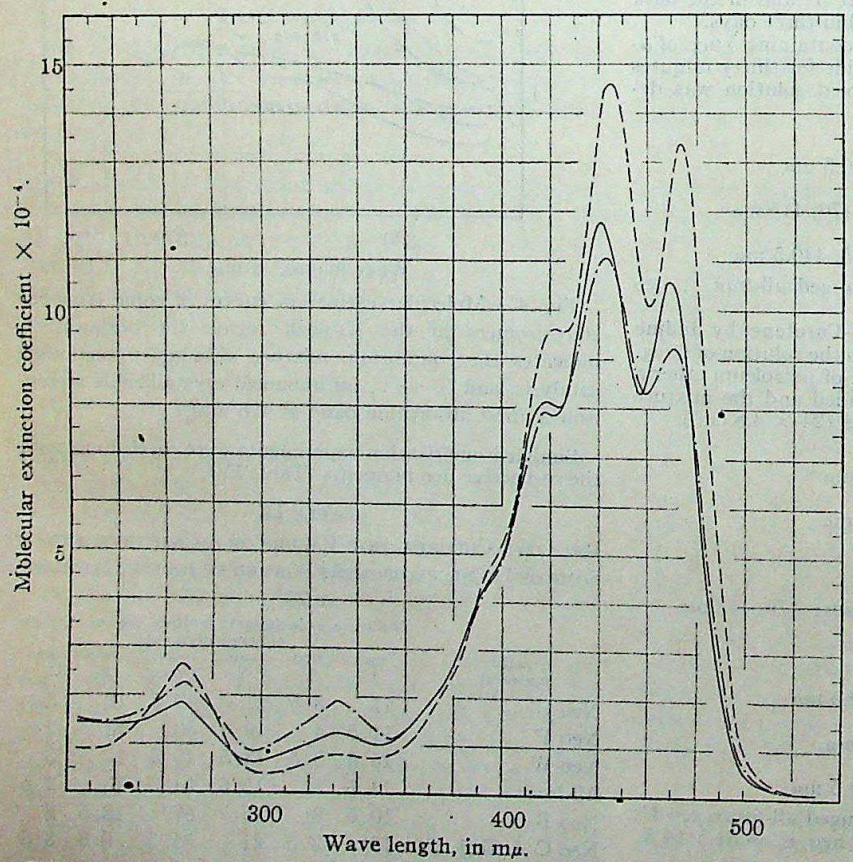

Fig. 5.—Molecular extinction curve of neo-α-carotene U, compared with that of α-carotene, in hexane: ——, neo-α-carotene U; –·–·–, neo-α-carotene U after iodine catalysis; – – – –, all-*trans*α-carotene.

The colorimetric ratio was, unchanged all-*trans*:neo U:neo V:neo W:neo X:neo B:neo D... = 35:12:6:19:7:14:7.

(e) **Neo-α-carotene U.**—To a solution of 110 mg. of α-carotene in 500 ml. of petroleum ether 3 mg. of iodine was added and, after standing at 25° for an hour, the solution chromatographed on two 29 × 8 cm. columns. The light orange neo U zone adsorbed near the top was cut out separately while the other pigments were combined, treated with iodine again and chromatographed. The neo U zones of both chromatograms were eluted together. This pigment was rechromatographed twice (29 × 8 cm.), transferred into petroleum ether and evaporated. The oily residue was dissolved in the minimum amount of benzene, mixed in a centrifuge tube with some methanol and dipped into a dry ice–acetone mixture for a few seconds. Upon scratching, crystals appeared (yield, 26.2 mg. = 24%). A single treatment of α-carotene with iodine yields about 14%. Neo-α-carotene U forms an orange crystal powder; under the microscope light orange 0.01 mm. long prisms appeared (Fig. 6); m. p. 65° (cor.). The compound is more soluble than natural α-carotene. The visually determined spectra are included in Table V. Upon addition of iodine the same maxima were observed as in case of a catalyzed all-*trans*-α-carotene solution, *viz.*, in carbon disulfide, 505.5, 474 mμ; in benzene, 488, 455.5 mμ; in chloroform, 486.5, 454 mμ; in petroleum ether, 474.5, 444 mμ; and

(13) A. Polgár and L. Zechmeister, This Journal, **65**, 1528 (1943).

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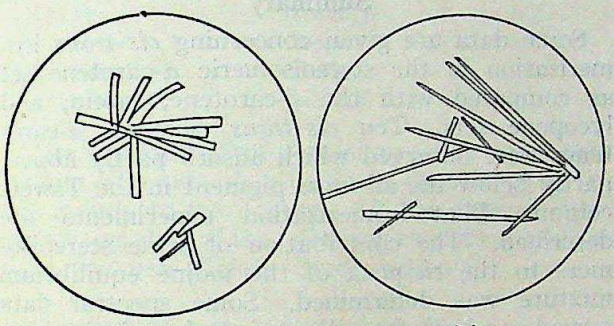
TABLE V

VISUALLY DETERMINED SPECTRAL MAXIMA OF NEO-α-CAROTENE U AND NEO-α-CAROTENE W COMPARED WITH THOSE OF ALL-*trans*-α-CAROTENE

Solvent	Neo-α-carotene U, mμ		Neo-α-carotene W, mμ		All-*trans*-α-carotene, mμ	
Carbon disulfide	503	470.5	502	469.5	509	475.5
Benzene	485.5	453.5	484	453.5	489.5	458
Chloroform	485	453	484	453	489.5	457
Petroleum ether (b. p. 86–100°)	473.5	444	473	443.5	478.5	448
Petroleum ether (b. p. 60–70°)	471.5	441.5	470.5	441	477	446.5
Hexane	470.5	441	470	441	476	445.5
Ethanol	472.5	442	472.5	442	478.5	448.5 (blurred)

in hexane, 473.5, 443 mμ.



(a) (b)

Fig. 6.—Crystals of (a) neo-α-carotene U, compared with those of (b) neo-β-carotene U (from benzene and methanol).

The molecular extinction values are listed in Table VI. The deviation of readings at the main maxima of the fresh all-*trans* solution was less than 0.1%; only single series of readings were taken in other cases.

The conversion of all-*trans*-α-carotene into its U isomer decreases the specific rotation.

$[\alpha]^{25}_{Cd} = +(100 \times 0.12°):(1 \times 0.0542) = +221°$ (±5%) [in hexane]

TABLE VI

MOLECULAR EXTINCTION COEFFICIENTS OF NEO-α-CAROTENE U AND OF ITS STEREOISOMERIC EQUILIBRIA AT THE MAXIMA (*italicized*) AND MINIMA IN HEXANE

Fresh solution		After heat isomerization		After iodine isomerization	
mμ	$E^{mol.}_{1 cm.}$	mμ	$E^{mol.}_{1 cm.}$	mμ	$E^{mol.}_{1 cm.}$
469–70	10.6	*469*	10.3	*471*	9.2
457	8.3	457	8.3	459–60	8.4
441	11.8	*440*	11.9	*443*	11.0
424	8.1	422	7.9	422	7.9
419	8.2	*418*	8.1	*418*	7.9
350	1.03	350	1.03	354	1.17
331	1.25	*330*	1.37	*332*	1.92
298–300	0.6(4)	294	0.6(5)	298	0.8(6)
267	1.85	*268*	1.94	*269*	2.29

A thirty-minute refluxing of neo-α-carotene U in petroleum ether formed the following mixture, expressed as percentage of the recovered pigment: 70% unchanged neo U, 17% neo X, 6.5% neo V, 1% neo B..., and only 5.5% all-*trans*-α-carotene.

Two milligrams of neo U crystals was melted in a sealed tube filled with carbon dioxide and kept in a bath at 74° for fifteen minutes. The chromatogram of the petroleum ether solution contained 66% unchanged neo U, 23.5% all-*trans*-α-carotene (with a trace of neo A), 7% neo X, and 3.5% neo B...

(f) **Neo-α-carotene W.**—Neo W solutions collected from several experiments were twice rechromatographed; the interzone below the U layer was in no case colorless. The separation of neo W from the all-*trans* form succeeds only upon a prolonged development with petroleum ether containing 0.5% acetone. Subsequent crystallization from benzene–methanol in a dry ice–acetone bath yielded narrow prisms, about 0.05 mm. long, showing a dull brownish orange color with brown crossings under the microscope (Fig. 7); m. p. 97° (cor.). The solubility is similar to that of the U isomer; specific rotation, $[\alpha]^{25}_{Cd}$ +365°, in petroleum ether.

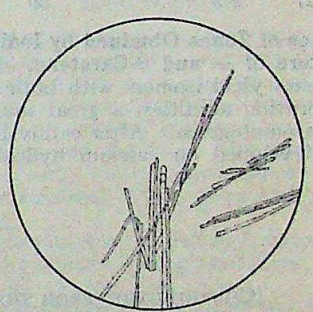


Fig. 7.—Neo-α-carotene W (from benzene and methanol).

(g) **Photo-isomerization.**—The petroleum ether solution (30 ml.) of 5 mg. of all-*trans*-α-carotene was exposed to bright sunlight in a transparent quartz test-tube (diameter, 22 mm.), filled with carbon dioxide, for forty-five minutes (final temperature, 29°). The colorimetric ratio was, unchanged all-*trans*:neo U:neo W:neo B:neo C... = 94:1.5:2:2:0.5.

A petroleum ether solution of 1 mg. of neo-α-carotene U in a quartz test-tube filled with carbon dioxide was exposed to bright sunlight for forty-five minutes and chromatographed (20 × 3.8 cm.).

4 orange, irreversible (could not be eluted)
15 almost colorless
45 light orange, neo U: 472.5, 441.5 mμ
4 colorless
5 yellow, neo V: 465.5, 438 mμ
7 colorless
14 pale orange, neo W: 470.5, 441.5 mμ
3 colorless
10 very pale orange, neo X: 463, 434.5 mμ
3 colorless
8 yellow, neo Y: 467.5, 437 mμ
3 colorless
15 dark orange, all-*trans*: 477, 446 mμ
3 colorless
10 very pale yellow, neo B...: 471.5, 442 mμ

The colorimetric ratio was, unchanged neo U:neo V:neo W:neo X:neo Y:all-*trans*:neo B... = 64.5:1.5:3.5:2:3:24:1.5.

In another experiment a homogeneous neo-α-carotene U solution was exposed at a distance of 10 cm. to the light of a 1000-watt Mazda bulb for forty-five minutes. A cold finger kept the temperature below 28.5°. The colorimetric ratio was, unchanged neo U:neo X:all-*trans* = 92:4.5:3.5. The light of an ultraviolet lamp (Hanovia, Luxor.

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Scientific Type) at 10 cm. distance isomerized only 2% of neo-α-carotene U in thirty minutes; some all-*trans* form, neo X, and neo Y appeared in the Tswett column. Solutions of the neo-α-carotenes V, W, and B were insolated for forty-five minutes. The colorimetric ratios are summarized in Table VII.

TABLE VII

RELATIVE COLORIMETRIC VALUES OF SOME MEMBERS OF THE α- AND β-CAROTENE SETS FORMED BY FORTY-FIVE MINUTES INSOLATION IN PETROLEUM ETHER SOLUTION

Starting material	Relative colorimetric values (% of the recovered pigment)								
	neo U	neo V	neo W	neo X	neo Y	all-*trans*	neo A	neo B	neo C...
				α-Carotene					
Neo U	64.5	1.5	3.5	2	3	24	—	1.5	—
Neo V	33	43	4	2	—	16	—	2	—
Neo W	7.5	5	32.5	1	—	41	4	7.5	1.5
All-*trans*	1.5	—	2	—	—	93.5	—	2.5	0.5
Neo B	1.5	—	34	—	—	56.5	—	8	—
				β-Carotene					
Neo U	36.5	—				55		6	2.5
All-*trans*	1	—				98		1	—
Neo B	27	2.5				60		5	5.5

(h) Sequence of Zones Obtained by Iodine Isomerization of a Mixture of α- and β-Carotene.—Since the two all-*trans* carotenes yield isomers with both increased and decreased adsorption affinities, a great number of zones overlap in a chromatogram. After catalysis the pigment mixture was developed on calcium hydroxide with petroleum ether containing 2% acetone. The chromatogram did not contain colorless sections; nevertheless, sections of different colors enabled the experimenter to cut out suitable zones. The addition of iodine to the solution of each pigment in the spectroscopic cell established the set to which the isomer belonged. This procedure was the basis for the chromatographic investigation of suitable binary mixtures. Such pairs were submitted to a prolonged development with petroleum ether. The sequence established in the order of decreasing adsorption affinity follows: neo-β-carotene U, neo-β-carotene V, neo-α-carotene U, all-*trans*-β-carotene, neo-α-carotene V, neo-β-carotene B, neo-β-carotene E, neo-α-carotene W, neo-β-carotene F, all-*trans*-α-carotene, neo-α-carotene B, and neo-α-carotenes C, D, etc.

Summary

Some data are given concerning *cis–trans* isomerization in the stereoisomeric α-carotene set as compared with the β-carotene, lutein, and lycopene sets. Ten *cis–trans* isomeric α-carotenes were observed which adsorb partly above, partly below the all-*trans* pigment in the Tswett column. Photo-isomerization experiments are described. The contribution of some stereoisomers to the *cis*-peak of the iodine equilibrium mixture was determined. Some spectral data served as a basis for a discussion of configurations.

PASADENA, CALIFORNIA RECEIVED AUGUST 2, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF OCCIDENTAL COLLEGE]

The Use of Potassium *t*-Amyloxide for the Alkylation of Acetoacetic Ester and its Alkyl Substitution Products

BY W. B. RENFROW, JR.

Alkylation of acetoacetic ester with sodium ethoxide in ethanol and an alkyl bromide gives yields of 70–80% with *n*-alkyl bromides,[1] but secondary alkyl bromides and bromides with a branch in the chain at the β-position (*i. e.*, isobutyl) generally give less than a 30% yield[2] of mono-substituted acetoacetic ester. Moreover, the further alkylation in the usual way of a mono-α-substituted acetoacetic ester with an *n*-alkyl bromide generally gives less than a 40% yield of disubstituted acetoacetic ester.[3]

Theoretical considerations indicated that the yields in the less favorable cases could be improved by the use of an alkoxide of greater proton-affinity than sodium ethoxide. Potassium *t*-amyloxide is a conveniently available base which is stronger than sodium ethoxide,[4] and was selected for investigation.

Table I gives the results obtained. The course of the reaction was followed by titration of aliquots with acid, and the approximate times were determined at the temperature of the refluxing solutions for one-half of the base to react.

Comparison of the data in Table I with similar data using sodium ethoxide[1,5,6] shows that potassium *t*-amyloxide in *t*-amyl alcohol and sodium ethoxide in ethanol are of about equal effectiveness for the alkylation of ethyl acetoacetate with primary, straight-chain bromides. However, potassium *t*-amyloxide gives considerably better yields of ethyl α-isopropylacetoacetate, ethyl α-isobutylacetoacetate, ethyl α,α-diethylacetoacetate and ethyl α,α-dibutylacetoacetate than can be obtained by use of sodium ethoxide in ethanol.[2,7,3]

(1) For the usual method of alkylation, see: Gilman, Blatt, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, New York, N. Y., 1941, p. 248.

(2) In the present investigation ethyl isopropylacetoacetate and ethyl isobutylacetoacetate were obtained in 20–25% yields by the method described in (1).

(3) Hess and Bappert, *Ann.*, **441**, 151 (1925), obtained a 38% yield of α,α-di-*n*-butylacetoacetic ester under certain conditions. Under other conditions the product was almost exclusively ethyl di-*n*-butylacetate. Compare also Billon, *Ann. chim.*, **7**, 355 (1927).

(4) McEwen, THIS JOURNAL, **58**, 1124 (1936), found the following relative values for pKa: methanol, 16; ethanol, 18; *t*-amyl alcohol, 19.

(5) Michael, *J. prakt. Chem.*, **72**, 553 (1905).

(6) Locquin, *Bull. soc. chim.*, **31**, 758 (1904).

(7) Conrad and Limpach, *Ann.*, **192**, 153 (1878).

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TABLE I

RESULTS OF ALKYLATIONS USING KO—C(CH$_3$)$_2$—C$_2$H$_5$ IN HO—C(CH$_3$)$_2$—C$_2$H$_5$

R (R =)	R′Br (R′ =)	Reaction half-time (minutes)	Yield of CH$_3$C(=O)—C(R)(R′)—C(=O)—OEt (per cent)	Boiling range °C.	Mm.	Ref.
H	Ethyl	10	80	96–98	26	5
H	*n*-Butyl	15	73	110–114	14–15	1
H	Isoamyl	20	72	120–123	15–16	6
H	Isobutyl	100	61	99–103	13–14	9
H	Isopropyl	200	50	200–203	748	10
Ethyl	Ethyl	10	75	96–99	13–14	7
n-Butyl	*n*-Butyl	15	70	143–147	18–19	3

The superiority[8] of potassium *t*-amyloxide over sodium ethoxide in ethanol is considered to be due mainly to two factors: (1) the stronger base causes less shift of the following equilibrium to the right (reverse Claisen condensation[11])

$$CH_3COCRR'CO_2C_2H_5 + HOR'' \underset{}{\overset{KOR''}{\rightleftharpoons}} CH_3CO_2R'' + HCRR'CO_2C_2H_5$$

and (2), the stronger base makes available a higher concentration of the desired metallic enolates of acetoacetic esters by shifting the following equilibrium further to the right.

$$CH_3COCHR'CO_2C_2H_5 + KOR'' \rightleftharpoons (CH_3COR'CO_2C_2H_5)K + HOR''$$

A slow rate of alkylation (as with isopropyl and isobutyl bromides) permits greater reversal of the Claisen condensation by necessitating a prolonged refluxing of acetoacetic esters with alcohol and alkoxide. The α,α-disubstituted acetoacetic esters are especially susceptible to cleavage by sodium ethoxide in ethanol and this side reaction is very troublesome when the usual alkylation procedure is followed.[3] Since it has been shown that a strong base favors the Claisen condensation[11b] (and hence should oppose reversal of the reaction), the higher yields obtained by use of the stronger base are probably mainly due to this factor.

The second factor is probably not significant in the alkylation of ethyl acetoacetate, since this compound is a sufficiently strong acid[12] to be converted almost completely into its enolate by means of sodium ethoxide. This factor may be of some importance, however, in the alkylation of more weakly acidic monosubstituted acetoacetic esters.

Experimental

The technical grade of *t*-amyl alcohol was refluxed for five hours with 2% of its weight of sodium, allowed to stand overnight, decanted through a plug of glass wool and distilled rapidly until the boiling point reached about 106°. The distillate was refluxed for four hours with 1% its weight of sodium and distilled. The fraction boiling at 100–100.8° (747 mm.) was collected as pure *t*-amyl alcohol. This amounted to about 73% of the starting material, and had d^{20}_4 0.809.

Ethyl acetoacetate was purified by fractionation through a 20-cm. column packed with glass helices. The fraction boiling at 83–85° (24 mm.) was used.

The alkyl bromides were thoroughly extracted with concentrated sulfuric acid, washed with bicarbonate solution, dried (calcium chloride) and fractionated.

Experiments were made using from 0.1 to 1.0 gram-atom of potassium. The most convenient amount was about 0.3 gram-atom, and the general procedure was as follows: Potassium (11.7 g., 0.3 gram-atom) was dissolved with stirring at reflux temperature in *t*-amyl alcohol (170 ml.). When larger amounts of potassium were added all at once, external cooling of the flask was usually necessary to prevent too violent refluxing. The solution was cooled (inert atmosphere) to room temperature, ethyl acetoacetate (42.9 g., 0.33 mole) was added and the solution stirred for about two minutes. The alkyl bromide (0.33 mole) was then added and the solution was refluxed and stirred until 90–100% of the base had reacted (usually about three hours).

The reaction mixture was diluted with water (about 100 ml.) and acidified with acetic acid (litmus). The organic layer was separated and distilled at atmospheric pressure until the boiling point reached 110°. The cooled residue was filtered and the filtrate was fractionated through a column packed with glass helices, and 10 to 20 cm. in length, depending upon the boiling point of the product. The columns were equipped with heaters to prevent excessive flooding. Ethyl ethylacetoacetate was further purified before fractionation by extracting it with aqueous sodium bisulfite (20%) to remove excess ethyl acetoacetate.

The procedure was the same for the alkylation of α-substituted acetoacetic esters, except that equivalent amounts of potassium and ester were used. A 10% excess of alkyl bromide was used in all cases.

The rate at which the alkali disappeared was determined as follows: After addition of the alkyl halide, 1.0-ml. aliquots were removed from time to time and added to ethanol (15 ml.) containing "Nitrazine"[13] indicator solution (2

(8) Other improved methods of alkylation that have been suggested involve the use of non-hydroxylic solvents: Wallingford, THIS JOURNAL, **64**, 580 (1942); Elderfield, *J. Org. Chem.*, **4**, 370 (1939); **6**, 57 (1941).

(9) Tafel and Jurgens, *Ber.*, **42**, 2555 (1909).

(10) Hauser and Breslow, THIS JOURNAL, **62**, 2611 (1940).

(11) (a) Concerning the reversibility of the Claisen condensation, see: Beckmann and Adkins, THIS JOURNAL, **56**, 1119 (1934). (b) For a discussion of the role of the base in the Claisen condensation, see: Hauser and Renfrow, THIS JOURNAL, **59**, 1823 (1937); **60**, 463 (1938).

(12) Goldschmidt and Oslan, *Ber.*, **33**, 1146 (1900), report the ionization constant of ethyl acetoacetate to be 2.0×10^{-11}.

(13) A solution of sodium dinitrophenylazo-naphthol disulfonate sold under the trademark of "Nitrazine" by E. R. Squibb and Sons, New York, N. Y.

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TABLE II

RESULTS OF KETONIC HYDROLYSES

Ketone	Boiling range °C.	Mm.	Yield, %	Melting point semicarbazone, °C.	Ref.
$CH_3(CH_2)_2COCH_3$	99–102	747	70	110	15
$CH_3(CH_2)_4COCH_3$	148–151	747	75	126–127	15
$(CH_3)_2CHCH_2COCH_3$	114–120	746	36	132–135	15
$(CH_3)_2CH(CH_2)_2COCH_3$	141–142	746	60	142–143	16
$(CH_3)_2CH(CH_2)_3COCH_3$	162–164	746	77	153–154	17
$(CH_3CH_2)_2CHCOCH_3$	135–139	746	45	98–99	18
$(CH_3CH_2CH_2CH_2)_2CHCOCH_3$	104–107	22	64	109[a]	3

[a] Apparently a new compound. Analyzed by method of Veibel, *Bull. soc. chim.*, **41**, 1410 (1917). Calculated for $C_{12}H_{25}ON_3$: $^1/_3$N, 6.16. Found: $^1/_3$N, 6.11.

drops). The solution was titrated with 0.100 *N* hydrochloric acid until the blue color changed to yellow. Since aliquots taken toward the end of the reaction required small volumes of titrating solution, water was added so that approximately equal volumes of ethanol and water were present at the end-points of all titrations.

The structure of alkylation products was confirmed by ketonic hydrolysis. The mono-substituted acetoacetic esters were hydrolyzed with aqueous sodium hydroxide (5%). The esters were first stirred with the alkali (1.5 moles to 1 of ester) for four hours at room temperature, after which the mixture was refluxed for about six hours. The ketones were removed from the cooled solution by ether extraction, the extracts were dried, the solvent was removed and the residue was fractionally distilled. The α,α-disubstituted acetoacetic esters were very resistant to hydrolysis. The following procedure, of many that were tried,[14] gave the best results: a solution of ethyl α,α-dibutylacetoacetate (26 g., 0.107 mole) in methanol (100 ml.) and water (20 ml.) containing potassium hydroxide (8 g., 0.14 mole) was refluxed for four hours. Additional potassium hydroxide (8 g.) and water (10 ml.) were added and the refluxing was continued for eight hours longer. The mixture was distilled from a water-bath, and when 105 ml. of distillate had been removed the residue was transferred to a separatory funnel. Water (25 ml.) was added and the mixture was thoroughly shaken; three layers separated. The lower layer was potassium carbonate solution; the middle layer yielded α-butylcaproic acid (3.7 g.) on acidification; and fractionation of the upper layer gave α,α-dibutylacetone (11.6 g.). The results of the ketonic hydrolyses are summarized in Table II.

(14) The method of Connor and Adkins (THIS JOURNAL, **54**, 3420 (1932)) could not be tried because the equipment was not available. α,α-Dibutylacetoacetic ester was recovered unchanged after it was stirred for six hours at 150–170° with 85% phosphoric acid (Dehn and Jackson, THIS JOURNAL, **55**, 4284 (1933)). Attempts to induce an ester interchange by refluxing α,α-dibutylacetoacetic ester with formic or acetic acid and zinc chloride were unsuccessful.

Summary

1. A procedure is described for the alkylation of acetoacetic esters, by action of potassium *t*-amyloxide in *t*-amyl alcohol and alkyl bromides.

2. The method was found to be advantageous for the preparation of certain α,α-disubstituted acetoacetic esters.

(15) Shriner and Fuson, "Identification of Organic Compounds," John Wiley and Sons, New York, N. Y., 1940, p. 221.
(16) Freylon, *Ann. chim.*, (8) **19**, 559 (1910).
(17) Wallach, *Ann.*, **381**, 86 (1911).
(18) Bardan, *Bull. soc. chim.*, **49**, 1875 (1931).

LOS ANGELES, CALIFORNIA

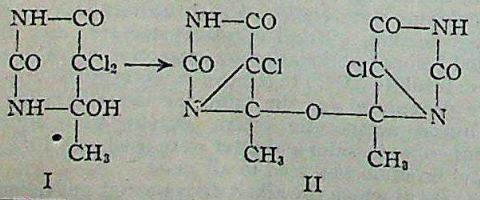
RECEIVED SEPTEMBER 17, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

Reactions Characterizing the Oxide of 6-Methyl-6-oxy-5-chloro-1,5-bicyclouracil[1]

BY TREAT B. JOHNSON[2]

The formula adopted to interpret the constitution of the 1,5-bicyclouracil derivative, under discussion in this paper, is expressed graphically in no. II. This cyclo-pyrimidine is produced in excellent yield by digestion of 5,5-dichloro-6-hydroxy-6-methylhydrouracil (I) with concentrated hydrochloric acid.[3]



I II

The specific reactions pertaining to this first representative of a new type of pyrimidine compound, which the author is prepared to discuss at this time, are reported below under the two headings of (a) Reduction and (b) Oxidation Reactions, respectively.

Reduction Reactions

The 1,5-bicyclouracil derivative (II) loses its characteristic bicyclo structure on reduction and reverts to the constitution of a true uracil derivative. Interaction with stannous chloride and hydrochloric acid leads to the quantitative formation of 5-chloro-6-methyluracil, while warming with hydriodic acid and red phosphorus removes

(1) Researches on Pyrimidines. CLXXXI. Experimental work conducted in the Bethwood Research Laboratory, Bethany, Connecticut.

(2) This research was supported in part by a grant from the Research Committee of the Council on Pharmacy and Chemistry, American Medical Association (Grant No. 423).

(3) Johnson, THIS JOURNAL, **65**, 1220 (1943).

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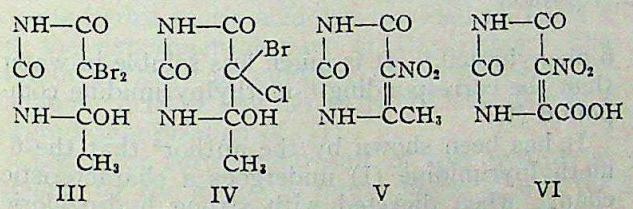
all halogen from the bicyclo pyrimidine (II) with regeneration of 6-methyluracil. No other reduction products have been identified.[3]

Oxidation Reactions

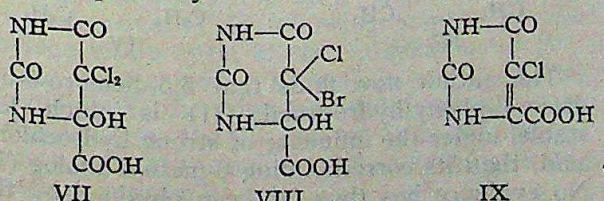
This section is confined to a discussion of the action of three different oxidizing reagents on the 1,5-bicyclouracil compound (II) namely: (a) superoxol and concentrated hydrochloric acid, (b) bromine water, and (c) concentrated nitric acid. Unexpected and characteristic reaction changes were disclosed as a result of this study.

The behavior of 6-methyluracil toward these three oxidising reagents is well known. Hydrogen peroxide in the presence of hydrochloric acid, and bromine water react quantitatively at ordinary temperature to give 5,5-dichloro-6-hydroxy-6-methylhydrouracil (I),[3,4] and 5,5-dibromo-6-hydroxy-6-methylhydrouracil[5] (III), respectively. With bromine water 5-chloro-6-methyluracil yields 5 - bromo - 5 - chloro - 6 - hydroxy - 6 - methylhydrouracil[5] (IV). In neither case is the methyl group of the respective uracil molecule converted by oxidation to a carboxyl group. Nitric acid is known to react with 6-methyluracil smoothly with formation of 5-nitro-6-methyluracil cil (V), but at elevated temperatures oxidation takes place yielding 5-nitro-6-uracil-carboxylic acid[6] (VI).



III IV V VI

This comparison of differences in chemical behavior on interaction of the 6-methyluracil molecule with these three oxidizing reagents is instructive and interesting, when we consider the action of these same reagents on the 1,5-bicyclouracil derivative (II). In this case the author finds that the 6-methyl group in (II) is oxidized easily by all three reagents with destruction of the bicyclo structure and formation of 5,5-dichloroxyhydroorotic acid (VII), 5-chlor-5-bromoxyhydroorotic acid (VIII) and 5-chloroorotic acid (IX), respectively.



VII VIII IX

5,5-Dichloroxyhydroorotic acid (VII) is reduced quantitatively to 5-chloroorotic acid (IX) by means of hydriodic acid and red phosphorus. It is of special interest to note here that this same hydropyrimidine derivative (VII) is not formed by the action of superoxol and hydrochloric acid directly on orotic acid.[7] The end-product resulting under such experimental conditions is 5-chloroorotic acid (IX).[8]

Experimental Part

The Action of Superoxol and Concentrated Hydrochloric Acid on the Oxide of 6-Methyl-6-oxy-5-chloro-1,5-bicyclouracil. (II)

Formation of 5,5-Dichloroxyhydroorotic Acid (VII).—Five-tenths gram of the finely pulverized pyrimidine compound (II) was exposed to the action of an oxidizing mixture containing 5 ml. of superoxol and concentrated hydrochloric acid, respectively. After standing for five to six days at ordinary temperature a clear liquid was obtained with 0.2 g. of colorless prismatic crystals in suspension. These prisms melted sharply at 182° with violent effervescence. After recrystallization from boiling water it still melted at the same temperature, 182–183° with effervescence. The compound was dried for analysis at 100–110°. *Anal.* Calcd. for 5,5-dichloroxyhydroorotic acid (VII), $C_5H_4O_5N_2Cl_2$: C, 24.69; H, 1.65; N, 11.50. Calcd. for 5,5-dichloro-6-hydroxy-6-methylhydrouracil (I), $C_5H_6O_3N_2Cl_2$: C, 28.12; H, 2.81; N, 13.1. Found: (I) C, 24.67; H, 1.88; N, 11.0. (II) C, 24.55; H, 1.90; N, 11.41.

Reduction of 5,5-Dichloroxyhydroorotic Acid (VII) to 5-Chloroorotic Acid (IX).[9]—Two grams of this pyrimidine (VII) and 0.5 g. of red phosphorus were suspended in 2 ml. of hydriodic acid (sp. gr. 1.5) diluted with an equal volume of water, and the mixture digested at its boiling point for fifteen to twenty minutes. The solution was then diluted with 5 ml. of hot water, filtered and finally evaporated at 100° to a sirupy consistency and cooled.

On adding cold water a colorless crystalline substance separated, which was difficultly soluble in boiling water. When heated in a capillary tube it turned brown at about 255°, shriveled and decomposed with effervescence at 294–296°. This decomposition point varies depending upon the rate of heating. The substance contained chlorine, and did not respond to the characteristic Wheeler and Johnson color test for uracil.[10] This same pyrimidine is formed by the direct action of superoxol and hydrochloric acid on orotic acid.[8] *Anal.* Calcd. for $C_5H_3O_4N_2Cl$: N, 14.68. Found: N, 14.60, 14.62.

The Action of Concentrated Nitric Acid on the Oxide of 6-Methyl-6-oxy-5-chloro-1,5-bicyclouracil (II). Formation of 5-Chloroorotic Acid (IX).—Five-tenths gram of this bicyclo pyrimidine was partially dissolved in 10 ml. of cold, concentrated nitric acid, and the mixture allowed to stand in a stoppered flask at ordinary temperature; red fumes were evolved slowly during a period of six days. After allowing to stand in the laboratory for nearly two weeks, a crystalline deposit of 0.15 g. was filtered off which did not melt or decompose below 280°. This was purified by recrystallization from boiling water and separated in the form of prismatic crystals. These shriveled and turned brown on heating finally decomposing with effervescence when heated above 285°. The compound contained chlorine and was dried for analysis at 100–110°. *Anal.* Calcd. for 5-chloroorotic acid (IX), $C_5H_3O_4N_2Cl$: N, 14.68. Found: N, 14.55, 14.59.

(4) Behrend, *Ann.*, **236**, 22, 59 (1886).

(5) Behrend, *Ann.*, **229**, 18 (1885); *ibid.*, **236**, 57 (1886); List, *ibid.*, **236**, 22 (1886).

(6) Behrend, *Ann.*, **229**, 32 (1885); *ibid.*, **240**, 4 (1887); Kohler, *ibid.*, **236**, 34 (1886).

(7) Biscaro and Belloni, *Chem. Zentr.*, **76**, II, 63 (1905); Wheeler, *Am. Chem. J.*, **38**, 358 (1907); Johnson and Schroeder, THIS JOURNAL, **53**, 1989 (1931).

(8) Johnson, *ibid.*, **65**, 1218 (1943).

(9) 5-Chlorouracil-4-carboxylic acid.

(10) Wheeler and Johnson, *J. Biol. Chem.*, **3**, 183 (1907); see "Researches on Pyrimidines" (No. 180), by Johnson, *Science*, **98**, 90 (1943) for description of a modification of this color test.

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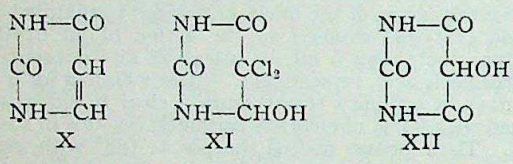
Formation of 5-Chloro-5-bromoxyhydroorotic Acid (VIII).—This acid is formed in excellent yield by the action of bromine water at ordinary temperature on the oxide of 6-methyl-6-oxy-5-chloro-1,5-bicyclouracil (II). The pyrimidine is moderately soluble in hot water and crystallizes in the form of prismatic crystals melting at 192–193°. It was dried for analysis at 100–110°. *Anal.* Calcd. for $C_5H_4O_5N_2BrCl$: N, 9.63. Found: N, 9.63.

The Conversion of 5,5-Dihalogenated-6-hydroxyhydroorotic Acids to Dialuric Acid.—The two new hydroorotic acid derivatives, namely: 5,5-dichloroxyhydroorotic acid (VII) and 5-chloro-5-bromoxyhydroorotic acid (VIII) bear the same structural relationship to orotic acid as 5,5-dichloroxyhydrouracil (XI) does to the uracil molecule (X).

The author now finds that these two hydropyrimidines (VII) and (VIII) cannot be distinguished from 5,5-dichlorhydrouracil (XI) by application of the standard



X XI XII

Wheeler and Johnson color reaction for uracil.[10] By application of their well-known technique the 6-carboxyl groups in the two pyrimidines (VII) and (VIII) are removed by the action of barium hydroxide yielding at once dialuric acid (XII), and its characteristic purple-colored barium salt.

These are the first pyrimidines of the halogenated 6-hydroxyhydrouracil type, so far discovered, which have responded to this characteristic color reaction reported by Wheeler and Johnson as a specific color test for uracil and cytosine.[10]

Summary

1. The oxide of 6-methyl-6-oxy-5-chloro-1,5-bicylouracil is converted smoothly by reduction to a true uracil derivative.

2. The chemical action of three different oxidizing reagents has thus far been studied namely: superoxol and hydrochloric acid, bromine water and nitric acid.

3. The methyl group of this 1,5-bicyclopyrimidine compound is oxidized to carboxyl by the action of all three reagents, with regeneration of the normal pyrimidine structure, yielding characteristic derivatives of hydroorotic acid.

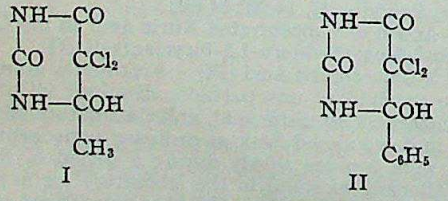
BETHANY, CONNECTICUT RECEIVED JULY 20, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, YALE UNIVERSITY]

The Acid Hydrolysis of a 6-Aryl-5,5-dichloroxyhydrouracil[1]

BY TREAT B. JOHNSON[2]

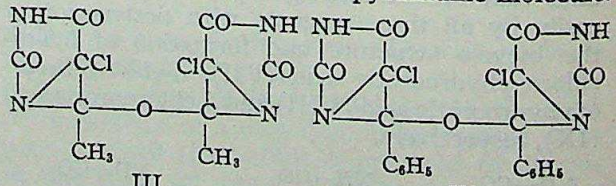
In the light of the results obtained during the previous experimentation on acid hydrolysis of 5,5-dichloro-5-hydroxy-6-methylhydrouracil[3] (I), it became of increased interest to the author to undertake a similar study with the simplest aromatic representative of this heterocyclic pyrimidine series, namely, 5,5-dichloro-6-hydroxy-6-phenylhydrouracil (II). Very little is known about the chemistry of such aromatic pyrimidine compounds as represented by (II).



I II

Judging from the experience of the author in other fields of pyrimidine research, it might be predicted that the study of such aryl derivatives as (II) would disclose further evidence in support of reaction mechanisms that have previously been postulated[3] regarding positions 1-, 5- and 6- in this type of hydrouracil compound. The pyrimidine (II) is easily prepared, without substitution of chlorine in the 6-phenyl group, by the action of superoxol and concentrated hydrochloric acid on 6-phenyluracil.[4] It is much less soluble in water than the corresponding 6-methylpyrimidine compound (I).

It has been shown by the author[3] that the 6-methylpyrimidine (I) undergoes a characteristic change when digested with strong hydrochloric acid yielding the first representative of a new type of pyrimidine compound to which has been assigned the constitution of the oxide of 6-methyl-6-oxy-5-chloro-1,5-bicyclouracil (III). In fact, the 1,5-bicyclouracil structure expressed in this formula (III) is favored by the oxide structure functioning in position 6- of the pyrimidine molecule.



III IV

The author now finds that 5,5-dichloro-6-hydroxy-6-phenylhydrouracil (II) is much less stable, under the influence of strong hydrochloric acid, than its corresponding 6-methyl-analog (I). No evidence has thus far been obtained by the author of the formation of a condensed 1,5-bicyclouracil compound (IV) by digestion of (II) with this mineral acid.

(1) Researches on Pyrimidines, CLXXXII.

(2) Experimental work conducted in the Bethwood Research Laboratory, Bethany, Connecticut.

(3) Johnson, THIS JOURNAL, 65, 1220 (1943).

(4) Fischer and Roeder, *Ber.*, 34, 3763 (1901); Wheeler and Merriam, *Am. Chem. J.*, 29, 490 (1903); Johnson and Hemingway, THIS JOURNAL, 37, 280 (1915).

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TABLE I

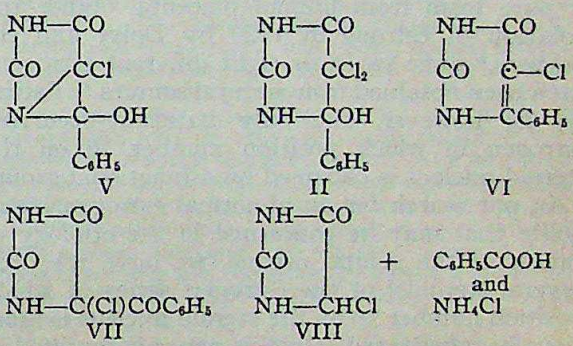
ACID HYDROLYSIS OF 5,5-DICHLORO-6-HYDROXY-6-PHENYLHYDROURACIL (II)

Reactant, g.	Hydrochloric acid, cc.	Digestion period, hr.	Reaction products	Analyses, $C_{10}H_8O_2N_2Cl_2$ Calcd.	Found
The hydropyrimidine (II), 1	100 of concd. acid	2 at 100°	Reactant recovered = 0.75 g., NH_4Cl identified	C, 43.66	43.9
				H, 2.91	3.17
				N, 10.18	10.09
1	100	6 at 100°	Reactant completely dextroyed. Benzoic acid and NH_4Cl identified		
1	100	4 at 100°	Recovered 0.4 g. benzoic acid and 4 mg. of reactant m. p. 209–210°. 5-Chloro-6-phenyluracil identified m. p. 260–261°. Also NH_4Cl	N, 10.18	9.95
1	100	4 at 100°	Recovered 0.5 g. of benzoic acid, and 3.5 mg. of reactant. NH_4Cl identified		

While aryl derivatives of uracil-like 6-phenyluracil and 5-chloro-6-phenyluracil, for example, can be heated with strong hydrochloric acid without degradation of the pyrimidine cycle, the hydrouracil derivative (II) suffers complete destruction of the pyrimidine ring by such treatment with formation of benzoic acid and ammonium chloride. The only pyrimidine degradation product identified after the hydrolysis was a few milligrams of 5-chloro-6-phenyluracil (VI). The results of four hydrolysis experiments obtained after two, four and six hours of digestion with strong hydrochloric acid are recorded in Table I of the experimental part of this paper. The author obtained no evidence of the formation of cinnamic acid or any derivative of this acid as a degradation product of (II).

The most surprising result of this hydrolytic change by the action of hydrochloric acid is the quantitative conversion of (II) to benzoic acid. To explain this molecular transformation of the pyrimidine (II), the author has presupposed the possibility of formation of different intermediate compounds, but he concludes at present, that the formation of a 1,5-bicyclouracil derivative (V) is probably the first intermediate product of hydrolytic change. According to this interpretation of reaction we are dealing with an hypothetical **ethylene-imide** cycle, which would be predicted to be unstable due to the influence of a free hydroxyl group in position 6- of (V) and (II), and to revert in acid solution to the hypothetical hydantoin derivative (VII) following scission of the **ethylene-imide** cycle in the 1,6-position of (V). In the corresponding hydrolysis study of the pyrimidine (I) the **ethylene-imide** ring structure is stabilized by the absence of hydroxyl due to the formation of the oxide or ether structure functioning in position 6- of (III).

This intermediate, hydantoin derivative (VII) would be predicted from our present knowledge of the chemistry of such heterocyclic compounds to undergo degradation easily, by hydrolysis with strong hydrochloric acid, leading to complete destruction of the hydantoin ring and production of benzoic acid and ammonium chloride. The hydantoin expressed by formula (VIII) has not, thus far, been isolated as a product of reaction. The study of the behavior on acid hydrolysis of aryl and alkyl substituted pyrimidine compounds of types (I) and (II) will be continued by the author.



Experimental Part

Formation of 5,5-Dichloro-6-hydroxy-6-phenylhydrouracil from 6-Phenyluracil.—Two grams of finely pulverized 6-phenyluracil[4] was stirred into a cold mixture of 30 cc. of superoxol and concentrated hydrochloric acid, respectively. The pyrimidine did not dissolve at any stage of the operation, and was allowed to stand for fully twenty-four hours when the colorless reaction product was filtered off and purified by recrystallization from hot water. It separated on cooling in the form of flat prisms melting at 209–210° with violent effervescence. The compound contained chlorine, and was dried at 100–110° before analysis.

Anal. Calcd. for $C_{10}H_8O_3N_2Cl_2$: N, 10.18. Calcd. for $C_{10}H_7O_2N_2Cl$: N, 12.58. Found: N, 9.75, 9.86.

In a second experiment 3.5 g. of 6-phenyluracil was triturated with a mixture of 50 cc. of superoxol and 50 cc. of concentrated hydrochloric acid for twenty-four hours. We obtained 4.0 g. of a colorless product melting at 195–196° with decomposition. After recrystallization from hot water this product melted at 209–210° with violent effervescence.

Reduction of 5,5-Dichloro-6-hydroxy-6-phenylhydrouracil (II). Formation of 5-Chloro-6-phenyluracil (VI).—One gram of the hydrouracil derivative mixed with 10 cc. of hydriodic acid (sp. gr. 1.5) and 0.5 g. of red phosphorus was heated to 100°, and the mixture diluted with 20 cc. of water. This was then digested for fifteen minutes at the boiling point and finally cooled. Following filtration, the phosphorus residues were triturated with dilute sodium hydroxide and filtered giving a clear alkaline solution. Acidifica-

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tion with hydrochloric acid gave an immediate precipitate of 6-phenyl-5-chlorouracil melting at 260–261° to a clear oil. The compound contained chlorine, and was dried for analysis at 100–110°.

Anal. Calcd. for $C_{10}H_7O_2N_2Cl$: N, 12.58. Found: N, 12.32.

Summary

1. 5,5-Dichloro-6-hydroxy-6-phenylhydrouracil (II) is formed in good yield by the combined action of superoxol and hydrochloric acid on 6-phenyluracil.

2. This hydrouracil compound is characterized by its behavior when digested with concentrated hydrochloric acid. This treatment leads to complete destruction of the pyrimidine ring with formation of benzoic acid and ammonium chloride.

3. A reaction mechanism has been proposed to explain this unexpected decomposition of (II) by action of hydrochloric acid.

BETHANY, CONNECTICUT RECEIVED AUGUST 6, 1943

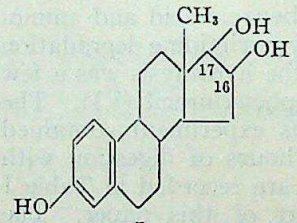
[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY]

16-Substituted Steroids. I. Isoestriol-A

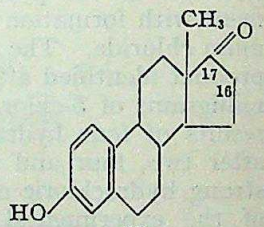
BY MAX N. HUFFMAN[1] AND HUGH H. DARBY

In 1930 Marrian[2] in England and Doisy[3] in America succeeded in isolating from human pregnancy urine the estrogen which is now known as estriol or theelol. Browne,[4] working in Collip's laboratory, subsequently obtained this hormone in pure form from human placenta. Since the isolation of estrone in 1929 by Doisy and coworkers,[5] some seven or eight different estrogens have been obtained from natural sources. Estriol (I) is, however, the only naturally-occurring estrogen in which position number 16 on the steroid nucleus is occupied by a functional group.

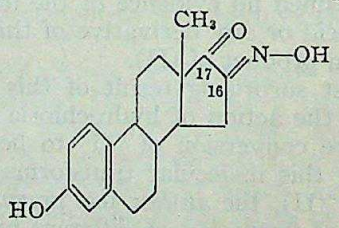
In our search for an abnormal estrogen metabolite that may be concerned in the etiology of cancer of the genital organs, we have prepared several steroids[6] of the estrogen series in which position number 16 on the steroid nucleus is functionally substituted. In this paper is reported in detail the preparation of an epimer of theelol. It is to be noted that there exists the theoretical possibility for four stereoisomeric estriols, considering only the spatial arrangements of the carbinols at positions 16 and 17 on the estrane skeleton. On the reduction of estrone (II) (which is ketonic at position 17) to the secondary alcohol stage, two isomeric estradiols are possible. Both these estradiols are known.[7] Similarly, the reduction of 16-ketoestrone (an α-diketone) should give rise to four isomeric estriols. Previously only one estriol was known—the naturally occurring theelol. The isomer prepared by us has been designated isoestriol-A in view of the fact that the geometric arrangement of the two carbinols at positions 16 and 17 has not as yet been determined. It is our goal to prepare the remaining two isomers in order that all four compounds of the series Δ1,3,5-estratrientriol-3,16,17 be on hand for experimentation on tumor production.



I



II



III

Isoestriol-A was prepared from estrone by a five step synthesis involving benzoylation of estrone, formation of the 16-oximino derivative, saponification of the ester, reductive hydrolysis of the oximino group, and, finally, hydrogenation of the ketol (or ketols).

Litvan and Robinson[8] in 1938 first prepared the 16-oximino derivative of a steroid when they submitted estrone methyl ether to reaction with isoamyl nitrite in a medium of *t*-butyl alcohol and potassium *t*-butoxide. We followed their procedure with modifications but were forced to employ an ester of estrone in order that the free phenol might be easily recovered. Estrone benzoate was chosen in the hope that with it, under the conditions of our reaction, saponification would occur much less readily than nitrosation. Such was very likely the situation, for, after saponification 16-oximinoestrone (III) was obtained in 80% yield.

(1) National Research Fellow in the Medical Sciences, 1941–1942.

(2) Marrian, *Biochem. J.*, **24**, 435 (1930).

(3) Doisy, Thayer, Levin and Curtis, *Proc. Soc. Exp. Biol. Med.*, **28**, 88 (1930).

(4) Browne, cited by Collip, *Proc. Calif. Acad. Med.*, **1**, 38 (1931).

(5) Doisy, Veler and Thayer, *Am. J. Physiol.*, **90**, 329 (1929).

(6) Huffman, THIS JOURNAL, **64**, 2235 (1942).

(7) Schwenk and Hildebrandt, *Naturwissenschaften*, **21**, 177 (1933); Whitman, Wintersteiner and Schwenk, *J. Biol. Chem.*, **118**, 792 (1937).

(8) Litvan and Robinson, *J. Chem. Soc.*, 1997 (1938).

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Recently Stodola, Kendall and McKenzie[9] found that the mild reduction of 16-oximinodehydroisoandrosterone using zinc and aqueous acetic acid yielded only a small amount (less than 5%) of the expected amine, the bulk of the compound having been changed to a mixture of isomeric α-ketols. Our experience with the zinc–acetic acid reduction of 16-oximinoestrone was similar, as we rocovered a nitrogen-free material in over 90% yield. The exact composition of this material is not known, but certainly the preponderating component is an α-ketol. On further reduction of the α-ketolic material with hydrogen and Adams catalyst a triol (m.p. 267–269°)[10] was obtained which on admixture with authentic theelol (m.p. 271°) showed a depression of some 10°. Furthermore, the new triol gave a triacetate melting at 152° and a monomethyl ether melting at 141–142°, as contrasted against the analogous derivatives[11] of theelol which melt at 127 and 159°, respectively. The values[11] listed in the literature for the optical rotation of estriol vary from +57 to +66°, while that of isoestriol-A was found to be +88°. Isoestriol-A is also less soluble in ethanol than naturally-occurring estriol.

Experimental

Benzoylation of Estrone.[11]—Estrone (II) was benzoylated by the Schotten–Baumann method. For each gram of estrone, 570 cc. of 0.5 *N* potassium hydroxide and 10 cc. of benzoyl chloride were employed.

16-Oximinoestrone (16-Isonitrosoestrone) (III).—Potassium metal (1.0 g.) was dissolved in 40 cc. of *t*-butyl alcohol and 766 mg. of powdered estrone benzoate (m. p. 215–216°) added. The mixture was stirred for five hours to dissolve the ester and then 0.8 cc. of freshly-prepared isoamyl nitrite pipetted into the solution, which at once turned red in color. After the red solution had been stirred for four hours, another 0.8-cc. portion of isoamyl nitrite was added, and the stirring continued for an additional eight hours. The whole procedure was conducted at room temperature under an atmosphere of dry nitrogen.

The reaction mixture was transferred to a separatory funnel containing a solution of 10 g. of glycine in 150 cc. of water, and the whole shaken with ethyl ether until solution of all components was effected. After separation, the ether was extracted once with water and then with 0.5 *N* potassium hydroxide. In order to ensure complete saponification, the yellow potassium hydroxide layer was allowed to remain at room temperature for four hours. It was then extracted twice with ether, acidified with concentrated hydrochloric acid, and placed at 0°. A bulky white precipitate soon formed. After standing overnight, the precipitate filtered easily, and it was submitted to copious washing with water. On drying in the desiccator over calcium chloride, 495 mg. (81% yield)[12] of α-oximino ketone melting at 210–211° was obtained. On recrystallization from aqueous methanol, the 16-oximinoestrone crystallized in small tufts of fine, practically colorless needles which melted at 214–215° with decomposition.

Anal. Calcd. for $C_{18}H_{21}O_3N$: N, 4.68. Found: 4.59.

16-Oximinoestrone is a typical α-oximino ketone[13] in that its solution is colorless in ether but yellow in alkali.

Reduction of 16-Oximinoestrone with Zinc and Acetic Acid.—16-Oximinoestrone (397 mg.) was dissolved in 12.0 cc. of glacial acetic acid and 0.5 cc. of water. Zinc dust (1.0 g.) was added and the mixture swirled in a water-bath at 40–45°. The α-oximino ketone soon dissolved to give a yellow solution with a greenish fluorescence. Water[14] (11.5 cc.) was then added and the solution heated under reflux in an oil-bath held at a temperature of 120–125°. At first the color of the solution deepened to an intense green but this gradually disappeared, and at the end of 1.5 hours only a slight color remained. The hot solution was then decanted from the zinc into a separatory funnel containing an ice-cold aqueous solution of 9.0 g. of sodium hydroxide. A further rinsing of the zinc was performed with 5.0 cc. of hot acetic acid and the latter combined with the previous decantation. The mixture was shaken out with ethyl ether, the ether separated and washed successively with 1.0 *N* hydrochloric acid, aqueous bicarbonate, and water. Evaporation of the ether yielded a crystalline, almost colorless residue which on recrystallization from aqueous methanol with the use of charcoal gave 320 mg. The principal constituent in this product is an α-ketol which will be described in a subsequent publication.

Isoestriol-A.—The 320 mg. of α-ketolic product from the zinc–acetic acid reduction of 16-oximinoestrone was dissolved in 150 cc. of 0.5 *N* sodium hydroxide and 600 mg. of Adams catalyst added. After being shaken for twenty-four hours under hydrogen, the solution was filtered from the platinum and the latter washed with 0.5 *N* sodium hydroxide. The alkaline filtrate was acidified and extracted with ethyl ether. After being washed with aqueous bicarbonate and then with water, the ether was distilled off. In order to remove any possible unreduced ketone, the ether residue was treated with carboxymethoxylamine by a procedure previously published.[15] The non-ketonic fraction was recrystallized twice from acetone to yield 110 mg. of white microscopic crystals melting at 267–269°. This melting point remained the same after treatment with charcoal and successive recrystallizations from acetone, methanol and ethanol. A mixed melting point taken with authentic theelol[16] showed a depression of about 10 degrees. $[\alpha]^{29.5}D$ +88° (0.227% solution in 95% ethanol).

Anal. Calcd. for $C_{18}H_{24}O_3$: C, 74.97; H, 8.39. Found: C, 74.88; H, 8.40.

Isoestriol-A Methyl Ether.—Isoestriol-A (35 mg.) was dissolved in 20 cc. of 0.5 *N* sodium hydroxide and 0.5 cc. of redistilled dimethyl sulfate added. After being shaken for one and one-half hours the reaction mixture was left at room temperature overnight. The white precipitate was then filtered, washed several times with 0.5 *N* sodium hydroxide, and finally with water. After being dried in the desiccator the product was dissolved in methanol, treated with charcoal, and recrystallized from aqueous methanol at 0°. The yield was 12 mg. of white microscopic crystals melting at 141–142°. For analysis the ether was dried to constant weight *in vacuo* over phosphorus pentoxide at 80°.

Anal. Calcd. for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.23; H, 8.72.

Isoestriol-A Triacetate.—To 42 mg. of Isoestriol-A, 3 cc. of acetic anhydride and 3 cc. of pyridine were added. The solution was heated for three hours on the steam-bath, cooled and diluted with 50 cc. of cold water. Well-formed

(9) Stodola, Kendall and McKenzie, *J. Org. Chem.*, **6**, 841 (1941).

(10) All melting points in this paper are uncorrected.

(11) Doisy, in "Sex and Internal Secretions," Williams and Wilkins Co., Baltimore, p. 866 (1939).

(12) This reaction has been carried out several times, and the yield is usually around 80%. Once, however, we obtained a 96% yield of pure product.

(13) Meyer and Jacobson, "Lehrbuch der Organischen Chemie," Veit & Co., Leipzig, Sec. Ed., I, Part 2, p. 829 (1913).

(14) After conducting several zinc–acetic acid reductions on 16-oximinoestrone by the procedure of Stodola, Kendall and McKenzie, we decided that it was advantageous to use a more dilute solution of acid and to reflux longer if necessary, since, by this alteration, less fluorescing by-product seemed to be formed.

(15) Huffman, MacCorquodale, Thayer, Doisy, Smith and Smith, *J. Biol. Chem.*, **134**, 594 (1940).

(16) Kindly supplied us by Dr. Louis Levin, College of Physicians and Surgeons, Columbia University.

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crystals came out at once; the mixture was left at 0° overnight, filtered, and the crystals washed with water and dried in the desiccator over calcium chloride and potassium hydroxide. On recrystallization from methanol at 0°, long slender needles were slowly deposited; yield, 24 mg. melting at 152°.

Anal. Calcd. for $C_{24}H_{30}O_6$: C, 69.54; H, 7.30. Found: C, 69.13; H, 7.51.

Solubility of Isoestriol-A.—No direct solubility measurements were made; however, in attempting to prepare a solution for polarimetry it was found impossible to dissolve 23.66 mg. of the triol in 3.00 ml. of 95% ethanol at room temperature. The solubility of theelol in 95% ethanol has been found to be 1.20 g. (10°) and 1.65 g. (30°) in 100 g. of solvent.[17] It was further observed that isoestriol-A dissolves in 0.5 *N* sodium hydroxide much more readily than does theelol.

Ultraviolet Absorption Spectrum.—Ultraviolet absorption spectra of isoestriol-A and of theelol were obtained by use of the Hilger medium spectrograph. The two curves were identical, each with the other, and with that of theelol previously published by Callow.[18] This finding was anticipated, since isomers of this nature are not expected to show differences in ultraviolet absorption spectra.

Acknowledgment.—The authors wish to thank Miss Georgiana Becker for technical assistance and to express their appreciation to Mr. William Saschek for the micro-analyses reported in this paper. The authors are very grateful to Mr. Floyd H. Eggert, U. S. Standard Products Company, for the generous gift of crude estrone. To Professor Hans T. Clarke, who furnished the facilities for this research and who was a constant counselor throughout, they are deeply indebted.

Summary

1. 16-Oximinoestrone has been prepared from estrone benzoate.

2. Using 16-oximinoestrone as an intermediate, an estriol isomeric with theelol has been synthesized. Like theelol, the new estriol is a Δ1,3,5-estratrientriol-3,16,17.

WOODWORTH, WISCONSIN RECEIVED OCTOBER 22, 1943

(17) Doisy, Huffman, Thayer and Doisy, *J. Biol. Chem.*, **138**, 283 (1941).

(18) Callow, *Biochem. J.*, **30**, 906 (1936).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF DUKE UNIVERSITY]

The Use of Certain Phenyl Esters in the Reformatsky Reaction[1]

BY MELVIN S. BLOOM AND CHARLES R. HAUSER

The Reformatsky reaction using ethyl esters instead of aldehydes or ketones as the carbonyl component has not generally been very satisfactory.[2] Since phenyl esters have a more reactive carbonyl group than the corresponding ethyl esters (judging from their relative rates of alkaline hydrolysis)[3] it seemed possible that phenyl esters might serve satisfactorily as the carbonyl component in the Reformatsky reaction. This has been realized in certain cases but not in others.

It has been found that, although ethyl benzoate fails, phenyl benzoate undergoes satisfactorily the Reformatsky reaction with ethyl α-bromoisobutyrate to form ethyl benzoyldimethylacetate.

$$C_6H_5CO_2C_6H_5 + BrC(CH_3)_2CO_2C_2H_5 \xrightarrow{Zn} C_6H_5COC(CH_3)_2CO_2C_2H_5 + C_6H_5OZnBr$$

The yield (52%) of the β-keto ester obtained by this method is essentially the same as that obtained by the benzoylation of ethyl isobutyrate in the presence of the triphenylmethide ion.[4]

Phenyl esters are satisfactory as the carbonyl component in the Reformatsky reaction apparently only when neither the phenyl ester nor the bromoester has α-hydrogens. With 4-phenylphenyl acetate and ethyl α-bromoisobutyrate, ethyl α,α-dimethylacetoacetate was obtained in only low yield (11%), while with phenyl benzoate and ethyl α-bromoacetate or with 4-phenylphenyl propionate and ethyl α-bromoacetate, only very low yields of the respective β-keto esters appeared to be formed. Since most of the zinc was used up in these experiments, the low yields in these cases appears to be due to the predominance of side or subsequent reactions, which, among others, may involve the self-condensation of the phenyl ester (when it has an α-hydrogen) and the enolization of the β-keto ester formed from bromoesters having α-hydrogens. Both of these reactions could probably be effected by the organozinc halide which is presumably the intermediate in the Reformatsky reaction.[2]

Experimental

Ethyl Benzoyldimethylacetate.—In a 500-cc. three-necked flask fitted with a mechanical stirrer, a separatory funnel, and a reflux condenser protected with a calcium chloride tube was placed 16.4 g. (0.25 mole) of zinc foil which had been sandpapered and cut into small strips. A mixture of 48.8 g. (0.25 mole) of ethyl α-bromoisobutyrate (b. p. 49–51° (10 mm.)), 49.6 g. (0.25 mole) of phenyl benzoate (m. p. 68–68.5°), 100 cc. of dry benzene, and 150 cc. of dry toluene was placed in the separatory funnel. About 50 cc. of this solution was added to the zinc and the flask was heated to 150° in an oil-bath until the reaction started. The mixture was then stirred and the rest of the solution introduced at such a rate that gentle refluxing occurred, about thirty minutes being required. Refluxing and stirring were continued for an additional three hours. The flask was cooled in an ice-bath and its contents poured into ice-cold 10% sulfuric acid with vigorous stirring. The acid layer was separated and the benzene–toluene layer was washed with water. The combined wash water and

(1) Paper XXI on "Condensations"; paper XX, THIS JOURNAL, **65**, 2051 (1943).

(2) See especially Shriner, "Organic Reactions," Roger Adams, Editor-in-Chief, John Wiley and Sons, New York, N. Y., 1942, Chapter I.

(3) See Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, p. 211.

(4) Hauser and Renfrow, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, New York, N. Y., 1943, p. 268.

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the acid layer was extracted with ether, and the combined ether and benzene–toluene solution was dried over anhydrous sodium sulfate followed by Drierite. The solution was distilled up to 140° and the residue was fractionated at 9 mm., collecting fractions at 72–130° and at 130–145°. To the residue was added the fraction boiling at 72–130° (9 mm.), and the mixture distilled, the material boiling at 129–149° (9 mm.) being collected and combined with the fraction boiling at 130–145 (9 mm.). Redistillation yielded 28.5 g. (52%) of ethyl benzoyldimethylacetate boiling at 132–135° (9 mm.). Some phenyl benzoate was recovered in the residues.

With hydroxylamine hydrochloride, the β-keto ester gave 3-phenyl-4-dimethylisoxazolone-5 (m. p. 69–70°)[5] in 90% yield. On ketonic hydrolysis by the acetic-sulfuric acid method,[6] the β-keto ester gave a 77% yield of phenyl isopropyl ketone (102–103° (15 mm.)); m. p. of 2,4-dinitrophenylhydrazone, 162–163°.[7]

In the Reformatsky reaction described above, in which approximately 80% of the zinc was used up, the zinc tended to become coated with a precipitate in the course of the reaction, and the yield was satisfactory only when the reaction mixture was stirred vigorously using zinc foil. With 20–30 mesh zinc 30% of the zinc was used up, giving an 18% yield of the β-keto ester. When magnesium turnings were used instead of zinc only an 18% yield of the β-keto ester was obtained even though practically all of the magnesium was used up.

In an experiment in which ethyl benzoate was used instead of phenyl benzoate, less than 10% of the zinc reacted, and the reaction was not further studied.

Other Reactions.—The following reactions were carried out essentially as described for the preparation of ethyl benzoyldimethylacetate.

Ethyl α-bromoisobutyrate with 4-phenylphenyl acetate[8] (m. p. 87–88°) gave an 11% yield of ethyl α,α-dimethylacetoacetate, b. p. 75–76° (14 mm.). When phenyl acetate was used instead of 4-phenylphenyl acetate, the β-keto ester could not be freed from the unreacted phenyl acetate. Ketonic cleavage by the acetic-sulfuric acid method,[6] gave a small amount of methyl isopropyl ketone, b. p. 93–95°; m. p. of 2,4-dinitrophenylhydrazone of the ketone, 118°.[9]

Ethyl bromoacetate with phenyl benzoate yielded a small fraction boiling at 141–143° (6 mm.) which apparently contained, in addition to phenyl benzoate, at least a trace of ethyl benzoylacetate since it gave the red enol test and the green copper salt.[10]

Ethyl bromoacetate with 4-phenylphenyl propionate[11] (m. p. 92.0–92.5°) yielded a small fraction of product boiling over a large range, giving the red enol test and the copper salt,[12] (m. p. 143–144°) of ethyl propionylacetate.

Summary

1. Phenyl benzoate has been found to undergo the Reformatsky reaction with ethyl α-bromoisobutyrate to form ethyl benzoyldimethylacetate in good yield.

2. Phenyl esters appear to be satisfactory as the carbonyl component for the Reformatsky reaction only when neither the phenyl ester nor the bromoester has α-hydrogens.

(5) Renfrow and Hauser, THIS JOURNAL, **60**, 464 (1938).

(6) Hudson and Hauser, *ibid.*, **63**, 3163 (1941).

(7) Huntress and Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, New York, N. Y., 1941, p. 391.

(8) This ester was prepared in 74% yield from 4-phenylphenol and acetic anhydride essentially as described for the corresponding propionate, see ref. 11.

(9) Huntress and Mulliken, *op. cit.*, p. 375.

(10) Huntress and Mulliken, *ibid.*, p. 268.

(11) Abramovitch and Hauser, THIS JOURNAL, **64**, 2272 (1942).

(12) Beilstein, "Handbuch der organischen Chemie," Julius Springer, Berlin, 1921, Vol. III, p. 671.

DURHAM, N. C. RECEIVED OCTOBER 18, 1943

NOTES

2,3,4-Triacetyl-α-methylglucopyranoside-6-nitrate and 3,4,6-Triacetyl-β-methylglucopyranoside-2-nitrate

BY E. K. GLADDING[1] AND C. B. PURVES

Although these two compounds were synthesized, apparently for the first time, by conventional methods as an incident in a larger research, it seems advisable to make a brief, separate record of their preparation and their properties.

The nitration of 2,3,4-triacetyl-6-trityl-α-methylglucoside[2] produced a crystalline residue consisting of triphenylmethyl carbinol and the desired 6-nitrate in equimolecular amount.[3] A fractional crystallization, carried out exactly as specified below, resulted in a 79% yield of pure 2,3,4-triacetyl-α-methylglucoside-6-nitrate, which occurred as well formed prisms having m. p. 112–113° (cor.). No wandering of acetyl groups occurred during the nitration because the same nitrate was obtained by heating 2,3,4-triacetyl - 6 - iodo - 6 - desoxy - α - methylglucopyranoside[4] with excess silver nitrate in acetonitrile. Conversely, the 6-iodo compound was produced in 91% yield by heating the nitrate with excess sodium iodide dissolved in acetonylacetone.[5] The specific rotation of the nitrate in 1.11% chloroform solution was $[\alpha]^{20}D$ 132°, and this value, in conjunction with that of −14.3° found for triacetyl-β-methylglucopyranoside-6-nitrate,[6] leads to a molecular rotation difference of 53,400. The fact that this difference is very close to that of 53,900, accepted for tetraacetyl α- and β-methylglucoside[7] supports the conclusion that the two isomeric nitrates differ only in the configuration of the glycosidic carbon atom,

(1) Du Pont Post-Doctoral Research Fellow, 1942–1943. Present address, Magnolia Petroleum Company, Field Research Department, Dallas, Texas.

(2) Haworth, Owen and Smith, *J. Chem. Soc.*, 88 (1941).

(3) *Cf.* Oldham and Bell, THIS JOURNAL, **60**, 323 (1938).

(4) Compton, *ibid.*, **60**, 395 (1938).

(5) Murray and Purves, *ibid.*, **62**, 3194 (1940).

(6) Oldham, *J. Chem. Soc.*, 2840 (1925).

(7) Hudson and Dale, THIS JOURNAL, **40**, 997 (1918).

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The experimental portion describes one or two manipulative improvements in the standard synthesis of 3,4,6-triacetyl-β-methylglucopyranoside.[8,9] Nitration of the latter gave a triacetyl methylglucoside nitrate in an over-all yield of about 15% from glucose pentaacetate. The nitrate occurred as small prisms, m. p. 117–118° (cor.) and with a specific rotation of $[\alpha]^{25}D$ −1° in 3.69% chloroform solution. Since acyl wandering is unlikely during nitration, and was not observed during several similar substitutions,[8,9] the nitrate group was assigned to the second position in the triacetyl-β-methylglucoside molecule.

Experimental

2,3,4-Triacetyl-α-methylglucoside-6-nitrate.—Commercial α-methylglucopyranoside, 50 g., was condensed with triphenylmethyl chloride,[2] and the product was acetylated prior to isolation.[10] Although the purified triacetyl-6-trityl derivative, 81 g., analyzed correctly and had the accepted rotation of $[\alpha]^{20}D$ 137° in pyridine,[11] it melted at 143–145° (cor.) instead of at 136°.[2,11] A solution of 15 g. of the 6-trityl derivative in 75 cc. of chloroform was mixed, at 3 to 5°, with 6 g. of phosphorus pentoxide previously dissolved in 75 cc. of nitric acid.[12] This nitric acid was prepared by distilling a mixture of concentrated sulfuric and nitric acids (1:1) in an all-glass apparatus and was miscible without turbidity with chloroform. After being kept at 3 to 5° for ten to fifteen minutes, the nitration mixture was poured, with stirring, into 750 cc. of cracked ice and water. The chloroform layer was separated, washed with dilute sodium bicarbonate solution and with water, and dried over anhydrous sodium sulfate. Evaporation under reduced pressure left a solid, crystalline residue consisting of triphenylmethyl carbinol and the desired nitrate. This mixture was completely, or almost completely, dissolved in 75 cc. of warm, glacial acetic acid, and exactly 50 cc. of water was added, drop by drop with continuous shaking, in order to precipitate the carbinol. After the mixture had stood at room temperature for several hours, 6.1 g., or 88% of the carbinol was removed by filtration and the 6-nitrate was then precipitated by slowly adding 150 cc. of water to the mother liquor. An easy recrystallization from 50 cc. of hot benzene and 100 cc. of ligroin left 7.7 g. of practically pure material, which was recrystallized once more from methanol.

Anal. Calcd. for a triacetyl methylglucoside mononitrate, $C_{13}H_{19}O_{11}N$: C, 42.7; H, 5.2; N, 3.84. Found: C, 42.8, 42.8; H, 5.2, 5.1; N, 4.12, 4.15.

3,4,6-Triacetyl-β-methylglucoside-2-nitrate.—The trichloroacetyl group was removed from 20 g. of pure, recrystallized 2-trichloroacetyl-3,4,6-triacetyl glucopyranosyl chloride[8] by solution at 0° in 350 cc. of dry ether previously saturated with dry ammonia gas.[8] The crystalline aggregates of crude triacetyl glucosyl chloride that promptly separated were broken up by occasional shaking. They were then washed with ether, 25 cc., and benzene, 50 cc., and were suspended without previous drying in 160 cc. of dry benzene. This procedure retained the highly swollen, flocculent condition of the crystals and resulted in a semi-permanent benzene suspension that gave reliable yields in the next operation. Suspensions of previously dried crystals gave erratic results. A slow stream of dry ammonia gas was passed through this suspension at room temperature for eight hours and benzene was occasionally added to replace that lost by evaporation. A rapid stream of gas greatly delayed the reaction because a quick evaporation of benzene chilled the mixture. Although it was easy to purify the crude 3,4,6-triacetyl anhydroglucose<1,5><1,2>, 11.8 g., that was produced,[8,9] for present purposes it was sufficient to dissolve the sirup in 200 cc. of dry methanol. A nearly quantitative yield, 12 g., of 3,4,6-triacetyl-β-methylglucoside was isolated on the following day. Trituration of the crude product with 20 cc. of cold ether left 8.9 g., m. p. 93–94° (uncor.), whose specific rotation of 18.8° in methanol[9] showed that it was pure enough for nitration. Recrystallization from absolute alcohol was slow and difficult but better results were obtained with an alcohol–petroleum ether mixture. Yields, melting points and rotations given for all intermediates in the synthesis were confirmed.[8,9]

A solution of 5 g. of triacetyl methylglucoside in 50 cc. of chloroform was nitrated with 50 cc. of chloroform-soluble nitric acid and 6 g. of phosphorus pentoxide in the way already described. The crude product, 4.5 g. or 76% of calcd., crystallized readily and was recrystallized from 25 cc. of hot methanol. The physical properties given in the Introduction for 3,4,6-triacetyl-β-methylglucoside-2-nitrate were not changed by further recrystallization.

Anal. Calcd. for $C_{13}H_{19}O_{11}N$: C, 42.7; H, 5.2; N, 3.84. Found: C, 42.6, 42.5; H, 5.2, 5.7; N, 3.90, 3.87.

CONTRIBUTION NO. 290 FROM THE
RESEARCH LABORATORY OF ORGANIC CHEMISTRY
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE, MASS. RECEIVED SEPTEMBER 22, 1943

(8) Brigl, *Z. physiol. Chem.*, **116**, 39 (1921); **122**, 262 (1922).
(9) Hickinbottom, *J. Chem. Soc.*, 3140 (1928); 1681 (1929); 1338 (1930).
(10) *Cf.* Müller, *Ber.*, **64**, 1820 (1931).
(11) Helferich and Becker, *Ann.*, **440**, 1 (1924).
(12) *Cf.* Behrend and Roth, *ibid.*, **331**, 359 (1904).

The Alkylation of *o*- and *p*-Xylene

BY DOROTHY NIGHTINGALE AND J. R. JANES[1]

Our experiences with various catalysts for the alkylation of *m*-xylene[2] indicated that it would be worth while to study their efficiency with *o*- and *p*-xylene, especially since one of these catalysts, boron trifluoride, is less likely to promote migration or rearrangement of alkyl groups already on the ring. *t*-Butyl compounds were selected as alkylating agents since they are more reactive than their isomers and the *t*-butyl radical does not undergo rearrangement.

o-Xylene alkylated readily with *t*-butyl chloride and anhydrous ferric chloride and with *t*-butyl alcohol and boron trifluoride to form 1,2-dimethyl-4-*t*-butylbenzene in good yield.

As might be expected *p*-xylene did not alkylate as readily as the *o*- and *m*-xylenes. It did not alkylate at all with *t*-butyl alcohol and 80% sulfuric acid, *t*-butyl chloride and ferric chloride, or isobutylene and ferric chloride. With boron trifluoride and *t*-butyl alcohol, the product distilled over a 45° range and no one compound could be isolated from the mixture. Toluene alkylated readily with isobutylene and ferric chloride so the failure of *p*-xylene to alkylate was not due to the reagents.

Experimental

Alkylation of *o*-Xylene with Ferric Chloride and *t*-Butyl Chloride.—*t*-Butyl chloride (25 g.) was added during one hour and with stirring to 150 g. of *o*-xylene and 12.5 g. of anhydrous ferric chloride in a one-liter round-bottom

(1) Present address, Hercules Powder Company, Wilmington, Delaware.
(2) Nightingale, Radford and Shanholtzer, THIS JOURNAL, **64**, 1662 (1942).

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three-necked flask equipped with a reflux condenser and motor stirrer. The temperature was maintained at −3 to 10° during the total reaction time of seven hours. The mixture was decomposed by pouring into 100 cc. of hydrochloric acid and 100 g. of cracked ice. The upper layer was extracted with petroleum ether (28–38°), washed and dried.

After removal of the solvent and excess *o*-xylene, the product (74 g.) distilled at 83–85° (3 mm.). Fractionation of this material yielded 30.5 g. (70%) of 1,2-dimethyl-4-*t*-butylbenzene, $n^{25}D$ 1.4970.

Anal. Calcd. for $C_{12}H_{18}$: C, 88.89; H, 11.11. Found: C, 88.83; H, 11.45.

Oxidation of 1,2-Dimethyl-4-*t*-butylbenzene.—The hydrocarbon (5 g.) was dissolved in 40 cc. of pyridine in a 3-necked conical flask and water added until the solution became slightly turbid. The flask was heated to 80° in a water-bath. Potassium permanganate (15 g.) was added with stirring during one hour and the mixture stirred an additional six hours. The manganese dioxide was separated by filtration. The filtrate was acidified with concentrated hydrochloric acid and the acid collected on a filter. Crystallization from dilute alcohol yielded 2 g. of white needles, m. p. 140–141°, the melting point recorded in the literature for 2-methyl-4-*t*-butylbenzoic acid.[3,4]

Anal. Calcd. for $C_{12}H_{16}O_2$: C, 75.00; H, 8.33; n. e., 197. Found: C, 74.60; H, 8.44; n. e., 197.

Alkylation of *o*-Xylene and Boron Trifluoride and *t*-Butyl Alcohol.—*o*-Xylene (102 g.) and 19 g. of *t*-butyl alcohol were placed in a 500-cc. three-necked conical flask equipped with a motor stirrer, gas inlet and outlet tubes for the boron trifluoride. The boron trifluoride (14 g.) was added according to the procedure previously described.[2] The product was worked up in the usual manner; yield of 1,2-dimethyl-4-*t*-butylbenzene 34.5 g., b. p. 76–81° (3 mm.), $n^{26}D$ 1.4970.

The acid obtained by oxidation of this hydrocarbon melted at 139–140° (n. e., 198) and did not depress the melting point of the acid described above.

(3) Effront, *Ber.*, **17**, 2333 (1884).
(4) Baur, *ibid.*, **33**, 2569 (1900).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF MISSOURI
COLUMBIA, MISSOURI
RECEIVED OCTOBER 4, 1943

Pyrazine–Water Azeotrope

BY HARRY F. PFANN[1]

In the course of an investigation involving the purification of pyrazine by fractional distillation, it was observed that an azeotrope was formed with water. This was found to distil at 95.5° (uncor.) at 760 mm., to have a refractive index $n^{25}D$ 1.4510, density of 1.06 at 25°, and a composition of 60% pyrazine—40% water. The mole ratio of 1:3.38 approaches the 1:3.31 ratio for the pyridine–water azeotrope, for which the boiling point is variously given as 92.6–94.0°.[2,3,4] The refractive index of pyrazine–water solutions appears to be a linear function of weight concentration. The pyrazine taken for this work had a melting range of 50–52° and boiling range 114–115°. Values in the literature[5,6] range from m. p. 47–54° and b. p. 111–118°.

The minimum boiling mixture was obtained from solutions containing an excess of either pyrazine or water. Essentially dry pyrazine resulted from fractionation of mixtures containing more than 60% pyrazine, the water being removed as the azeotrope. No azeotrope was observed with methyl or ethyl alcohols.

(1) Present address: Koppers United Company, Butadiene Division, Monaca, Pa.
(2) E. Baud, *Bull. soc. chim.*, **5**, 1022–1033 (*C. A.*, **4**, 703 (1910)).
(3) Lange, "Handbook of Chemistry," 4th edition, p. 1210.
(4) Lecat, "La Tension de Vapeur des Melanges des Liquids," Brussels, 1913.
(5) Beilstein, Vol. XIII, p. 91.
(6) Aston, Peterson and Holowchak, THIS JOURNAL, **56**, 153–154 (1934).

STAMFORD RESEARCH LABORATORIES
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RECEIVED OCTOBER 14, 1943

Carbon–Carbon Cleavage in the Hydrogenolysis by Raney Nickel Catalyst of Ethylenedithiol and its Ethers

BY H. R. SNYDER AND GEORGE W. CANNON

In the determination of the structure of ω,ω'-bimethionine $[HO_2CCH(NH_2)CH_2CH_2SCH_2CH_2SCH_2CH_2CH(NH_2)CO_2H]$ the *bis*-phenylhydantoin obtained from the substance was subjected to hydrogenolysis by Raney nickel catalyst.[1] This treatment converts a monosulfide (RSR′) into the two molecules RH and R′H,[2] and accordingly was expected to convert the *bis*-phenylhydantoin into two molecules of *dl*-3-phenyl-5-ethylhydantoin and one molecule of ethane. The first of these products was isolated in good yields.[1] However, analysis of the gas produced during the hydrogenolysis has shown that not only ethane but also methane is formed. The occurrence of these two hydrocarbons indicates that the hydrogenolysis of ethers of 1,2-dithiols may take two courses.

$$RSCH_2CH_2SR \begin{cases} \rightarrow 2RH + CH_3CH_3 & (a) \\ \rightarrow 2RH + 2CH_4 & (b) \end{cases}$$

To determine whether carbon–carbon cleavage may be expected of other similar substances ethylenedithiol and certain of its ethers have been subjected to the hydrogenolysis. The hydrogenolyses were run as described by Mozingo, Wolf, Harris and Folkers[2] and the evolved gases were passed through a tower containing 20% aqueous sodium hydroxide into a liquid-air trap. At the end of each reaction the collection tube was connected momentarily to a vacuum pump while still immersed in liquid air, and the residual liquid was allowed to vaporize into gas sample tubes. The gas then was analyzed by standard methods.[3] The results are shown in the table.

(1) Snyder, Cannon, Howe and Nyman, THIS JOURNAL, **65**, 2211 (1943).
(2) Mozingo, Wolf, Harris and Folkers, *ibid.*, **65**, 1013 (1943).
(3) The authors are indebted to Mr. Cameron D. Lewis for certain of the gas analyses.

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HYDROGENOLYSIS OF ETHYLENEDITHIOL AND CERTAIN OF ITS ETHERS

R in $RSCH_2CH_2SR$	Composition of hydrocarbon fraction of gas evolved, % Methane	Ethane
$HO_2CCH(NH_2)CH_2CH_2$—	34	66
$CON(C_6H_5)COCHCH_2CH_2$— (NH)	44	56
$HOCH_2CH_2$—	0	100
C_6H_5—	23	77
H	14	86

In all five instances ethane was the major product, but in only one was it the sole product. Thus it is evident that carbon–carbon cleavage (reaction b) may occur as an important side reaction in the hydrogenolysis of derivatives of ethylenedithiol, but it is not yet possible to evaluate the structural factors which influence the two reactions (a and b).

CONTRIBUTION FROM THE NOYES LABORATORY
THE UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS RECEIVED NOVEMBER 15, 1943

Reaction of Diazomethane with α-Tetralone

BY R. B. THOMPSON[1a]

The ring expansion of cyclic ketones with diazomethane[1b] should be of considerable interest when applied to α-tetralone, since this system, stabilized by a fused ring, might permit preparation of more highly unsaturated compounds.

Although Burger and Mosettig reported that[2] α-tetralone did not react with diazomethane in ether, O. Pauli[3] found that the alcohol–sodium carbonate method gave a slow reaction yielding chiefly a mixture of ethylene oxides plus a ketonic fraction too small to identify.

The following experiments were carried out to investigate this reaction further: to 1 mole (146 g.) of α-tetralone, b. p. 87–88° (0.7 mm.) and $n^{20}D$ 1.5660, were added 130 cc. of absolute alcohol and 1.5 g. of finely powdered sodium carbonate and the temperature adjusted to 10–15°. Nitrosomethylurethan (246 g.) was added with stirring over a period of twenty-six to twenty-eight days, during which gas was regularly evolved.

After filtering, the low-boiling alcohol, water and methyl ethyl carbonate were distilled. Careful fractionation of the remainder gave 80–85% of unchanged α-tetralone, 7–8% of non-ketonic material, b. p. 93–96° (0.7 mm.) and 6–7% of a higher ketone, b. p. 103–106° (0.7 mm.).

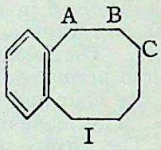
The ketone was crystallized by hydrolyzing the semicarbazone, which could not be obtained in a pure condition for analysis. The ketone then recrystallized from methyl alcohol melted at 73–75° and possessed a camphor-like odor.

Anal. Calcd. for $C_{12}H_{14}O$: C, 82.7; H, 8.1. Found: C, 82.5; H, 8.4.

The ketone gave an oxime that after recrystallization from ethyl alcohol melted at 164–165°. In one instance an oxime melting at 89–90° was obtained.

Anal. Calcd. for $C_{12}H_{15}NO$: C, 76.1; H, 8.0. Found: (165°) C, 76.4; H, 8.3; (90°) C, 75.9; H, 7.7.

These analytical data indicated that two methylene groups had been added to α-tetralone. Since diazomethane reacts with other cyclic ketones to give ring expansion, it is believed that this reaction has occurred here. Therefore, three structural formulas are possible, namely, those having the keto group at I-A, -B, or -C.



I

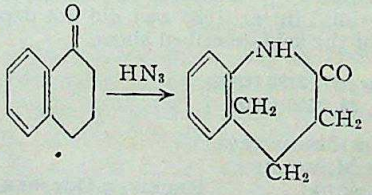
The structure has not been rigidly proved, but there is considerable evidence to show that it is IB.

Fry and Fieser[4] have prepared IC. It melts at 49–50° and gives an oxime melting at 112.5–114° while the ketone from the present experiment melts at 73–74° and gives an oxime melting at 165°.

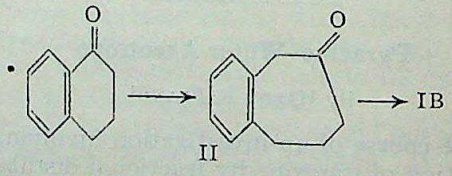
The following evidence tends to reject formula 1A. Mosettig and Jovanovic[5] found that diazomethane reacts with acetophenone to insert a methylene group next to the benzene ring.

$$C_6H_5COCH_3 \longrightarrow C_6H_5CH_2COCH_3$$

Briggs and DeAth[6] obtained the same results in the reaction of hydrazoic acid (the ammonia analog of diazomethane) with α-tetralone.



Since the reaction probably goes



II

it is easy to see why efforts to isolate II failed. Thus, α-tetralone, having the ketone group in the α-position, is relatively unreactive, but II, with a β-keto group, has an enhanced activity and will react as rapidly as formed. The final product IB is still a β-ketone but has lost most of its activity through resistance of the eight-membered ring to further expansion.[1b] Presumably, therefore, any higher ketones are present in quantities too small to be isolated from the mixture.

CHICAGO, ILLINOIS RECEIVED SEPTEMBER 20, 1943

(1a) Present address: Universal Oil Products Co., Riverside, Illinois.

(1b) Kohler, Tishler, Potter and Thompson, THIS JOURNAL, 61, 1057 (1939).

(2) Burger and Mosettig, *ibid.*, 58, 2295 (1931).

(3) Otto Pauli, Dissertation, Marburg (1935).

(4) Fry and Fieser, THIS JOURNAL, 62, 3489 (1940).

(5) Mosettig and Jovanovic, *Monatsh.*, 54, 427 (1929).

(6) Briggs and DeAth, *J. Chem. Soc.*, 456 (1937).

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COMMUNICATION TO THE EDITOR

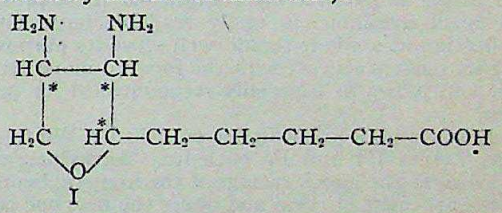
THE SYNTHESIS OF TWO STEREOISOMERIC 3,4-DIAMINO-2-TETRAHYDROFURAN-VALERIC ACIDS

Sir:

Recently[1] a convenient procedure has been described for the preparation of 3,4-dicarboxy-2-furan-valeric acid. These studies have been continued in order to develop synthetic procedures for the preparation of biotin analogs. The purpose of the present communication is to report the synthesis of two stereoisomeric 3,4-diamino-2-tetrahydrofuran-valeric acids.

3,4-Dicarbethoxy-2-furanpentanol was prepared from 2-furanpentanol[2] (α-naphthyl-urethan m. p. 58–59°; calcd.: C, 74.27; H, 6.55; N, 4.33. Found: C, 73.97; H, 6.46; N, 4.41) and diethylacetylene dicarboxylate by the procedure outlined in the aforesaid publication. This material was subjected to high pressure hydrogenation and the reduction products were treated with hydrazine to yield two crystalline hydrazides, $C_{11}H_{22}O_4N_4$, m. p. 208–211° (calcd. C, 48.16; H, 8.08; N, 20.41. Found: C, 48.15; H, 7.85; N, 20.18) and m. p. 177–180° (Found: C, 48.01; H, 7.95; N, 20.27). These two dihydrazides of the stereoisomeric 3,4-dicarboxy-2-tetrahydrofuranpentanols were degraded by the Curtius method to the corresponding 3,4-diaminocarbethoxy-2-tetrahydrofuranpentanols, $C_{15}H_{28}O_6N_2$, m. p. 110–113° (calcd.: C, 54.21; H, 8.49; N, 8.42. Found: C, 53.92; H, 8.09; N, 8.57) and m. p. 128–130° (Found: C, 53.84; H, 8.19; N, 8.64). The primary alcohol group at the end of the aliphatic side chain was then converted to a carboxyl group by oxidation with chromic acid in glacial acetic acid and the resulting 3,4-diaminocarbethoxy-2-tetrahydrofuran-valeric acids (m. p. 118–124° and 157–159°, respectively) were hydrolyzed with concentrated barium hydroxide to the corresponding 3,4-diamino-2-tetrahydrofuran-valeric acids. In order to characterize these compounds by means of sharply melting derivatives, the dibenzoyl methyl esters, m. p. 183–186° (calcd. C, 67.89; H, 6.64; N, 6.60. Found: C, 67.87; H, 6.38; N, 6.62) and m. p. 171–172° (Found: C, 67.62; H, 6.36; N, 6.68), respectively, were prepared, the higher melting isomer being derived from the higher melting hydrazide.

The molecule of 3,4-diamino-4-tetrahydrofuran-valeric acid I contains 3 asymmetric carbon atoms (denoted by means of asterisks).



I

and may exist in eight optically active forms. Four racemic mixtures therefore may be expected, two of which contain the amino groups in the *cis* and two which contain the amino groups in the *trans* configuration. The above-described diamino-carboxylic acids undoubtedly represent two of the four possible racemic forms; further work in this connection is at present under way in this Laboratory.

RESEARCH LABORATORIES
CIBA PHARMACEUTICAL PRODUCTS, INC.
SUMMIT, NEW JERSEY KLAUS HOFMANN

RECEIVED DECEMBER 9, 1943

(1) Hofmann, THIS JOURNAL, 66, 51 (1944).
(2) Hofmann, unpublished results.

NEW BOOKS

The Chemical Background for Engine Research. Editors, R. E. BURK, Director of Research, The Standard Oil Company, Cleveland, Ohio, and OLIVER GRUMMITT, Morley Chemistry Laboratory, Western Reserve University, Cleveland, Ohio. (Frontiers in Chemistry. Volume II.) Interscience Publishers, Inc., 215 Fourth Avenue, New York, N. Y., 1943. vii + 297 pp. Illustrated. 15.5 × 23.5 cm. Price, $3.50.

"Prominent scientists report on recent investigations and interpretations of combustion processes and lubrication":—this brief advertisement which appears on the front jacket page of the volume expresses its contents much better than does the overly ambitious title. Actually, the work is a group of lectures on particular topics by six leading authorities; it is the second successful course of this type given by Western Reserve University in a commendable effort to present both the student and the mature chemist with an intelligible—but by no means superficial—view of current knowledge in the field.

Of the six chapters, "A Survey of Combustion Research," by Ernest F. Fiock, presents a brief but excellent historical review and description of modern methods of studying flame travel. "Chemical Thermodynamics of Hydrocarbons," by Frederick D. Rossini, gives the calculation and best values of the entropy, heat and free energy of formation, and isomerization equilibria. "Synthetic Methods for Hydrocarbons," by Frank C. Whitmore, contains a survey of the typical laboratory Grignard reactions used, and a brief mention of some of the industrial methods of synthesis. "Kinetics of Flame and Combustion," by Guenther von Elbe, is restricted to the slow oxidation and self-ignition of hydrogen and the paraffin-

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hydrocarbons. "The Experimental Side of Combustion Research in Engines," by Bernard Lewis, explains the devices used to measure flame travel, pressure, and temperature in the automobile (Otto-cycle) engine, and reviews present knowledge of knocking combustion. Finally, "Some Physicochemical Aspects of Lubrication," by Otto Beeck, is a comprehensive survey covering engine ring sticking and bearing corrosion, oil oxidation and detergency studies, and boundary lubrication theory and testing.

As is perhaps inevitable in a collection of separate papers such as this, there are some conspicuous omissions. For example, the Diesel engine receives only a page and a half; safety fuels and their ignition are not mentioned nor are fuels of the non-hydrocarbon type; the effects of supercharging and of charge dilution (as by exhaust gas or by water injection) might have been noted; the chemical aspects of work on spark plugs, valves, and bearings is not described, despite its practical importance. Numerous other examples could be adduced but would only serve to illustrate further the obvious fact that the field as a whole is far too large to be completely covered in one small volume.

As a matter of fact, the authors are to be congratulated on having made a judicious selection of important topics and significant details from the mass of information available to them, and on having compressed these into the limited space available, in easily readable form withal. The collection as a whole should well serve its purpose of keeping its readers abreast with the forward movement of science, and it can be especially recommended for school libraries.

The reviewer noticed but few errors. In Dr. Whitmore's chapter, Tables III and IV both list "2-ethylpentane"; Table IV gives the knock ratings of the isomeric heptanes but lists only eight of them and omits the best one of all, triptane; the omission, like others in the book, may have been intentional, although the quality of triptane is surely no military secret.

The volume is printed in large type on high-quality paper, and contains numerous photographic illustrations including some excellent pictures of flame travel. A praiseworthy innovation is the inclusion of two pages giving photographs of the six authors and short biographical sketches about each of them.

HAROLD A. BEATTY

The Adsorption of Gases and Vapors. Volume I. Physical Adsorption. By STEPHEN BRUNAUER, Chemist, Bureau of Plant Industry, United States Department of Agriculture. Princeton University Press, Princeton, New Jersey, 1943. vii + 511 pp. 169 figs. 16.5 × 23.5 cm. Price, $7.50.

This is a very interesting and worth-while contribution to the literature of adsorption. The author has dealt with a great mass of heterogeneous and sometimes contradictory material, and has been markedly successful in achieving an orderly and logical presentation. A general description of the main phenomena and the methods of investigating them is followed by more detailed developments of particular topics such as the shape of the adsorption isotherms, the surface of the adsorbent, and the kinetics of the process. A certain amount of repetition is inevitable, but the net effect is satisfactory.

The author discusses a great many different theories connected with one or another aspect of the subject. Holding definite views of his own, he does not allow them to obtrude themselves unduly into his presentation and evaluation of the work of others. In fact, if fault must be found, it would be rather on the opposite grounds that the various theories are presented as put forth by their authors without sufficient analytical criticism by the author. However, the reviewer is not inclined to reproach the author for this. If the net impression after a forced march through the considerable bulk of this book is that of a mass of theories most of which are limited to the explanation of a few facts and many of which are mutually incompatible, the reasons are to be found in the complexities and difficulties inherent in the subject itself. The careful reader will likely be stimulated to try what he can do to improve the situation.

A. S. COOLIDGE

BOOKS RECEIVED

November 10, 1943–December 10, 1943

FRITZ EPHRAIM. "A Text-Book of Inorganic Chemistry." English Edition by P. C. L. Thorne and E. R. Roberts. Fourth Edition, Revised and Enlarged. 924 pp. Gurney and Jackson, 98 Great Russell Street, London, W.C.1, England (Oliver and Boyd, Ltd., Tweeddale Court, Edinburgh). 28/- net. Interscience Publishers, Inc., 215 Fourth Ave., New York, N. Y. $8.75.

O. A. HOUGEN AND K. M. WATSON. "Chemical Process Principles. Part I. Material and Energy Balances." John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y. 452 pp. $4.50.

GEORGE S. JAMIESON. "Vegetable Fats and Oils." Second Edition. Reinhold Publishing Corporation, 330 West 42nd Street, New York, N. Y. 508 pp. $6.75.

PAUL O. POWERS. "Synthetic Resins and Rubbers." John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y. 296 pp. $3.00.

PETER PRINGSHEIM AND MARCEL VOGEL. "Luminescence of Liquids and Solids." Interscience Publishers, Inc., 215 Fourth Avenue, New York, N. Y. 201 pp. $4.00.

W. T. READ. "Industrial Chemistry." Third Edition. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y. 631 pp. $5.00.

G. W. WEINGART. "Pyrotechnics, Civil and Military." Chemical Publishing Company, Inc., 234 King Street, Brooklyn, New York. 220 pp. $5.00.

L. E. YOUNG AND C. W. PORTER. "General Chemistry." Revised Edition. Prentice-Hall, Inc., 70 Fifth Avenue, New York, N. Y. 527 pp. $3.75.

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Claims for missing numbers will not be allowed (1) if received more than sixty days from date of issue (owing to the hazards of war-time delivery, no claims can be honored from subscribers outside of North America), (2) if loss was due to failure of notice of change of address to be received before the date specified in the preceding paragraph, or (3) if the reason for the claim is "missing from files."

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The American Chemical Society also publishes *Chemical Abstracts*, *Industrial and Engineering Chemistry* (Industrial and Analytical Editions), and *Chemical and Engineering News*. Rates on request.

NOTICE TO AUTHORS OF PAPERS

Manuscripts for THIS JOURNAL should be submitted to the Editor ready for publication, typewritten (double space), with 2–3 cm. margins, on a good quality, durable paper, preferably of 8.5″ × 11″ size. In addition to the original typewritten copy, one or more carbon copies should be submitted so that the time required for examination by the Editorial Board may thus be considerably shortened. Care should be taken that all pages in a manuscript, including tables (but not the diagrams) be numbered consecutively. In preparing manuscripts authors are requested to observe, for reasons of economy, the utmost conciseness consistent with clarity of presentation. The manuscripts should be addressed to specialists in their particular field rather than to the general reader. Extensive reviews of the literature cannot be accepted. When well-known or previously published procedures have been followed in the experimental work they should only be designated or referred to.

Form of Presentation.—There should be one or more introductory paragraphs setting forth the occasion, significance and main objectives of the investigation and the method of attack. This should be followed by the experimental results and a discussion of them, either *seriatim* or at their conclusion. Finally, there should be a brief summary of the main achievements of the investigation. Sometimes, particularly when the subject matter is involved and there are many details which, though essential for a successful repetition of the experiments, are unnecessary for the main account of the investigation, these details can with advantage be relegated to an appendix or supplement, just preceding the Summary. In intermediate cases it is often advisable to retain a single, straightforward presentation but to intercalate sections in fine print giving the experimental details of procedure. This has the great advantage of keeping the experimental details close to the more general statements based upon them and yet at the same time permitting the reader if he wishes to pass over this section without inconvenience.

It will be of great assistance to the Editor's Office if the style, arrangement and orthography of the manuscripts are made to conform to the usages of the JOURNAL as exemplified in its recent issues and as set forth in the following paragraphs.

Center headings should be employed sparingly; side headings should be indented and run into the text to which they apply, using period and dash. References to the literature and all footnotes regardless of their nature (except those in tables) should be numbered in one consecutive series, repetition of notes being avoided by using simply the superscript number corresponding to the original reference. They should follow immediately in separate lines the line of text containing the text words to which they refer, and may be set off by short rules above and below. The items in the references to the literature should conform to the uniform usages of the Journal as regards order and punctuation, and to the abbreviations as given by *Chemical Abstracts* in its "List of Periodicals Abstracted." The names of all simple compounds rather than their formulas should be used whenever they occur in the text. Periods of time (unless fractional) should be written in words and quantities of material in Arabic numerals, unless occurring at the beginning of a sentence. Letters used to represent quantities in mathematical expressions should be underscored to indicate that they are to be printed in italics, and Greek or other unusual characters should be written plainly or should be explained by annotations. Simple fractional expressions should be written with a slant line rather than in the conventional manner, so that only a single line of type is required. All subscripts and superscripts should be carefully made and placed (the degree sign ° or a small o should not be used to represent zero). For economy, except in unusual circumstances the abbreviations %, °A., cm., cc., ml., g., Å., m. p., f. p., b. p., cal., kcal., expt. and Fig., should be used rather than the words.

Figures and graphs should be carefully prepared line drawings on plain white drawing paper, blue drawing cloth or coördinate paper printed in blue only. The

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originals are preferable, but clear, well-prepared photographic prints or photostats are acceptable. Illustrations are most conveniently handled when made in the conventional 8.5″ × 11″ manuscript size; if they are of necessity larger, and therefore liable to damage in mailing, duplicate rough sketches or photographic prints of smaller size should be furnished for dispatch to the Referees. Diagrams should be designed to occupy a single column width and should therefore be tall rather than wide. Particular attention should be given to the correct proportions of the various parts of the figure, especially the experimental points, and if any letters, numbers, or legends must be placed on the diagram to their proportions also. In graphs the frame and actual curves should be ruled and inked more heavily than the coördinate lines, and these latter should not be too close together. Experimental points should always be given and should be indicated not by crosses but by circles or other symbols carefully drawn with drafting instruments. Where feasible it is often helpful to have the diameter of the circles indicate the precision of the measurements. The numbers and legends on coördinate axes are set up in type by the printer; the author, therefore, should place them in pencil outside the axes. The numbers and titles of figures should be placed below the diagrams, or on the back, or collected on a separate sheet. Small photographic prints should be mounted on cardboard and any composite series of photographic prints should be mounted in the order and arrangement desired. Each piece of illustration copy should be marked on the margin or back with the name of the author and brief title of the article (for identification purposes).

Tables.—Tables should not be used indiscriminately as they are much more expensive, line for line, than running text. If reasonably possible, they should be designed to occupy fully a single column (3 inches), which will take 50–75 characters and spaces. Tables occupying the full width can be used, but they are undesirable for the same reasons advanced with regard to page wide figures; their preparation should follow the same principles as for those of single width. Care should be taken to avoid any arrangement which unduly increases the depth of a table, and column heads should be made as small as possible, using abbreviations liberally. Lines of data should not be numbered nor run numbers given unless these numbers are needed for reference in the text. Columns should not be used to contain only one or two entries, nor should the same entry be repeated numerous times consecutively, since these cases may be taken care of more economically in footnotes, or by entries following the title of the table. Data should not be included in one column which are deducible easily by simple arithmetic from data in another column. Tables should be interspersed in the manuscript as near as possible to the places where they are referred to in the text, and need not be placed alone on separate sheets.

Formulas and Equations.—Empirical and structural formulas and mathematical and chemical equations should be arranged to fill adequately the width of a single column. This will often require a continuation of the equation in additional lines, and although this is a disadvantage it is in general preferable to intrusion into the adjoining column. Subscripts and superscripts, especially the latter, should be written with care and the conventional fractional arrangements should not be used in exponents. Organic structural formulas should be arranged to fill the space economically, and arrows should be used horizontally or vertically, not diagonally, wherever possible.

Notes do not differ fundamentally from Articles. They describe fragmentary or less complete studies and hence particular attention must be given to brevity and conciseness of presentation. Summaries are not included. They are collected in a special section near the end of each number of the Journal.

New Compounds.—This department is for brief accounts of new substances which do not appear of sufficient importance to justify separate publication and cannot be described appropriately as part of any other Article or Note. These accounts should report the preparation of the new compound succinctly, yet fully enough so that the operations can be duplicated. Significant properties, formulas and analytical data to establish the identity and purity of the substance should be given. Material appearing in this classification will not be accepted for subsequent publication.

Communications to the Editor are designed to afford prompt, brief, preliminary publication in our Journal of new and significant observations or discoveries. Their total length may in no case exceed 500 words or the equivalent. They will be given as rapid editorial consideration as possible, but at best it will usually be out of the question to include them in a given issue of the Journal if they arrive at the Editor's office later than the 20th of the preceding month. Communications like other contributions should be self-sustaining; that is, they should present experimental or other evidence adequate to establish the *prima facie* credibility of the results or conclusions stated or to permit their appraisal by an expert in the field although because of the 500-word limit a complete presentation cannot usually be expected. These requirements make Communications on many subjects impracticable, particularly those of an involved or theoretical nature.

Communications differ from ordinary Articles or Notes in that their publication does not prevent the re-publication of their subject matter in a later, more complete article in the Journal. In view of this special provision and their expedited publication, it is clear that the contribution made by the Communication should be of special interest or timeliness; mere abstracts of forthcoming articles cannot be accepted. Proof and reprint order will be sent to authors whenever possible, but as this cannot always be done, a memorandum as to the reprints desired should accompany the manuscript.

Microfilm Supplements.—By arrangement with Science Service material supplementary to articles in THIS JOURNAL, such for instance as extensive tables, graphs or calculations, can be distributed at small cost as American Documentation Institute Documents in the form of microfilms with images 25 mm. high on standard 35-mm. film or photoprints 6 × 8 inches legible to the unaided eye. Such material must, however, have been submitted to the Editor of the Journal and must have been approved by him for publication. Attention will then be called to these documents by means of footnotes at appropriate points in the text of the article concerned.

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JOURNAL OF THE
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VOLUME 66 FEBRUARY 10, 1944 NUMBER 2

[CONTRIBUTION FROM THE RESEARCH LABORATORY, UNITED STATES STEEL CORPORATION]

The Adsorption of Gases on Smooth Surfaces of Steel[1]

BY MARION H. ARMBRUSTER AND J. B. AUSTIN

This paper reports the results of measurements of the adsorption of hydrogen, argon, neon, nitrogen, carbon monoxide and carbon dioxide at pressures up to 0.1 cm. and at 20, −78, −183 and −195° on three surfaces of cold-rolled steel of the same nominal composition. The sorption on each surface was determined first after degreasing and degassing and subsequently on the identical surface after reduction in carefully purified hydrogen. In some cases it was necessary to condition the surface many times before adsorption was reproducible within the experimental error.

Apparatus and Materials.—The apparatus is described in an earlier paper.[2] The fixed temperatures were: (1) that of a mixture of solid carbon dioxide and alcohol (−78°); (2) the boiling point of oxygen (−183°); and (3) the boiling point of nitrogen (−195°). All temperatures were checked by means of a copper–constantan thermocouple immersed in the bath. Proper corrections, as described in the earlier paper, were made for the difference in temperature between the several parts of the system, a correction which also took account of the effect of thermal diffusion.

Argon, neon, nitrogen and carbon dioxide of the Air Reduction Company's "spectroscopically pure" grade were obtained in glass flasks which were sealed to the gas manifold of the adsorption system before being opened.

Carbon monoxide, prepared by the reaction of formic acid with sulfuric acid, was freed of carbon dioxide by passage through a solution of potassium hydroxide and was then dried over phosphorus pentoxide.

Hydrogen used in the measurement of sorption was of the Air Reduction Company's "spectroscopically pure" grade; that used for reducing the surface was tank hydrogen, freed from traces of water vapor and oxygen by passage through sulfuric acid, then successively over calcium chloride, hot platinized asbestos, activated alumina and phosphorus pentoxide.

Steel Surfaces.—These were all cold-rolled flat wire whose chemical composition is given in Table I. Sample 1 (no. 25261), the surface used in our measurements of the sorption of ethyl iodide,[3] was a bundle of strips 0.08 mm. in thickness, 110 mm. in length and 19 mm. in width; it weighed 357.1 g. The total surface area, determined by measuring the dimensions of each strip, was 11130 sq. cm. Examination of a polished section under the microscope showed that this sample contained an unusually large number of non-metallic inclusions which appeared on the surface as small ellipsoids elongated in the direction of rolling; there were also a number of spheroidized carbide particles. The portion of the surface covered by each of the several phases, as estimated by cutting up photomicrographs and weighing the bits of paper representing each phase, was: inclusions about 5%, carbides about 30%, and iron about 65%.

TABLE I

CHEMICAL COMPOSITION OF THE STEELS

Sample	C	Mn	S	P	Si
1	0.39	0.70	0.049	0.016	0.128
2	.31	.58	.024	.011	.115
3	.12	.47	.041	.016	.003

Sample 2 (no. 25277) was a similar bundle of strips 0.07 mm. in thickness; it weighed 308.4 g. The total area was again 11130 sq. cm. This sample contained very few non-metallic inclusions; the carbides, which were spheroidized, covered about 25% of the surface, the rest of which was iron.

Sample 3 (no. 25278), was a bundle of strips 0.04 mm. thick; it weighed 366.7 g. The total measured area was 24680 sq. cm. or 2.22 times that of the other samples. This sample contained few inclusions, which covered not more than 2% of the surface; the carbides, which were spheroidized, covered about 15% of the surface, the remainder of which was iron.

Orientation of Grains.—Photomicrographs showed that initially the grains of each sample were elongated in the direction of rolling, the elongation being greatest on Sample 3 which had been rolled thinner than the others. The X-ray pole figure of each sample showed, as expected, a marked preferred orientation of the grains with the (100) planes in the rolling plane. Examination of a strip from each sample after the sorption measurements had been completed showed that the grains had become equiaxed but that preferred orientation persisted.

Treatment of Surfaces.—Before use, each piece of metal was degreased with absolute alcohol and anhydrous

(1) Presented in part before the Division of Physical and Inorganic Chemistry at the meeting of the American Chemical Society, Atlantic City, N. J., September 8–12, 1941.

(2) Armbruster and Austin, THIS JOURNAL, 61, 1117 (1939).

(3) Armbruster and Austin, *ibid.*, 61, 1117 (1939).

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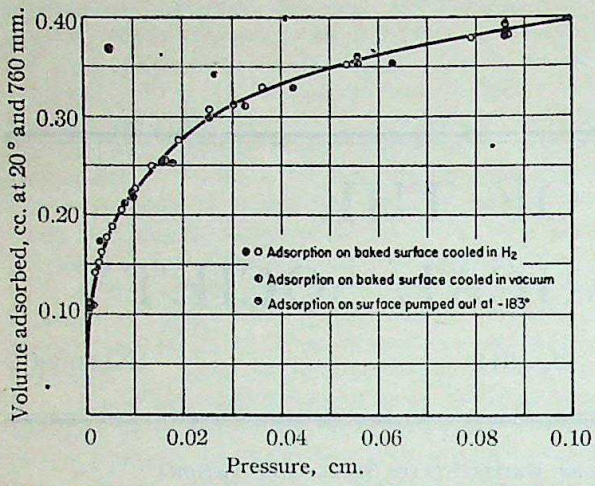

Fig. 1.—Sorption of argon at −183° on reduced surface of Sample 1: ●, surface outgassed and cooled in hydrogen, measurements made by increasing pressure; ○, surface outgassed, cooled in hydrogen (decreasing pressure); ◐, sample outgassed and cooled in vacuum (increasing pressure); ◓, surface pumped out at temperature (increasing pressure).

ether, care being taken to avoid touching the strips with the fingers. The first set of measurements was made on the degreased surface after it had been baked for two hours at 300° at a pressure of less than 10^{-6} mm. In the first few runs on each surface the results were not satisfactorily reproducible, the amount of adsorption increasing slightly on successive runs, but this increase became successively smaller and was negligible after about 20 measurements so that the volume of gas sorbed at a given pressure was reproducible within 5%. Although the magnitude of the adsorption of a specific gas changed during this initial period, the relative adsorption of different gases remained substantially the same, indicating that the increasing adsorption was due to an effective increase in surface area rather than to a change in the nature of the surface. Since tests using longer time of baking or higher temperature failed to show any significant deviation from the results obtained by baking for two hours at 300°, this latter procedure was adopted as standard. In the first set of measurements no attempt was made to reduce the invisible "oxide" always present on iron which has been exposed to oxygen, hence, the degreased and outgassed surface is referred to as "unreduced."

A second set of measurements was made after the surface had been reduced at 450° in a stream of purified tank hydrogen introduced at the bottom of the adsorption bulb, the surface being freshly reduced before each run. The period of reduction ranged in general from twenty-four to forty-eight hours, although in a few cases it was as much as sixty hours. After reduction of the surface the hydrogen inlet tube was sealed off and the sample was given the standard degassing treatment at 300° which yielded a surface, apparently free of oxide, on which adsorption was satisfactorily reproducible. The absence of an oxide film on the reduced surface was demonstrated by an accident which occurred during one of the runs. In replenishing the liquid air around one of the traps, the trap cracked and mercury was blown into the adsorption bulb, where it wet the iron wherever there was contact, a reaction which is observed only when an iron surface is substantially oxide-free. There was a tendency for the amount of adsorption on the reduced surface to decrease slightly on successive runs, the change being relatively the same for all gases, indicating a slight decrease in effective surface area. This change usually became negligible after a number of check runs had been made. The purified hydrogen used in reducing the surface tends to decarburize as well as to deoxidize, but the rate of decarburization with the carefully dried gas employed is so small that no significant loss of carbon from the surface was observed.

The adsorbent was cooled either in vacuum or in hydrogen, which direct measurement shows is not measurably sorbed on a smooth surface of steel in the temperature range studied. Direct comparison showed that the amount of adsorption was independent of the method of cooling, as is evident from Fig. 1 which shows the sorption of argon on the reduced surface of Sample 1 as determined by different procedures. Since cooling was most rapid in hydrogen, this gas was used in most runs. The trap between the adsorption train and the diffusion pump was immersed in liquid air from about half way through the baking period to the end of a run. A number of check runs, up to as many as 25, were made for each combination of gas, surface and temperature.

Procedure.—After the surface of the sample had been suitably prepared and brought to equilibrium at the temperature of test, adsorption was determined by admitting successive increments of gas; this is the procedure of building up to the pressure in steps described in our earlier paper.[4] The pressure was then diminished by steps to determine the amount of gas desorbed as the pressure decreased. A difference between the results on adsorption and on desorption at a given pressure was taken to indicate the existence of some irreversible sorption which was checked by measuring the adsorption a second time after the system had been pumped down to a pressure of less than 10^{-6} mm. at the temperature of test. A typical example of the agreement obtained when the adsorption was completely reversible[5] is shown in Fig. 1.

Results

Neither neon nor hydrogen was measurably sorbed on any of the surfaces within the temperature range investigated. Likewise none of the gases investigated was measurably sorbed at room temperature (20°). The sorption of the several gases on the three reduced surfaces at −78, −183 and −195° is shown by typical isotherms in Figs. 2, 3 and 4; representative iso-

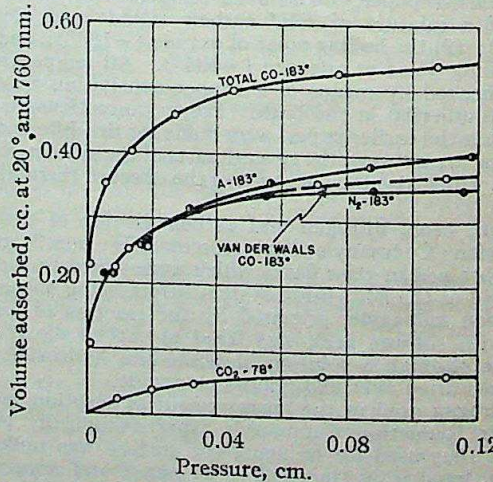

Fig. 2.—Adsorption isotherms for the several gases on reduced surface of Sample 1.

(4) Armbruster and Austin, THIS JOURNAL, 61, 1117 (1939).

(5) The term reversible adsorption is used to describe that part of the total sorption which can be removed by evacuation at temperature. It is used without any connotation as to the forces involved and implies nothing more than the observation that the sorbed gas can be removed by reducing the pressure to the order of 10^{-6} mm. at the temperature of test. Adsorption which cannot be removed by evacuation at temperature is designated as irreversible.

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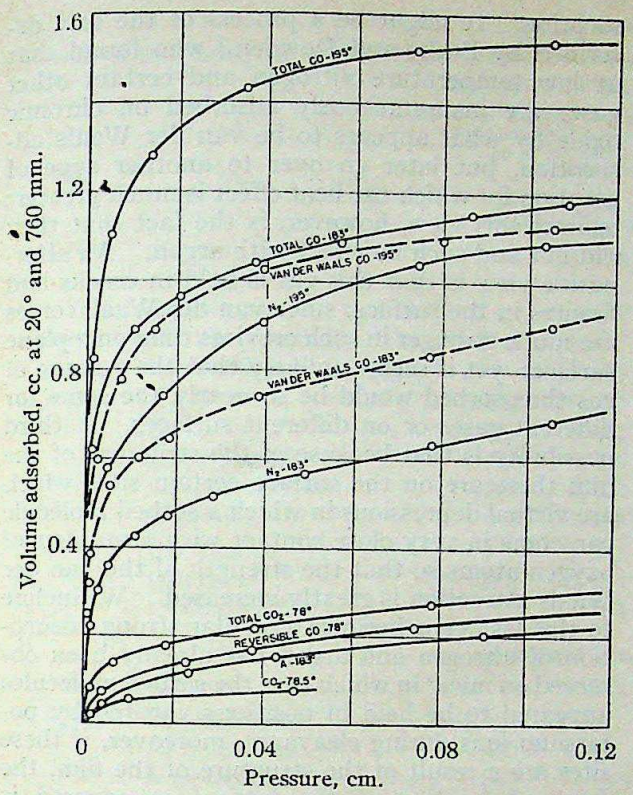

Fig. 3.—Adsorption isotherms for the several gases on reduced surface of Sample 2.

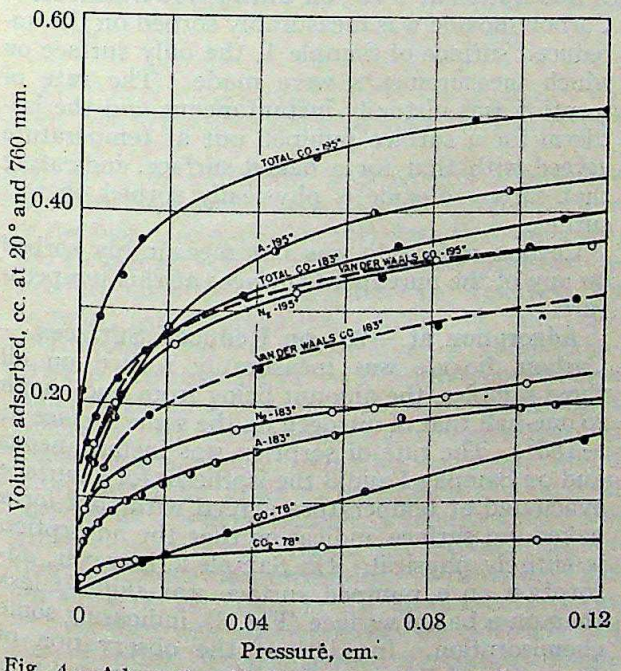

Fig. 4.—Adsorption isotherms for the several gases on reduced surface of Sample 3.

therms for the unreduced surfaces are shown in Figs. 5 and 6. For ease of comparison the data for Sample 3 are corrected to correspond to the surface area of the other two samples. The limiting volume sorbed (v_s) as derived by means of the Langmuir equation, the ratio of this volume to that of nitrogen at −183°, and the apparent

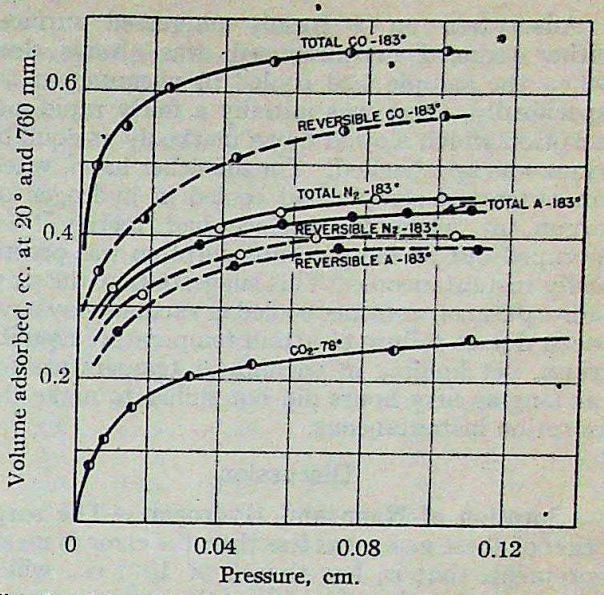

Fig. 5.—Adsorption isotherms for the several gases on unreduced surface of Sample 1.

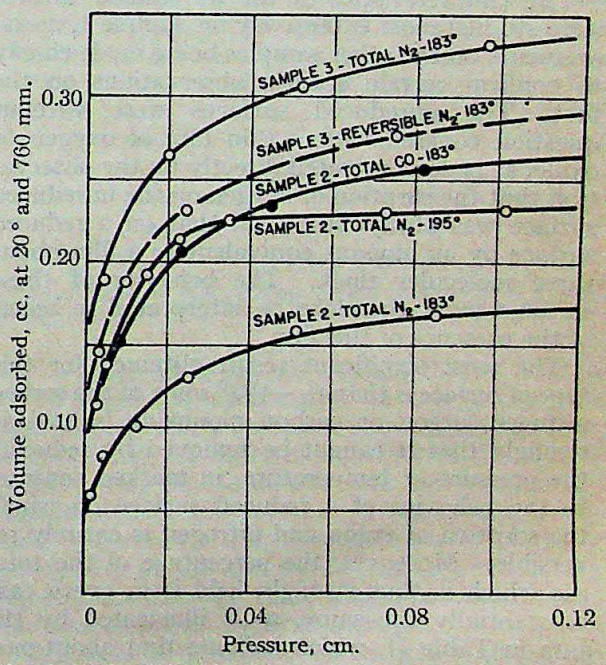

Fig. 6.—Adsorption isotherms for the several gases on unreduced surface of Samples 2 and 3.

coverage of the surface by a close-packed monolayer as derived from the corresponding value of v_s, the nominal or geometric area of the surface, and the cross-section[6] of the adsorbed molecule are given in Table III.

(6) The apparent coverage is calculated from the relation: $v_s \times 2.5 \times 10^{19} \times$ cross section per molecule/geometric area of surface. The exact value to be taken for the cross-sectional area is not as yet well established; in fact, data reported by Harkins and Jura (*J. Chem. Physics*, 11 431 (1943)) suggest that it may not be constant for all surfaces. We have selected the areas used by Langmuir, namely, A 12.9, N_2 15.2, CO 15.2, CO_2 16.4 sq. Å. which lie between the two sets calculated by Brunauer, Emmett and Teller from the density of the respective liquid and solid phases. They are believed to be a reasonable compromise and in any case are sufficiently accurate for the present purpose.

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Adsorption on a freshly outgassed surface, either reduced or unreduced, was always slow when the sample had cooled in vacuum; more specifically, there was initially a fairly rapid adsorption which slowed down markedly as equilibrium was approached. On the other hand, when an outgassed sample had cooled in hydrogen or argon, or when the surface had merely been pumped out at temperature, sorption was practically instantaneous. This suggests that the slow adsorption on a surface cooled in vacuum may have been due to failure to attain temperature equilibrium, yet holding in vacuum at temperature for as long as fifty hours did not suffice to make the sorption instantaneous.

Discussion

Sorption of Neon and Hydrogen.—The sorption of these gases was less than the error of measurement, that is, less than 3×10^{-4} cc., which corresponds to less than 1% of the surface covered.

Adsorption at −183° on Unreduced Surfaces.—The characteristics of the unreduced surface were studied most extensively on Sample 1, measurements on the other samples being made chiefly to confirm certain specific observations on the first. The unreduced surfaces were without question covered with a thin film of oxygen or oxide, as is demonstrated directly by the observation that the sorption of oxygen on the unreduced surface was always less than that on a reduced surface by an amount equivalent to a film about three molecules thick. The behavior of these surfaces must therefore be interpreted in terms of the presence of this film.

The most significant result obtained for this type of surface is that at −183° some of the sorbed nitrogen, argon or carbon monoxide is held so strongly that it cannot be removed by reducing the pressure at temperature, in marked contrast to the behavior of a reduced surface on which the sorption of argon and nitrogen is entirely reversible. Moreover, the percentage of the total gas which is thus strongly held is in every case substantially the same, as is illustrated by the data in Table II, which indicate that about one-seventh of the total amount adsorbed was not removed by reducing the pressure to 10^{-6} mm.

TABLE II

Difference between amount of gas sorbed at −183° on a baked out surface and that on a surface pumped out at temperature, expressed as a percentage of the former.

Gas	Sample 1	Sample 3
N_2	14.5	11.0
A	16.1	..
CO	11.8	..

The exact nature of this strong adsorption is not clear; but the instantaneous rate of sorption and the improbability that argon is held to the surface by anything other than physical forces indicates that it is basically van der Waals adsorption. It might be a process of the sort described by Beebe and Dowden,[7] who found that at low temperature nitrogen and certain other gases are instantaneously adsorbed on chromic oxide by what appears to be van der Waals adsorption, but later go over to another type of sorption for which the heat effect is much greater; against this view, however, is the fact that they did not find such an effect with argon. An alternative view is that this gas is held in cracks and fissures in the surface, since van der Waals forces are much stronger in such crevices than on a plane surface; yet it seems unlikely that the volume of gas thus sorbed would be so nearly the same for different gases or on different surfaces. A third possibility is that because of the structure of the film there are on the surface certain sites which are virtual depressions in which a sorbed molecule can come in very close contact with a number of oxygen atoms so that the strength of the van der Waals attraction is greatly increased. We incline to this last view because a similar strong adsorption of nitrogen and argon has already been observed on mica[8] in which case the sorbed molecules appeared to be held in positions vacated by potassium ions during cleavage; moreover, if these sites are a result of the structure of the film, the constant fraction of the surface so covered is easily explained.

Adsorption at −78° on Unreduced Surfaces.—Carbon dioxide was measurably sorbed on the unreduced surface of Sample 1, the only surface on which measurements were made. The rate of sorption was virtually instantaneous and the isotherm for a surface pumped out at temperature agreed with that for a baked surface, indicating that carbon dioxide is physically sorbed on this surface.

Carbon monoxide was not measurably sorbed on any of the unreduced surfaces at this temperature.

Adsorption at −78° on Reduced Surfaces.—Carbon dioxide was measurably sorbed on all three samples, the amount being from one-fourth to one-half that of nitrogen on the same surface at −183°. The rate of sorption was instantaneous and on Samples 1 and 3 the isotherm for a surface evacuated at temperature agreed with that for a baked out surface, indicating that the adsorption is entirely physical. On Sample 2, however, adsorption on a pumped surface was slightly less than on a baked surface (Fig. 3), indicating some chemisorption. In view of the observation of Emmett and Brunauer,[9] that on a promoted iron catalyst at −78° carbon dioxide is chemisorbed on the alkali promoter but not on iron, it is likely that this chemisorption on the smooth surface occurs on some non-metallic phase.

The amount of carbon monoxide sorbed at −78° differed widely, ranging from none on

(7) Beebe and Dowden, THIS JOURNAL, 60, 2912 (1938).
(8) Armbruster and Austin, *ibid.*, 60, 467 (1938).
(9) Emmett and Brunauer, *ibid.*, 59, 310 (1937).

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TABLE III

VALUES OF THE LIMITING VOLUME SORBED (v_s), OF THE RATIO OF v_s TO THAT FOR NITROGEN AT −183°, AND OF THE APPARENT COVERAGE OF THE SURFACE

Temp., °C.	Gas	v_s, limiting volume derived by means of Langmuir equation, cc. at 20° and 760 mm.[a] Sample no. 1	2	3[b]	Ratio of v_s to that for N_2 at −183° Sample no. 1	2	3[b]	Apparent coverage of surface by monolayer, % Sample no. 1	2	3[b]
				Surface Reduced in Hydrogen						
−195	N_2		1.154	0.416		1.60	1.72		396	143
	A			.483			2.00			142
	CO (reversible)		1.158	.384		1.60	1.59		397	131
	CO (chemisorbed)		0.377	.180		0.52	0.74		130	62
	CO (total)		1.535	.564		2.12	2.33		527	194
−183	N_2	0.381	0.722	.243	1.00	1.00	1.00	131	248	83
	A	.440	0.272	.238	1.15	0.38	0.98	129	80	70
	CO (reversible)	.410	0.966	.363	1.07	1.34	1.49	141	331	125
	CO (chemisorbed)	.252	0.290	.088	0.65	0.40	0.36	86	100	30
	CO (total)	.662	1.256	.451	1.72	1.74	1.85	227	431	155
− 78	CO (total)	0	0.083	.384		0.15	1.59	>1	29	132
	CO_2 (total)	.083	0.329	.067	0.22	0.46	0.28	31	122	25
	CO_2 (reversible)	...	0.315	...	..	0.44	..	...	117	...
				Degreased (Unreduced) Surface						
−195	N_2 (total)		0.250			1.30			85	
−183	N_2 (reversible)	0.410		0.300	0.85		0.88	141		104
	N_2 (total)	.480	0.191	.337	1.00	1.00	1.00	165	65	116
	A (reversible)	.390			0.80			115		
	A (total)	.465			0.97			137		
	CO (reversible)	.600			1.25			205		
	CO (total)	.680	0.280	...	1.41	1.45	..	233	147	
− 78	CO_2	.290	...	...	0.60			108		
	CO	0	0	0						

[a] 1 cc. = 41.6 micromoles = 2.5×10^{19} molecules. [b] The observations for Sample 3 have been divided by 2.2 to reduce them to the same geometric surface area as for the other samples.

Sample 1 to something approaching a complete layer on Sample 3, as estimated by comparison of the values of v_s (Table III) with that for nitrogen sorbed at −183°. The gas was adsorbed instantaneously but could not be desorbed by pumping at temperature. Brunauer and Emmett report that a complete layer of carbon monoxide is chemisorbed at −78° on iron catalysts, a result confirmed, insofar as strength of binding is concerned, by the calorimetric measurements of Beebe and Stevens.[10] On this basis one would expect a similar layer to be sorbed on a smooth surface, as it was on Sample 3, though not on the other two surfaces. Again the explanation for this difference is uncertain. Brunauer[11] has stated, however, that in his experiments if the iron surface was strongly sintered, not only did the quantity of chemisorbed carbon monoxide decrease but also the binding of the adsorbed gas to the iron was weakened as is evident from the fact that it was possible to pump off a part of the carbon monoxide at −78° from a strongly sintered catalyst. These observations, together with the fact that the surface of Sample 1, on which there was no measurable adsorption, had been baked out a great many times, whereas that of Sample 3, on which a complete layer of carbon monoxide was sorbed, had been baked out only a few times, suggest that the different behavior of the several samples was due to an effective difference in the smoothness of the surface. Thus, if the reduction of the oxide film were to leave a relatively rough skin on the iron which then sintered during subsequent bakings, there might be variations of the sort described by Brunauer.

It should be noted that on Sample 3, all the carbon monoxide was chemisorbed at −78° whereas at −183° only a small fraction of it was chemisorbed, a result in accord with the observation of Beebe and Stevens,[10] that the heat of adsorption is greater at −78° than at −183°.

Adsorption at −183 and −195° on Reduced Surfaces.—Since most of the isotherms are represented reasonably well, especially at the higher pressures, by the Langmuir equation, the results for −183 and −195° are most conveniently discussed in terms of the limiting volume sorbed (v_s), as derived by means of this equation. The value of this limiting volume is given in Table III along with the ratio of this value to that for nitrogen at −183°, which in effect reduces the observations to a common effective surface area.

(10) Beebe and Stevens, THIS JOURNAL, 62, 2134 (1940).
(11) See footnote 14, Beebe and Stevens, ref. 10.

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This ratio for carbon monoxide (total) at −183° is approximately constant; moreover, the fraction of the surface covered by chemisorbed carbon monoxide is substantially constant and is roughly 0.4 times the coverage by nitrogen. This is less than half that reported by Emmett and Brunauer,[12] who observed a complete layer of chemisorbed carbon monoxide as well as a complete layer of van der Waals adsorption. The reason for this difference is not clear.

Specific Surface Area.—The coverage, shown in Table III, indicates that the layer of sorbed gas does not exceed one molecule in thickness, and the close agreement in coverage by the several gases at the same temperature is presumptive, though not conclusive, evidence that the monolayer covers substantially the whole surface. Emmett and his colleagues[13] have had considerable success in estimating the surface area of a powder from the observed adsorption of nitrogen or argon at low temperature by assuming that the volume, corresponding to the point at which the isotherm ceases to be concave to the pressure axis and becomes substantially linear (the point they call B, which corresponds to v_m calculated by means of their equation for multimolecular adsorption) represents the volume of gas required for complete coverage by a close-packed monolayer. Since, as is shown later, our isotherms are very probably of the same type as theirs, the coverage by nitrogen and argon, as derived from the value of v_s, should likewise represent the completion of a monolayer on the cold-rolled steel. Investigations of adsorption on the smooth surface of other metals, notably silver and platinum,[14] have demonstrated, however, that under certain conditions substantial saturation of the surface may be achieved by a monolayer in which the effective cross-sectional area of the sorbed molecules is much greater than that commonly assumed, which indicates that the Emmett–Brunauer–Teller method may not always be reliable when applied to a smooth metallic surface; this makes necessary some reservation on the above conclusions.

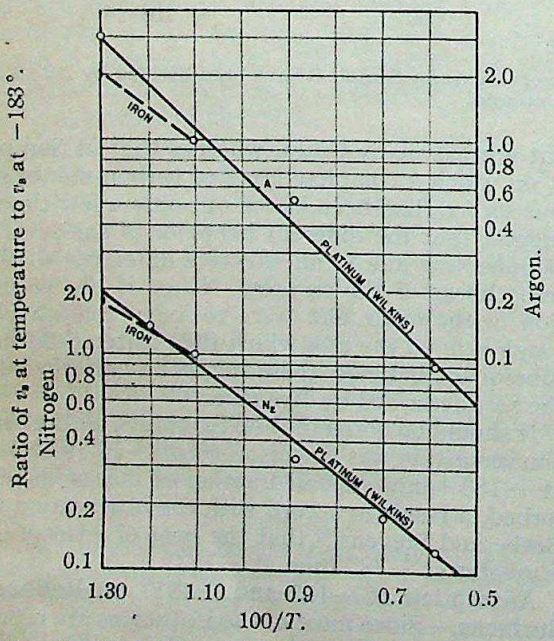

Fig. 7.—Variation with temperature of the limiting volume (v_s), as derived by means of the Langmuir equation, plotted as the ratio v_s at temperature to v_s at −183°. Solid lines and circles represent Wilkins' data for nitrogen and argon on smooth platinum; dashed lines, our data for smooth iron.

On the basis that the limiting volume (v_s) corresponds to the completion of a relatively close-packed monolayer, the specific surface of the steel, relative to the geometric area of the strips, is approximately 1.5 for Sample 1, 3 to 4 for Sample 2 and about 1 to 1.5 for Sample 3, which indicates that these surfaces are remarkably flat.

Variation of v_s with Temperature.—The value of v_s increases markedly with decreasing temperature, as is common in systems of this type. Although the exact form of the variation cannot be determined from observations at only two temperatures, it appears to be consistent with that reported by Wilkins for the sorption of argon and nitrogen on platinum foil. He found that for the range −100 to −195° v_s is satisfactorily represented by the relation

$$v_s = v_0 e^{\beta/T} \qquad (1)$$

where v_0 and β are constants. His more extensive data are plotted along with ours in Fig. 7 in which, to eliminate the effect of the difference in surface area and to permit direct comparison of the two sets of observations, log (v_t/v_{-183}) is plotted against $1/T$. The agreement between the two sets of data is as close as could be expected, indicating that in this temperature range the variation of v_s for nitrogen and argon is substantially the same on both platinum and iron foil.

Heat of adsorption can be calculated by means of an analog of the Clausius–Clapeyron equation or by means of an equation developed by Brunauer, Emmett and Teller.[15] The former method, based upon the adsorption isostere, is commonly assumed to give the heat of sorption corresponding to a given volume of gas sorbed; the second method, which requires but a single isotherm, yields the average heat of sorption in the less active portion of the first layer. In several instances the results of application of these two methods to our data differ significantly; moreover, the heat calculated by means of the Clausius–Clapeyron equation in a number of cases increases as the fraction of the surface covered increases, a result which is hardly acceptable in view of the great body of evidence, including di-

(12) Emmett and Brunauer, THIS JOURNAL, **59**, 310 (1937).
(13) *Cf.* Emmett and DeWitt, *Ind. Eng. Chem., Anal. Ed.*, **13**, 28 (1941).
(14) Armbruster, THIS JOURNAL, **64**, 2545 (1942); Wilkins, *Proc. Roy. Soc.* (London), **A164**, 510 (1938).
(15) Brunauer, Emmett and Teller, THIS JOURNAL, **60**, 309 (1938).

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rect calorimetric measurement, that on iron the heat of adsorption decreases with increasing coverage. For example, the heat of adsorption for nitrogen on the reduced surface of Sample 2 as derived by means of the Clausius–Clapeyron equation varies from 1370 cal. per mole at 200 cu. mm. sorbed to 2800 cal. at 600 cu. mm.; the corresponding heat calculated by means of the Brunauer–Emmett–Teller relation is 2750 cal. at −195° and 3160 cal. at −183°. The values derived by means of the Clausius–Clapeyron equation are, therefore, significantly lower in the range of small fraction of the surface covered, which is, however, just the range in which they should be higher. These discrepancies led us to suspect that the heat of sorption derived by means of the Clausius–Clapeyron equation may not be reliable under all circumstances and resulted in a critical examination of its accuracy and precision as compared to those of the Brunauer–Emmett–Teller method.

For monomolecular adsorption, the Brunauer–Emmett–Teller relation is

$$p/v = \frac{p_0}{v_m c} + \frac{p}{v_m} \qquad (2)$$

where v is the volume sorbed at pressure p, v_m is the volume of gas required to complete a close-packed monolayer, p_0 is the saturation pressure of the liquid adsorbate at the given temperature, and c is a quantity defined by the relation

$$c = fe^{-(\Delta H_a - \Delta H_L)/RT} \qquad (3)$$

where ΔH_a is the average heat of adsorption, ΔH_L is the heat of liquefaction of the gas and f is a coefficient whose value is close to unity.

The most convenient form of this relation for ordinary use, and the one best fitted to show the accuracy and precision of the calculation, is

$$\Delta H_a = A - 2.303\ RT \log v_m I \qquad (4)$$

in which v_m and I are, respectively, the numerical value of the reciprocal of the slope and the intercept derived from the linear plot of p/v against p, and

$$A = \Delta H_L + 2.303\ RT \log p_0 \qquad (5)$$

Inspection of equation (4) shows that the use of this method tends greatly to reduce the effect of any observational error. The only term containing a factor derived from the adsorption data is log $(v_m I)$, whose value is commonly smaller, and frequently is very much smaller, than that of A, so that this term is in essence merely a correction to A, whose value can in most cases be determined with considerable accuracy. Furthermore, the value of this correction is, because of the logarithmic form of the term, relatively insensitive to an error in the value of v_m or I. For example, if the value of the product $(v_m I)$ is in error by a factor of 2, the change in the logarithm is only 0.301 unit, corresponding to an error of (4.57 T × 0.301) calories in the heat effect; for T = 100°K., this is about 150 calories.

The analog of the Clausius–Clapeyron equation is

$$\left(\frac{\partial \ln p}{\partial (1/T)}\right)_v = \frac{\Delta H_a}{R} \qquad (6)$$

in which p is the pressure required at absolute temperature T to cause the sorption of volume v.

Its accuracy appears to be open to serious question. The limitations of the Clausius–Clapeyron equation when applied to vaporization are well recognized but no corresponding evaluation of equation (6) as applied to adsorption appears to have been reported, although we have not exhaustively searched the early literature. On the other hand, the use of the equation has been criticized on several different grounds. The primary objection is a practical one, namely, that if the isotherms indicate saturation of the surface at the higher pressures, as they do in monomolecular adsorption, and if the maximum volume sorbed increases with decreasing temperature, as it commonly does, then the isostere can be constructed for a limited range of volume only.

Wilkins,[16] from statistical calculations, has concluded that equation (6) should be used not at constant volume but at constant concentration on the surface, that is, at constant fraction of the surface covered, a procedure which removes the primary difficulty in constructing the isostere. Wilkins has shown further that, if equation (1) is valid, then the heat of adsorption calculated by means of equation (6) is in error by the amount $R\beta$,[17] where R is the gas constant.

Since it is clear that the use of equation (6) may yield a result significantly in error, it is instructive to compare it with the Brunauer–Emmett–Teller equation, which may be written

$$p = p_0 e^{-\Delta H_a - \Delta H_L/RT} \left(\frac{v}{v_m - v}\right) \qquad (7)$$

whence

$$\left(\frac{\partial \ln p}{\partial(1/T)}\right)_v = \left(\frac{\partial \ln p_0}{\partial(1/T)}\right)_v + \frac{\Delta H_a}{R} - \frac{\Delta H_L}{R} - \left(\frac{\partial \ln (v_m - v)}{\partial(1/T)}\right)_v \qquad (8)$$

but

$$\left(\frac{\partial \ln p_0}{\partial(1/T)}\right) = \frac{\Delta H_L}{R} \qquad (9)$$

hence

$$\Delta H_a = R\left[\left(\frac{\partial \ln p}{\partial(1/T)}\right)_v + \left(\frac{\partial \ln (v_m - v)}{\partial(1/T)}\right)_v\right] \qquad (10)$$

On this basis, the ordinary analog of the Clausius–Clapeyron equation yields a value of ΔH_a which is in error by the amount $R(\partial \ln (v_m - v)/\partial(1/T))_v$. Under optimum conditions, as for example a very small variation of v_m with temperature, this error is negligible, but under less favorable circumstances it may be appreciable.

If v_m can be represented as a function of $(1/T)$,

(16) Wilkins, *Proc. Roy. Soc.* (London), **A164**, 496 (1938).

(17) Wilkins' paper gives this difference as β, but this is clearly a typographical error and should be $R\beta$.

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equation (10) can be simplified. Thus, on the basis of Wilkins' suggestion that $v_m = v_0 e^{\beta/T}$

$$\left(\frac{\partial \ln (v_m - v)}{\partial(1/T)}\right)_v = \frac{\beta v_0 e^{\beta/T}}{v_0 e^{\beta/T} - v} = \frac{\beta v_m}{v_m - v} \qquad (11)$$

For $v \ll v_m$, this correction reduces to β, whence

$$\Delta H_a = R\left(\frac{\partial \ln p}{\partial(1/T)}\right) + R\beta \qquad (12)$$

which is the same relation as was obtained by Wilkins.

Equation (10) is clearly limited in use to the range of v in which the isostere can be constructed, a restriction which, however, is inherent in any calculation based on constant volume. This difficulty can be avoided, as suggested by Wilkins, by the use of constant concentration, a procedure which gives the true heat of adsorption. Thus, if the ratio v/v_m be represented by θ, equation (7) leads to the relation

$$\left(\frac{\partial \ln p}{\partial(1/T)}\right)_\theta = \frac{d \ln p_0}{d(1/T)} + \frac{\Delta H_a}{R} - \frac{\Delta H_L}{R} \qquad (13)$$

whence

$$\Delta H_a = R\left(\frac{\partial \ln p}{\partial(1/T)}\right)_\theta \qquad (14)$$

In contrast to the Brunauer–Emmett–Teller method, in which the adsorption data yield a relatively small correction to be applied to a quantity which is known precisely, the Clausius–Clapeyron relation and its several modifications tend to magnify experimental error and are, in consequence, less likely to give satisfactory results. In view of this conclusion, we report only the average heat as derived by the method of Brunauer, Emmett and Teller.

The average heat of reversible adsorption of the several gases is given in Table IV, which includes for comparison the heat of liquefaction of each gas at its normal boiling point. In each case the heat effect is 2 to 3 times the heat of liquefaction which indicates that the sorbed molecules are held to the surface by fairly strong physical forces. These data show further that, except for the sorption of carbon dioxide at −78°, the heat is substantially the same for all the gases on all the surfaces; moreover, these heats are virtually identical with those for the sorption of the same gases at the same temperature on smooth surfaces of silver or platinum, as is illustrated in Table V. They are, however, significantly higher than the heat effect of 2170 ± 70 cal. reported by Brunauer, Emmett and Teller[18] for the sorption of both argon and nitrogen at −183° on porous iron catalysts. A similar difference in the heat of adsorption of oxygen on silver at −183° has already been described.[19]

TABLE IV

AVERAGE HEAT OF REVERSIBLE ABSORPTION (ΔH_a) OF THE SEVERAL GASES ON SMOOTH IRON AS DERIVED BY MEANS OF THE EQUATION OF BRUNAUER, EMMETT AND TELLER

Gas	Temp., °C.	Surface	Sample	Value of c	ΔH_a, cal./mole	Heat of liquefaction of gas at normal boiling point
N_2	−183	Unreduced	1	52480	3280	
		Unreduced	2	225900	3577	
		Reduced	1	33110	3205	
		Reduced	2	251200	3568	1330
		Reduced	3	245500	3560	
	−195	Unreduced	2	438	2276	
		Reduced	2	6918	2705	
		Reduced	3	69180	3073	
A	−183	Unreduced	1	19500	3280	
		Reduced	1	7943	3120	
		Reduced	3	4217	3007	1505
	−195	Reduced	3	13650	2984	
CO	−183	Unreduced	1	67610	3400	
		Reduced	1	17780	3170	
		Reduced	2	305500	3680	1410
		Reduced	3	245500	3642	
	−195	Reduced	2	20420	3306	
		Reduced	3	263200	3350	

TABLE V

COMPARISON OF MOLAR HEAT OF ADSORPTION ON A SMOOTH SURFACE OF IRON, SILVER OR PLATINUM

	Fe		Ag,[a] cal.	Pt,[b] cal.
	Unreduced, cal.	Reduced, cal.		
A	3280	3200	3500	3280
N_2	3280	3120	3600	3385
CO		3400	3170	3600

[a] Derived from data of Armbruster. [b] Derived from data of Wilkins.

The difference between the heat effect on the two kinds of iron surface appears, moreover, to be characteristic of the physical condition of the surface rather than of its chemical nature; since Brunauer, Emmett and Teller found that the heat of sorption of nitrogen at −183° on twelve different catalysts, including iron, copper, silica gel, and chromic oxide is always 2170 ± 70 cal., whereas the data in Table V indicate that on a smooth metallic surface, whether it be iron, silver, or platinum, the heat is always close to 3000 cal. Moreover, since both argon and nitrogen have the same heat of sorption on the same surface, it is concluded that at a given temperature the heat of sorption is chiefly a function of the physical state of the surface and relatively independent of the chemical nature of either adsorbent or adsorbate.

The difference between the heat of adsorption on smooth iron and that on an iron catalyst provides a possible explanation for the seemingly different form of the isotherm for the two kinds of surface, and makes it possible to show that the isotherm for sorption on a smooth surface, though apparently of the saturation type, is probably of the sigmoid type characteristic of sorption on a catalyst. Thus the Brunauer–Emmett–Teller relation for multimolecular adsorption may be written

$$v/v_m = \frac{p/p_0 \Big/ \left(1 - \frac{p}{p_0}\right)}{\left(\frac{1}{c} + \frac{c-1}{c}\frac{p}{p_0}\right)} \qquad (15)$$

(18) Brunauer, Emmett and Teller, THIS JOURNAL, 60, 309 (1938).
(19) Armbruster, *ibid.*, 64, 2815 (1942).

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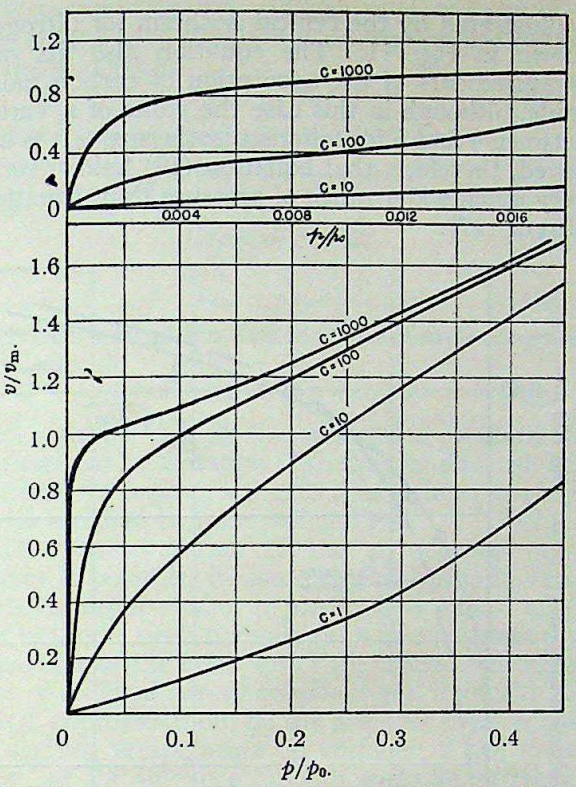

Fig. 8.—Variation of ratio v/v_m with p/p_0 for different values of c as derived by means of the equation of Emmett, Brunauer and Teller.

where the symbols have the significance explained earlier. Since the difference $\Delta H_a - \Delta H_L$ enters exponentially into the quantity c, this quantity, hence, the shape of the isotherm, is very sensitive to a change in ΔH_a, as is illustrated in Fig. 8 which shows v/v_m plotted against p/p_0 for different values of c. As c increases, v/v_m approaches unity at a much lower value of p/p_0, and tends to remain virtually constant at unity over an appreciable range of p/p_0, as is illustrated in the upper part of Fig. 8 which shows the low-pressure portion of the several curves on a greatly enlarged scale. For sorption on iron catalysts at −183°, the value of c is between 10 and 100, whereas for the smooth surface it is well over 1000 (see Table IV). On this basis, the isotherms in Figs. 2 to 6 are probably of the same type as those described by Brunauer, Emmett and Teller, and had our measurements been carried to a higher pressure, the isotherms would have become convex to the pressure axis.

Form of Isotherms.—The isotherms in Figs. 2 to 6 are of the form apparently typical of sorption at a relatively low pressure on a smooth metallic surface, which has generally been considered by investigators in this specific field to be of the saturation type. There is reason to doubt the justification for this classification, as has been pointed out earlier, yet it is instructive to consider our results from the standpoint of two common adsorption equations

$$v = ap^{1/n} \quad (16)$$

$$v = \frac{av_s p}{1 + ap} \quad (17)$$

where v is the volume of gas sorbed at pressure p, v_s is the maximum volume of gas sorbed at apparent saturation of the surface, and a and n are constants.

The first of these is the parabolic isotherm, variously and inaccurately called the classic, Freundlich or exponential isotherm, in which the value of n is almost always positive and greater than unity. Applied to our data, it fits very well over the low pressure range, as is illustrated in Fig. 9 by typical data for nitrogen plotted on double logarithmic coördinates to yield a straight line. These data yield a straight line over the 200 fold pressure range 0.0001 to 0.020 cm.; moreover, the several lines are substantially parallel, with a slope corresponding to a value of n of about 4. A similar plot of the data for argon yields an analogous set of parallel straight lines with a slope corresponding to a value of n of about 3. The equation fails, as it must, as the surface approaches saturation.

Equation (7) is the relation originally derived by Langmuir,[20] which yields a straight line when the ratio p/v is plotted against p. When this test is applied to our results, the equation holds over a considerable range of pressure, yet there are marked deviations in the low pressure range as is well illustrated by the typical isotherms for nitrogen shown in Fig. 10. These deviations are all of the same kind—the volume adsorbed at a given pressure in the low range being greater than that calculated by extrapolation of the data in the high

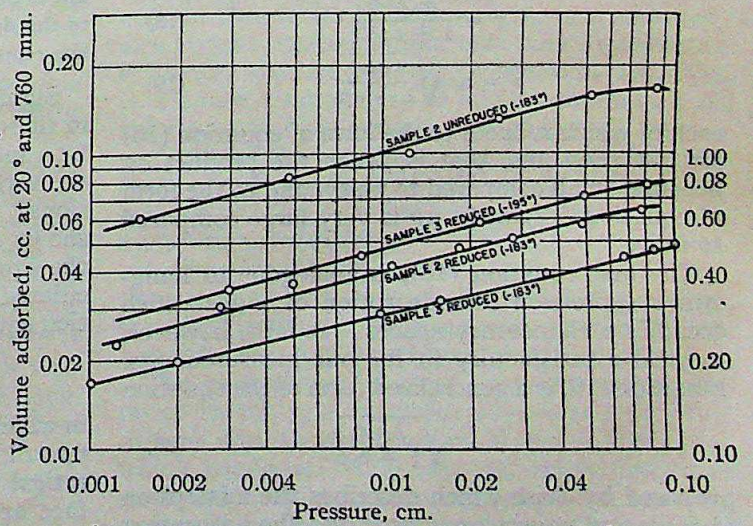

Fig. 9.—Adsorption of nitrogen on different surfaces plotted on double logarithmic coördinates on which data following the parabolic isotherm yield a straight line.

(20) Langmuir, THIS JOURNAL, 40, 1361 (1918).

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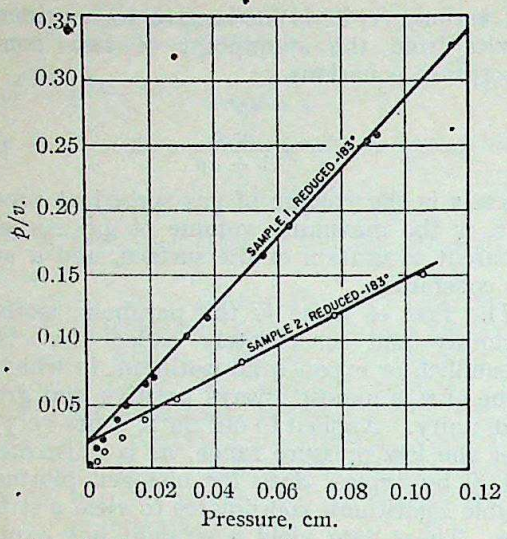

Fig. 10.—Isotherm at −183° for nitrogen adsorbed on reduced surface of Samples 1 and 2 plotted as p/v against p.

pressure range. Such deviations, which seem to be quite common, have been discussed at some length by Barrer,[21] who cites a number of examples in addition to those in his own measurements of adsorption of gases in graphite; similar behavior has been noted by Wilkins in his studies of adsorption on platinum foil.[22] These deviations from the Langmuir equation occur in the range of low pressure, precisely that in which the parabolic isotherm fits, which suggests that a combination of the two equations might hold over the whole range. Such a combination can be made in two ways

$$v = \frac{av_s p^{1/n}}{1 + ap^{1/n}} \qquad (18)$$

$$v = v_s \sqrt[n]{\frac{ap}{1 + ap}} \qquad (19)$$

each of which reduces to the form of equation (16) for low pressures, that is, when the product ap becomes small compared to unity, and to the form of equation (17) when ap is very large compared to unity.

The first equation (18), is analogous to Langmuir's expression for adsorption of a gas which occupies n elementary spaces. It fails, however, to yield a satisfactory fit for our measurements. Equation (19) is a generalized form of the equation

$$v = \sqrt{\frac{k_1 k_2 p}{1 + k_1 p}} \qquad (20)$$

proposed by Zeise which describes the adsorption of gases and vapors on glass,[23] and the adsorption of hydrogen on nickel.[24] Our results do not conform to equation (20) but the data for argon and nitrogen are represented satisfactorily by equation (19), if n is taken as 3 and 4, respectively, as is illustrated by the typical isotherm for nitrogen shown in Fig. 11. The equation also fits our measurements of the adsorption of carbon monoxide, although in this case the value of n varies between 4 and 5 for different isotherms. It is believed, therefore, that equation (19) holds over a very much wider range of pressure than equation (16) or (17).

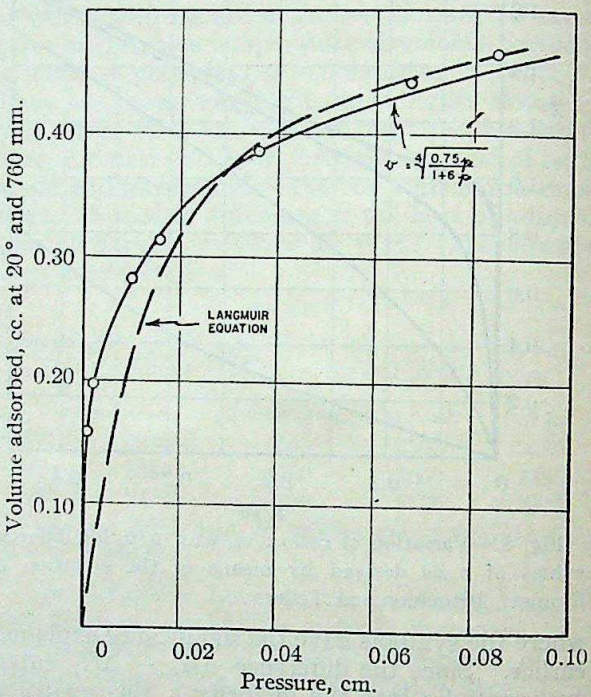

Fig. 11.—Adsorption of nitrogen on reduced surface of Sample 3. Circles represent the observations; the dashed line is derived by means of the Langmuir equation, fitted to the data over the higher range of pressure; the solid line represents equation (19) fitted to the observations.

Significance of Exponent n.—The exponent n in these several equations can be demonstrated to be a measure of the departure of the behavior of the sorbed film from that of an ideal two-dimensional gas. Thus, Innes and Rowley[25] have shown that, if the adsorption equation is known, the equation of state of the sorbed gas can be calculated by a modified form of the Gibbs adsorption equation, specifically

$$m_1 \frac{\mathrm{d}(RT \ln p_1)}{\mathrm{d}m_1} = A_s \frac{\mathrm{d}F}{\mathrm{d}m_1} \qquad (21)$$

in which F is the spreading force (more strictly the two dimensional pressure exerted against a theoretical barrier) of the film, A_s is the total surface area, and m_1 is the number of moles of gas sorbed at pressure p_1. By means of this relation they have also demonstrated that if the adsorption isotherm is linear, that is, if $v = ap$ (or $n = 1$), the sorbed film is an ideal two-dimensional gas, in which case the equation of state may be written $FA = kT$, where A is the cross-sectional area occupied by a single molecule and k is the

(21) Barrer, *Proc. Roy. Soc.* (London), **A161**, 476 (1937).
(22) Wilkins, *ibid.*, **A164**, 510 (1938).
(23) Zeise, *Z. physik. Chem.*, **136**, 385 (1928).
(24) Müller and Schwabe, *Z. Elektrochem.*, **35**, 185 (1929).
(25) Innes and Rowley, *J. Phys. Chem.*, **45**, 158 (1941).

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Boltzmann constant. If instead of a linear isotherm, one uses equation (16), expressed in terms of moles, that is

$$p_1 = bm_1^n \quad (22)$$

where b is a constant, then

$$\mathrm{d} \ln p_1/\mathrm{d}m_1 = n/m_1 \quad (23)$$

and

$$A_s \mathrm{d}F/\mathrm{d}m_1 = nRT \quad (24)$$

or

$$FA_s = nm_1RT \quad (25)$$

Expressing equation (25) in terms of area occupied per molecule

$$FA = nkT \text{ [26]} \quad (26)$$

which shows that if the adsorption isotherm is represented by equation (16), the two-dimensional pressure for a given value of A is n times as great as for an ideal two-dimensional gas.

This interpretation of the significance of n makes it possible, in some special cases, to estimate the value of n, or to predict how it may vary. For example, since the value of n characterizes the departure of the behavior of the sorbed film from that of an ideal two-dimensional gas, it should, as a first approximation, be the same for a given gas at a given temperature on surfaces of the same type, as for instance smooth metallic surfaces. This conclusion is supported by Wilkins'[27] data for the sorption of argon and nitrogen at low pressures on platinum foil at −183° which fit equation (16) satisfactorily and which at the same temperature yield a value of n of approximately 3 and 4, respectively, in agreement with the value of n derived from our measurements on the sorption of these gases on smooth iron. Moreover, since the deviation from ideality in the sorbed film should decrease as the temperature is increased, the value of n should for all systems approach unity at the higher temperatures; stated in other terms, deviation from the Langmuir equation should be most marked for a gas or vapor which deviates widely from ideal behavior and should, therefore, become more evident as the temperature of the system is decreased toward the critical temperature of the adsorbate. That this is in fact the case is amply confirmed by evidence available in the literature. To mention but two examples, Wilkins' measurements on the sorption of argon on platinum[27] show that the lower the temperature, the greater the deviation from the Langmuir isotherm, and Titoff's[28] measurements of the sorption of vapors on charcoal show clearly that the value of n approaches unity at the higher temperature, Table VI.

On the basis of this interpretation of the significance of n, it is possible to derive equation (19) by a reasonable modification of the postulates which Langmuir used to derive equation (17). Specifically, he assumed: (1) that the rate of condensation of atoms on the surface is equal $\alpha\mu\theta$, where μ is the number of molecules striking the surface in unit time, θ is the fraction of the surface still uncovered; and (2) that the rate of evaporation of adsorbed molecules is equal to $\nu\theta_1$, where ν is the rate of evaporation when the surface is covered by a complete monolayer and θ_1 is the fraction of the surface covered. The fact that at low pressures, that is, when θ is small, the observed adsorption is greater than that derived by extrapolation of the data at higher pressures indicates that the Langmuir postulates yield a rate of condensation which is too small, or a rate of evaporation which is too large, or, more probably, both. The general validity of the postulate that the rate of evaporation is a linear function of θ_1 is extremely doubtful in view of Becker's measurements of the rate of evaporation of cesium atoms from tungsten, which show that the rate varies exponentially[29] with θ_1; hence, if ν is the rate where $\theta_1 = 1$, the rate when $\theta_1 = 0.5$ should be much less than the value of $0.5\ \nu$ calculated on the basis of the Langmuir postulate, and this is in the direction of the observed deviations.

TABLE VI

Values of the exponent n in the parabolic isotherm for the sorption of different gases on charcoal at different temperatures (derived from the data of Titoff).

Temp., °C.	Gas N_2	Gas CO_2	Gas NH
151.5	1.0	1.1	...
80	1.1	1.4	1.3
30	1.1	2.0	1.7
0	1.2	2.7	3.3
−79	2.2	11.6	...

In place of Langmuir's postulate that the rate of evaporation varies linearly with θ_1, it is assumed, as a second approximation, that the rate varies as θ_1^n, where n is the exponent in equation (19), that is, the rate is assumed to be a function not only of the fraction of the surface covered but also of the strength of the intermolecular forces within the film. On this basis, if ν be the rate of evaporation where $\theta_1 = 1$, the rate for a lesser coverage is $\nu\theta_1^n$, a variation which for $n = 1$, that is, for an ideal two-dimensional film, reduces to the linear variation assumed by Langmuir, but which, for a value of n greater than unity, approximates the type of variation observed experimentally by Becker.

The rate of condensation is taken as proportional to the rate at which molecules strike the surface and to the fraction of those impinging which condense. The rate at which molecules strike the surface is proportional to the pressure and it is assumed that the fraction which condenses varies with the fraction of the surface covered and with the value of n, specifically, it is taken as proportional to $(1 - \theta_1^n)$, on which basis the rate of condensation is equal to $\alpha p(1 - \theta_1^n)$ where α is a proportionality constant. This result is admittedly somewhat arbitrary but never-

(26) If A is expressed in sq. Å. and F in dynes/cm. $FA = 1.372\ nT$.

(27) Wilkins, *Proc. Roy. Soc.* (London), **A164**, 510 (1938).

(28) Titoff, *Z. physik. Chem.*, **74**, 641 (1910).

(29) J. A. Becker, *Trans. Am. Electrochem. Soc.*, **55**, 153 (1929).

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theless meets two of the ends desired: namely, for a film which is an ideal two-dimensional gas, that is, one for which $n = 1$, this rate reduces to $\alpha p\theta$, where θ is the fraction of the surface not covered, which is the rate of condensation postulated by Langmuir; for a value of n greater than unity this variation is in accord with the general principle that the rate of condensation is initially high but falls off rapidly with increasing fraction of the surface covered.

Since at equilibrium the rate of condensation must equal the rate of evaporation

$$\alpha p(1 - \theta_1^n) = \nu\theta_1^n \qquad (27)$$

whence

$$\theta_1 = \frac{v}{v_s} = \sqrt[n]{\frac{\alpha p/\nu}{1 + \alpha p\nu}} \qquad (28)$$

which is identical with equation (19).

Force–Area Curves.—Two methods, both based on Gibbs' adsorption equation, have been considered for deriving the force-area curve of a sorbed film from the adsorption isotherms. The first, that of Innes and Rowley,[30] depends upon the relation

$$FA = v_1RT + RT\int_{p/v \text{ as } v \to 0}^{p_1/v_1} v\,d\ln(p/v) \qquad (29)$$

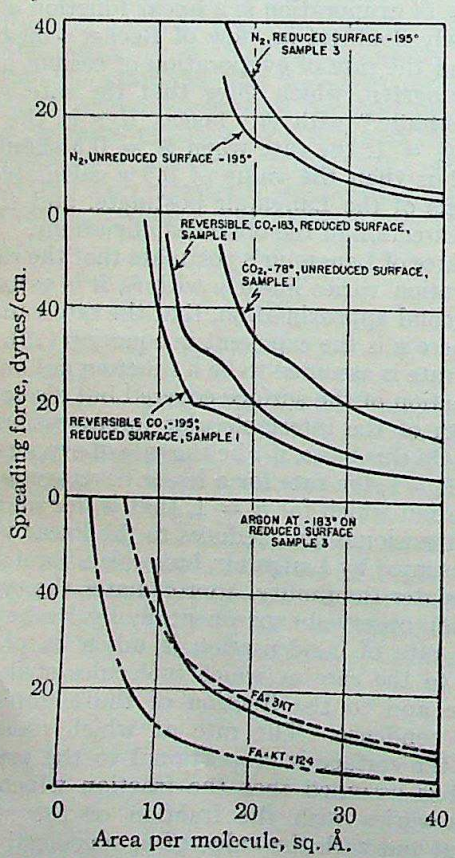

Fig. 12.—Force–area curves for sorbed films derived by the method of Innes and Rowley: (a) argon at −183° on reduced surface of Sample 3; (b) CO and CO_2 on Sample 1; N_2 at −195° on Sample 3.

(30) Innes and Rowley, *J. Phys. Chem.*, **45**, 158 (1941).

in which F is the surface pressure in dyne/cm., A is the area of the absorbing surface and v and v_1 are, respectively, the volume of gas adsorbed at pressure p and p_1. The integration can be carried out mathematically if the variation of v with p can be represented satisfactorily, or it can be carried out graphically, which is in general more convenient. The second method was devised by Palmer[31] on the assumption that the logarithm of φ, the adsorption potential, varies linearly with the volume sorbed, a postulate which in many instances is valid over a fairly wide range of pressure.

These two methods yield significantly different results, as has been pointed out in an earlier paper.[32] The cause of this difference is not certain but is probably the extrapolation to $v = 0$ which must be made with either method and, on this basis, the Innes and Rowley method is to be preferred. For the Palmer method assumes that $\log \varphi$ is linear with v down to $v = 0$, which cannot be so if the behavior of the sorbed film is to approach that of an ideal film, as it should. Moreover, it has already been demonstrated that if the isotherm is represented by equation (19) the force–area curve should lie above that for the ideal two-dimensional gas. For these several reasons we report here only force–area curves derived by the method of Innes and Rowley.

Typical force–area curves are shown in Fig. 12, the lowest section of which shows the curve for argon sorbed at −183° on a reduced surface of Sample 3. These data were selected because the specific surface of this sample appears to be very nearly unity and because the isotherm is closely represented, over most of the range studied, by the relation $v = ap^{1/3}$. It is evident that over the whole range the curve derived by means of equation (29) lies close to that representing the equation $FA = 3\,kt$, as it should, on the basis of equation (26). The curve is also smooth over the whole range of measurement. Similar smooth curves were obtained for the sorption of argon or nitrogen on all the reduced surfaces at both −183 and −195°, another example being the curve for nitrogen sorbed at −195° on a reduced surface of Sample 3, shown in the top section of Fig. 12.

In a number of instances, however, the force–area curve was not smooth but showed a plateau, as is illustrated by several typical curves shown in the middle and upper sections of Fig. 12. These curves are derived from a curve of $\ln(p/v)$ *vs.* v based on the experimental observations, not on the smooth isotherms shown in Figs. 2 to 6. These curves are entirely analogous to those for an insoluble liquid film on water,[33] and indicate the existence of phase transformations in the sorbed film. The two curves in the middle sec-

(31) Palmer, *Proc. Roy. Soc.* (London), **A160**, 254 (1941).

(32) Innes and Rowley, *loc. cit.*; Armbruster, THIS JOURNAL, **64**, 2545 (1942).

(33) See, for example, the curves for octadecanol given by Harkins and Kahrl, *J. Phys. Chem.*, **46**, 272 (1942).

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tion of Fig. 12 for carbon monoxide sorbed at −183 and −195° also show that with increasing temperature the plateau appears at a higher surface pressure and at a slightly lower value of A, as is usually observed for a monomolecular film on water.

These plateaus appear only when some molecules are held to the surface very strongly, either by physical or chemical forces; for instance, in the physical sorption of carbon monoxide, the surface already has on it some molecules which are chemisorbed. Another illustration is given in the top section of Fig. 12, which shows the sorption of nitrogen at −195° on the unreduced and reduced surface of Sample 3. The curve for the reduced surface, in which adsorption is completely reversible, is smooth whereas the curve for the unreduced surface, from which some nitrogen molecules cannot be removed by pumping at temperature, shows a plateau, which suggests that the molecules which are strongly held are attached to definite sites whereas those which can be desorbed by reducing the pressure are not. As the concentration of mobile molecules increases their mobility is diminished because of the interference by what is equivalent to a lattice of rigidly held molecules so that the film condenses to a less fluid structure and undergoes a phase transformation.

Summary

The adsorption on cold-rolled steel of argon, neon, hydrogen, nitrogen, carbon monoxide and carbon dioxide has been determined at 20, −78, −183 and −195° and at pressures up to 0.1 cm. Measurements were made first on a degreased and outgassed surface and subsequently on the same surface after reduction by hydrogen. In some cases the surface had to be conditioned a number of times before adsorption was reproducible within the error of measurement. Neither hydrogen nor neon was measurably adsorbed on either surface within the range of temperature or pressure investigated. A monomolecular layer of physically-held nitrogen, argon or carbon monoxide was sorbed on the unreduced surface at −183° but in each case approximately 15% of the total volume of gas sorbed was held so strongly that it could not be desorbed by reducing the pressure at temperature. A similar monolayer of physically-held nitrogen and argon was adsorbed on the reduced surface but could be entirely desorbed by evacuation of the system at temperature. On this same surface a complete monolayer of physically-held carbon monoxide was adsorbed along with a partial layer of chemisorbed molecules.

The isotherms appear to be of the saturation type but it is believed that they are in fact merely the low pressure section of an isotherm of the sigmoid type characteristic of adsorption on iron catalysts.

The ordinary analog of the Clausius–Clapeyron equation does not in principle yield a correct value for the heat of adsorption. The Emmett–Brunauer–Teller equation appears to be preferable. The heat of adsorption calculated by this method is, for all the physically-held sorption, approximately 3000 cal./mole. The heat of adsorption is influenced more by the physical nature of the surface than by the chemical nature of the gas.

The isotherms are represented in the low pressure range by the parabolic or Freundlich, equation and in the high pressure range by the Langmuir relation. A combination of these equations

$$v = v_\infty \sqrt[n]{\frac{ap}{1 + ap}}$$

represents most of our results over the whole range of pressure. The exponent n is interpreted as a measure of the departure of the behavior of sorbed film from that of an ideal two-dimensional gas. The value of n decreases with increasing temperature; when it is unity, the film is ideal and the isotherm equation reduces to the Langmuir relation.

Force–area curves for the sorbed films show that when some of the gas is held to the surface very strongly phase-transformations similar to those occurring in monomolecular films on water may take place.

The surface of cold-rolled steel is remarkably flat, the specific surface being not more than 4 times the geometric area of the steel.

KEARNY, N. J. RECEIVED JULY 15, 1943

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF STANFORD UNIVERSITY]

The Photolysis of Hydroxylamine[1]

BY R. NELSON SMITH[1a] AND PHILIP A. LEIGHTON[1b]

The photolyses of ammonia, hydrazine, water and hydrogen peroxide have been studied with care, and while many questions yet remain concerning the mechanisms of these reactions, the experimental evidence suggests that amino or hydroxyl radicals are produced as intermediates in all of them, and that the secondary processes consist largely of reactions of these radicals. The work here reported indicates that this is true also of hydroxylamine, and provides added support for some of the specific reactions of amino and hydroxyl radicals which have already been postulated.

Materials.—Hydroxylamine was prepared by the method of Hurd and Brownstein.[2] After removing all traces of solvent retained from the preparation, the solid hydroxylamine was purified by sublimation *in vacuo*. The hydroxylamine reservoir was kept evacuated and at dry-ice temperature at all times except when withdrawing samples. The melting range of one sample thus prepared was determined to be 31.8–32.8°, in good agreement with reported data.

The ammonia used was stored over sodium to remove water. All traces of air were removed by alternately warming the ammonia to atmospheric pressure and then freezing the ammonia with liquid air and evacuating.

Oxygen and hydrogen samples were taken from commercial tanks in a manner which prevented contamination by air. The purity of new samples was always determined by combustion before use in analysis, and if impurities were present, a different sample was collected.

The hydrogen peroxide used at one point was prepared by concentrating a 30% commercial aqueous solution from about 30 cc. to 3 cc. by distillation *in vacuo* at room temperature. The purity of this product was estimated to be well over 90%.

Ultraviolet Absorption Spectrum of Hydroxylamine.—The literature reveals no spectrochemical data for hydroxylamine other than the results of the determination of the infrared spectrum of aqueous solutions[3] and the infrared and Raman spectra of solid hydroxylamine hydrochloride and its aqueous solutions.[3,4]

To determine its ultraviolet absorption spectrum, a 150-cm. focal length quartz prism spectrograph and an Allen–Franklin type hydrogen discharge tube[5] were employed. A slit width of 0.001″ was used. The absorption cell was made of fused silica, 3.5 cm. in diameter and 134.7 cm. long. It was connected to a hydroxylamine reservoir and a diamyl phthalate differential manometer by interchangeable ground joints. The entire absorption system was capable of being highly evacuated. Eastman Kodak Co. No. 33 photographic plates coated with a thin film of transil oil were used for recording the light transmitted. After each exposure, the absorption tube and reservoir (at dry-ice temperature) were evacuated. If such a procedure was not followed, the diffuse ammonia bands and the characteristic bands and fine structure of nitric oxide at 2269, 2260 and 2154 Å. appeared. These products apparently arise from the thermal decomposition of hydroxylamine, especially after long standing at the higher hydroxylamine pressures.

Figure 1 shows a microphotometer tracing of spectrograms taken at different hydroxylamine pressures. It is evident that in this region only continuous absorption is observed. For the length of cell used here, "complete" absorption sets in at about 2140 Å., at 3.02 mm. and about 2015 Å. at 0.15 mm., but at the higher pressure some absorption takes place at wave lengths as long as 2350 Å. It is evident that the measurements were taken to the limit of the transmission of silica. Photographic plate characteristics were not obtained, and hence absorption coefficients have not been calculated.

Apparatus and Method.—The reaction system is shown in Fig. 2. The fused silica reaction cell, M, was connected to the rest of the system by a silica-to-Pyrex graded seal. The cell was cylindrical in shape, 10 cm. long and 3.0 cm. in diameter, with plane windows at either end. The hydroxylamine reservoir was at R. The amount of hydroxylamine added to the system was measured on the wide-bore mercury manometer, J, by means of a cathetometer. T_1 was a small freeze-out trap where first liquid air and then dry-ice was used to effect a partial separation of the products. The products obtained in each fraction were collected in a gas cup at Z by means of the atmospheric Toepler pump, W. The system was evacuated between runs through f_6.

The light source consisted of a spark discharge between two rapidly rotating zinc disks with a 5 mm. gap which could be accurately maintained and reproduced. A potential difference of 11,000 volts was supplied. The variation in light intensity with this apparatus was never more than 1 or 2%. The effective wave lengths were chiefly the 2025, 2062, 2100 and 2138 Å. lines of zinc.

The crystal quartz lens, L, was arranged to give a convergent beam of ultraviolet light through M with the ultraviolet focus somewhere past N. The volume effectively illuminated was a conical section of average cross section 150 mm.^{2} and volume 15 cc. Proper shielding of the cell and leads from stray radiation was provided.

An ammonia actinometer was used to measure the amount of light absorbed by the hydroxylamine. The actinometer cell, N, was 11 mm. deep and of slightly larger diameter than the reaction cell. At first it was sealed directly to the rear window of M with de Khotinsky cement, but the cement reacted slowly with ammonia and for most of the runs a crystal quartz window sealed to N with paraffin was used. With this arrangement N was about 1 mm. from the rear window of M. In use, N was first evacuated through f_1 and f_6, then with f_6 closed and f_7 open the ammonia reservoir P was warmed and N filled to 600 mm. Hg pressure, which in a cell of 11 mm. depth may be taken as completely absorbing for the wave lengths concerned.

After irradiation, the undecomposed ammonia in N was frozen out in T_2 with liquid air. The hydrogen and nitrogen resulting from irradiation were passed through f_1, collected in a gas cup, and their volume measured with a microburet.

To calculate the number of quanta of light absorbed, let A be the volume (cu. mm., corrected to S. T. P.) of hydrogen and nitrogen produced in M when filled with ammonia at 600 mm., B the volume of hydrogen and nitrogen formed in N with M empty, and C the volume of hydrogen and nitrogen formed in N with hydroxylamine in M. Then, using Wijg's value[6] of 0.18 for Φ_{NH_3} at this pressure and recognizing the fact that the volume of hydrogen and nitrogen

(1) Original manuscript received February 15, 1943.

(1a) Present address: School of Mines and Metallurgy, University of Missouri, Rolla, Mo.

(1b) Present address: Dugway Proving Ground, Tooele, Utah.

(2) Hurd and Brownstein, THIS JOURNAL, 47, 67 (1925).

(3) Freymann, Freymann and Rumpf, *J. phys. radium*, 7, 30 (1936).

(4) Ananthrakrishman, *Nature*, 138, 803 (1936); Edsall, *J. Chem. Phys.*, 5, 225 (1937); Heintz, *Arch. phys. biol.*, 14, 131 (1937).

(5) Allen and Franklin, *J. Opt. Soc. Am.*, 29, 453 (1939).

(6) Wijg, THIS JOURNAL, 57, 1559 (1935); 59, 827 (1937).

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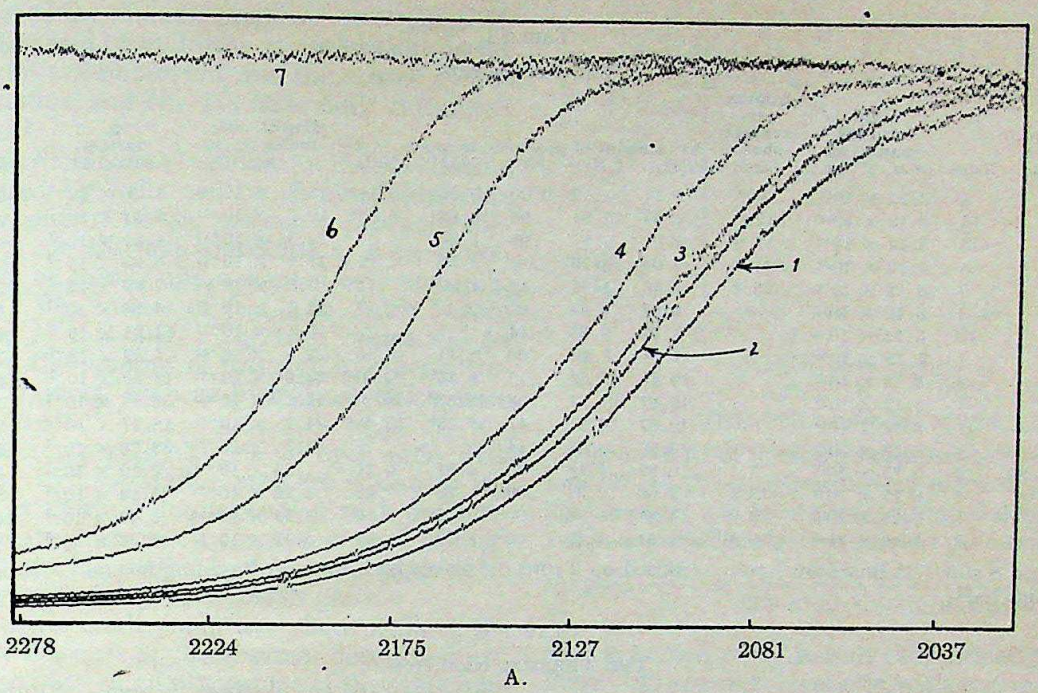

Fig. 1.—Microphotometer tracing of absorption spectrograms of hydroxylamine at different pressures. Exposure time is 20 minutes; light absorbing path is 134.7 cm.

Tracing.....	1	2	3	4	5	6
Hydroxylamine pressure, mm.	0.00	0.15	0.38	0.76	1.51	4.02

7 Background; corresponding to complete absorption

formed is twice the volume of ammonia decomposed, the number of quanta absorbed by hydroxylamine is

$$q = \frac{6.02 \times 10^{23}}{2.24 \times 10^{7}} \times \frac{1}{2\Phi_{NH_3}} \times \left(1 - \frac{C}{B}\right)A = \frac{7.47 \times 10^{16}\,(B - C)A}{B}$$

Parameter A remained nearly constant over a long period of time and did not often have to be redetermined. B tended to decrease over a period of time, but not regularly, and it was necessary to determine it daily. The measurement of C was a part of each run.

Variations in light intensity were accomplished by reducing the intensity with varying thicknesses of 0.001″ cellophane. It was shown that the cellophane did not measurably change the spectral distribution of the light effective in the decomposition.

In carrying out a run, the system was first evacuated, and ammonia added to N to a pressure of 600 mm. The ammonia was then frozen in T_2 with liquid air and the hydroxylamine frozen in R with dry-ice while the entire system was re-evacuated. Then with f_1 and f_2 closed, T_2 and R were allowed to warm to room temperature. Hydroxylamine was allowed to sublime into M to the desired pressure as measured on J. This was done slowly to

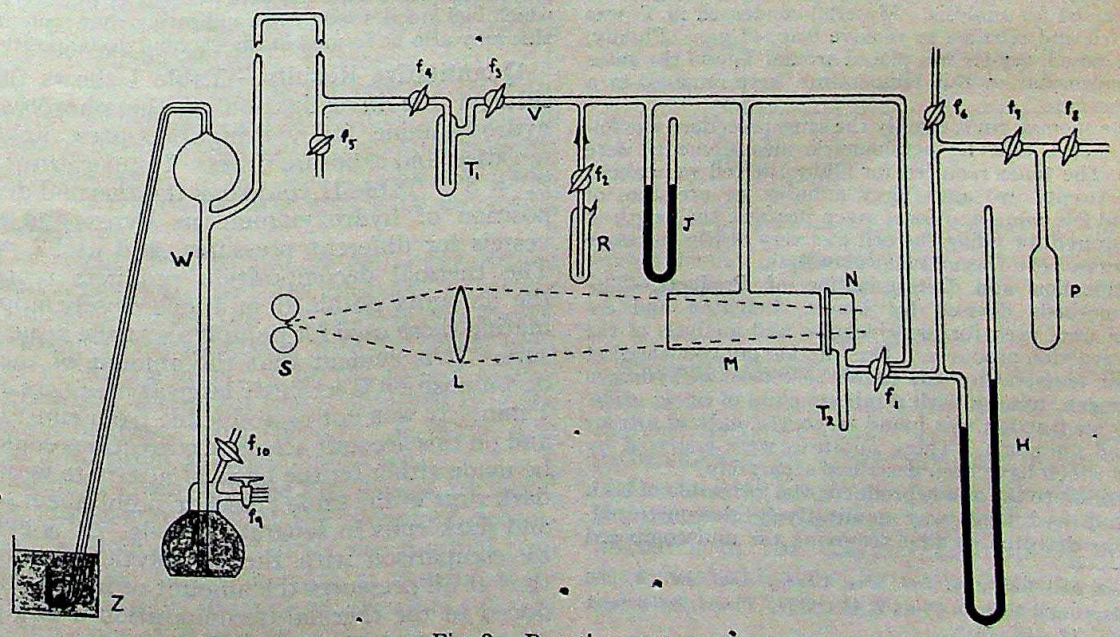

Fig. 2.—Reaction system.

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TABLE I

THE PHOTOLYSIS

Av. NH_2OH press., mm.	Expt. time, min.	Runs	Light intensity, quanta/sq. mm. × sec.	Approx. per-centage photo-lyzed	Av. amount of products, in moles, × 10^7 H_2	N_2	NO	N_2O	NH_3	dH_2/dt, obs., moles/cc. × sec.	Q, einsteins absorbed	Φ_{H_2}	Φ_{NH_2OH} [f]
1.0	1	5	3.12×10^{13}	6.6	1.11	1.09	0.00	0.56	0.14	12.3×10^{-11}	1.26×10^{-7}	0.88	2.19
1.0	2	13	3.12×10^{13}	12.0	1.93	1.91	.08	0.88[a]	.03[a]	10.7×10^{-11}	2.13×10^{-7}	.90	2.34[a]
1.0	3	5	3.12×10^{13}	17.9	2.91	2.80	.08	1.20	.01	10.8×10^{-11}	4.64×10^{-7}	.63	1.60
1.0	4	5	3.12×10^{13}	24.7	4.04	3.76	.10	1.75	.12	11.2×10^{-11}	6.93×10^{-7}	.58	1.48
1.0	5	9	3.12×10^{13}	29.2	4.40	4.99	.12	1.90[b]	.73[b]	9.8×10^{-11}	7.99×10^{-7}	.55	1.52[b]
2.0	2	4	3.12×10^{13}		4.07	3.44	.00	3.42	2.87	22.6×10^{-11}	4.98×10^{-7}	.82	
2.1	5	10	3.12×10^{13}		7.79	9.35	.14	...	...	17.3×10^{-11}	12.23×10^{-7}	.64	
3.1	2	4	3.12×10^{13}		4.04	6.49	.06	8.74	13.45	22.5×10^{-11}	5.59×10^{-7}	.72	
3.1	5	5	3.12×10^{13}		10.45	15.52	.12	9.83[c]	19.51[c]	23.2×10^{-11}	18.50×10^{-7}	.57	
3.2	10	1	3.12×10^{13}		19.87	27.57	.08	12.63[d]	26.53[d]	22.1×10^{-11}	36.64×10^{-7}	.54	
3.9	5	11	3.12×10^{13}		10.87	16.86	.47	16.35[e]	33.68[e]	24.2×10^{-11}	18.97×10^{-7}	.57	
3.7	10	1	3.12×10^{13}		20.90	28.30	.14	...	...	23.2×10^{-11}	38.78×10^{-7}	.55	
1.0	8.80	2	0.71×10^{13}	7.1	0.99	1.18	.00	0.54	0.21	1.25×10^{-11}	2.19×10^{-7}	.45	1.35
1.0	17.6	1	0.71×10^{13}	13.6	2.00	2.31	.00	.86	.00	1.26×10^{-11}	5.19×10^{-7}	.39	1.09
1.0	5	3	1.25×10^{13}	9.2	1.41	1.54	.00	.71	.00	3.13×10^{-11}	2.49×10^{-7}	.57	1.53
1.0	3.11	3	1.91×10^{13}	9.3	1.51	1.47	.00	.72	.17	5.41×10^{-11}	2.34×10^{-7}	.64	1.65

[a] Based on 8 runs. [b] Based on 1 run. [c] Based on 2 runs. [d] Based on 3 runs. [e] Based on 6 runs. [f] Assuming formation of no N_2H_4.

TABLE II

THE THERMAL REACTION

Av. NH_2OH, press., mm.	Runs	Av. amount of products, in moles, × 10^7 H_2	N_2	NO	N_2O	NH_3	H_2/N_2, av. Photo+thermal	Thermal	NH_3/N_2O, av. Photo+thermal	Thermal
1.0[b]	4				~ 0.25	~ 0	0.996	...	0.067	~ 0
2.1	3	0.09	1.09	0.01	3.02	2.69	.971	0.083	0.81	0.89
3.3	5	.08	1.72	.79	8.14	16.39	.673	.047	1.85	2.01
3.8	5	.13	2.95	1.24	11.34	22.12	.653	.044	2.06	1.95
3.4[a]	7	.15	2.86	0.93	18.08	27.90		.053		1.54

[a] Pyrex vessel. Values corrected for differing vessel sizes. [b] The combined vol. of H_2, N_2 and NO was only 0.25 cu. mm. at S. T. P. at this pressure, and was insufficient for analysis.

minimize thermal decomposition. After filling, f_2 was closed and dry-ice restored around R. After irradiation liquid air was placed around T_1 and the products noncondensable at that temperature were transferred to a gas cup at Z. Liquid air was again placed around T_2 and with liquid air still around T_1, the hydrogen and nitrogen formed in the actinometer were removed from the system to a second gas cup. This volume was measured, but the gas was not retained for analysis. Material condensed in T_2 was vaporized and refrozen to remove trapped gas. Finally, with f_1 closed, dry-ice was placed around T_1 and the gases non-condensable at this temperature were removed to a third gas cup.

In the thermal runs, exactly the same procedure was followed except that no actinometric measurements were made. The times required for filling the cell were about fifteen, twenty-two and thirty minutes for pressures of 1, 2, and 3–4 mm., and for a given pressure the length of time required for filling the cell was very nearly the same for all runs, both thermal and photolytic.

Identification and Determination of Products.—The micro methods devised by Blacet, Leighton and coworkers[7] were used for identification and analysis of the gaseous reaction products. The fraction not condensed at liquid air temperature was found to consist of hydrogen and nitrogen, usually with small amounts of nitric oxide. The dry-ice fraction was found to consist only of nitrous oxide and ammonia. These mixtures were analyzed by methods which have been described separately.[8]

In addition to the above products, the formation of both water and hydrazine was qualitatively demonstrated. Water was detected by first removing the undecomposed hydroxylamine, then passing the remaining gas over magnesium metal at 300°. Hydrazine was identified by the method of Curtius and Schrader,[9] *viz.*, the reduction of auric ion in 9 *M* sulfuric acid. The test for hydrazine was much stronger when the photolysis was carried out in a flowing system, by distilling hydroxylamine from one flask to another through an illuminated section of silica tubing. Slight tests were obtained with samples of hydroxylamine which had stood a long time, indicating that some hydrazine may also be formed in the thermal decomposition.

Quantitative Results.—Table I shows the results of the investigation of the photolysis of hydroxylamine for varying pressures, light intensities, and exposure times. Temperatures were 27 ± 3°. Table II compares the thermal decomposition of hydroxylamine in Pyrex and silica vessels for different pressures, and at 27 ± 1°. The thermal decomposition products represent the amounts obtained in times closely approximating those used for photolyses at the same pressure. It is evident that the amount of thermal decomposition is seriously large at pressures above 1 mm. It was not reproducible from run to run, and on this account accurate corrections could not be made either on the basis of alternate light and dark runs in the same vessel or simultaneous light and dark runs in separate vessels. It is evident by comparison with the photolytic experiments that at all pressures the amount of hydrogen produced in the thermal decomposition is negligible

(7) Blacet and Leighton, *Ind. Eng. Chem., Anal. Ed.*, **3**, 266 (1931); Blacet and Volman, *ibid.*, **9**, 44 (1937); Blacet, Sellers and Blaedel, *ibid.*, **12**, 356 (1940).

(8) Smith and Leighton, *ibid.*, **14**, 758 (1942).

(9) Curtius and Schrader, *J. prakt. Chem.*, **50**, 311 (1894).

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compared to the amount produced on irradiation. Hence the yield of hydrogen is useful as an index of the extent of photolysis, and the rate of hydrogen formation and the Φ_{H_2} have been calculated for all runs.

A lower limit for the amount of hydroxylamine decomposed by light can be obtained from the nitrogen content of the measured products corrected for the thermal contribution, a correction which can be closely approximated only at 1 mm. pressure. The values of Φ_{NH_2OH} in Table I were estimated in this way. The true values will be higher by the amount of nitrogen in other nitrogenous products, such as hydrazine, which were not measured.

The decrease in hydrogen–nitrogen ratio with increasing hydroxylamine pressure is due to the increase in thermal decomposition with pressure. Approximate corrections for the amount of thermal reaction indicate a hydrogen–nitrogen ratio of nearly unity for the photolysis alone.

Since nitric oxide comprises about 31% of the liquid air fraction of the thermal decomposition, but only a very small percentage of the same fraction of the combined thermal and photolytic products, it seems likely that nitric oxide is formed only in the thermal reaction.

Any quantitative statement regarding the amounts of nitrous oxide or ammonia formed in the photolysis is impossible because of the magnitude of the contribution of the thermal decomposition and its erratic character. Except for a 1-mm. pressure of hydroxylamine, one can say only that the dry-ice fraction obtained from a photolysis is on the average only slightly larger than the dry-ice fraction from the thermal reaction at the same pressure and that the ammonia–nitrous oxide ratio is about the same in both cases and increases markedly with pressure.

At constant light intensity and for a given period of irradiation, the observed rate of hydrogen formation increases with increasing hydroxylamine pressure. From the per cent. of light absorbed at each pressure it is possible to calculate the rate of hydrogen formation for equal amounts of light absorbed. When this is done it is found that the rate actually decreases with increasing pressure (Fig. 3).

At constant pressure and for equal amounts of incident light (obtained by properly adjusting the irradiation time), the rate of hydrogen formation increases very markedly with increasing light intensity. If one plots $I_a^{1/2}$ *vs.* the rate of hydrogen formation, a straight line is obtained (Fig. 4), while Φ_{H_2} increases with the $I_a^{1/2}$. I_a is the rate of light absorption, in einsteins/cc. sec.

The figures given in Table I for Φ_{NH_2OH} are based on the nitrogen content of the measured decomposition products, corrected for the thermal contribution. Due to the increase in thermal reaction with pressure the values could be closely estimated only at 1 mm., and since some hydrazine is known to be found, they are only a lower limit. Φ_{NH_2OH} also increases with increasing light intensity, and, as with Φ_{H_2}, the drop in Φ_{NH_2OH} with increasing exposure time may be attributed to absorption by products.

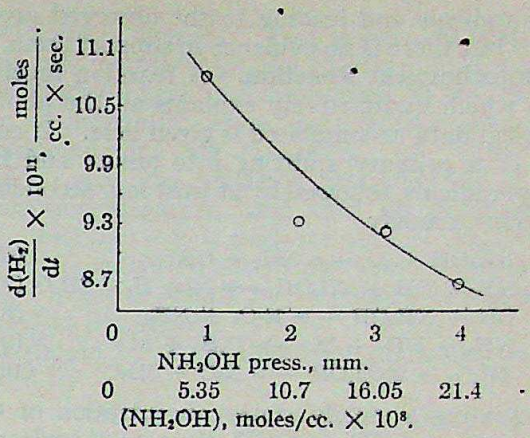

Fig. 3.—Rate of hydrogen formation at room temperature (27 ± 3°) *vs.* hydroxylamine pressure at constant light intensity and for a given amount of light absorbed. Points are experimental, but curve is calculated from the equation $\frac{d(H_2)}{dt} = \frac{5.74 \times 10^{-14}}{[2.3 \times 10^{-7} + (NH_2OH)]^{1/2}}$.

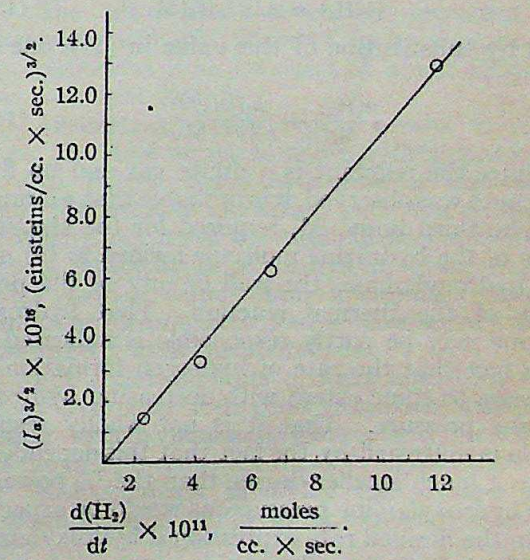

Fig. 4.—Rate of hydrogen formation *vs.* $(Ia)^{3/2}$, for hydroxylamine pressure of 1 mm. and equal amounts of light absorbed at each intensity.

Discussion

Thermal Reaction.—Little evidence is available upon which to base any mechanism for the thermal decomposition. It is evident that wall surfaces play an important part in the process. Hofmann and Kroll[10] postulated the formation of the mono- and diamides of nitrous acid as intermediates in the thermal decomposition of hydroxylamine hydrochloride in solutions and in the solid state. Reactions may be written involving

(10) Hofmann and Kroll, *Ber.*, **57**, 937 (1924).

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these radicals and leading to the observed products,[11] but there is no evidence to support them.

Photochemical Reaction.—A reaction mechanism which qualitatively explains all the photochemical data accumulated is given here. It consists of a primary splitting into amino and hydroxyl radicals, followed by at least four secondary reactions, namely

$$\phi I_a \quad NH_2OH + h\nu \longrightarrow NH_2 + OH \qquad (6)$$
$$k_1 \quad NH_2 + OH + NH_2OH \longrightarrow N_2 + H_2 + 2H_2O \qquad (7)$$
$$k_2 \quad OH + NH_2OH \longrightarrow H_2O_2 + NH_2 \qquad (8)$$
$$k_3 \quad NH_2 + NH_2 + M \longrightarrow N_2H_4 + M \qquad (9)$$
$$2H_2O_2 + 2NH_2OH \longrightarrow N_2O + 5H_2O \qquad (10)$$

Assuming a steady state concentration of the intermediates, NH_2 and OH, the rate of hydrogen formation becomes

$$d(H_2)/dt = k_1(NH_2)(OH)(NH_2OH) = k_1k_3(M)(NH_2)^3/k_2 \qquad (11)$$

The amino radical concentration may be obtained as the solution of the equation

$$(NH_2)^3 + \frac{k_2}{k_1}(NH_2)^2 - \frac{k_2\phi I_a}{k_1k_3(M)} = 0 \qquad (12)$$

The solution is greatly simplified if it is assumed that $k_2/k_1 \gg (NH_2)$ (*vide infra*). With this assumption

$$(NH_2) = \sqrt{\phi I_a/k_3(M)} \qquad (13)$$

and by substitution of this value in (11), one obtains

$$\frac{d(H_2)}{dt} = \frac{k_1(\phi I_a)^{3/2}}{k_2k_3^{1/2}(M)^{1/2}} \qquad (14)$$

Since the reactant is a dilute gas and no fluorescence was observed, it is probable that ϕ is unity.

The third body, M, required for the stabilization of the hydrazine molecule formed in (9) may be hydroxylamine, the wall or any of the products of the thermal reaction. That hydroxylamine may be partly responsible is indicated by the fact that the rate of hydrogen formation increases to some extent with decreasing hydroxylamine pressure. That it is not wholly responsible is suggested by the fact that this dependence is to a much smaller degree than the $^1/_2$ power of the hydroxylamine pressure, as would be expected from the derived rate expression if hydroxylamine replaced M. Considering the nature of amine radicals and of hydrazine itself, and the low pressures used in the experiments, it is conceivable that the walls play a role in the stabilization. Hence it should be possible to divide M into two parts, M = (W + N), where W represents the part played by the walls and N the concentration of hydroxylamine. If either W or N were greatly predominating, (M) would depend only on the one which predominated, but since it depends on both, W and N must be of the same order of magnitude. Figure 3 may be exactly reproduced by the equation

$$\frac{d(H_2)}{dt} = \frac{5.74 \times 10^{-14}}{[2.3 \times 10^{-7} + (NH_2OH)]^{1/2}} \qquad (15)$$

where (NH_2OH) is expressed in moles per cc., and the rate is expressed in moles per cc. per sec. The dependence of W on hydroxylamine pressure is neglected here because of the short pressure range (4 mm.) studied. Similarly, equation (14) may be modified to give

$$\frac{d(H_2)}{dt} = \frac{k_1(I_a)^{3/2}}{k_2k_3^{1/2}[2.3 \times 10^{-7} + (NH_2OH)]^{1/2}} \qquad (16)$$

also

$$\Phi_{H_2} = \frac{d(H_2)/dt}{I_a} = \frac{k_1(I_a)^{1/2}}{k_2k_3^{1/2}[2.3 \times 10^{-7} + (NH_2OH)]^{1/2}} \qquad (17)$$

It is evident from (17) that the slope of Φ_{H_2} *vs.* $(I_a)^{1/2}$ will yield some information regarding the rate constants. For a pressure of 1 mm., it is found that

$$\text{slope} = 1.19 \times 10^{-5} = k_2k_3^{1/2}(2.8 \times 10^{-7})^{1/2}/k_1$$

and

$$\frac{k_2}{k_1} = \frac{2.24 \times 10^{-2}}{k_3^{1/2}}$$

If k_3 is assumed to be of the same order of magnitude as rate constants for atomic recombination, *i. e.*, about 10^{15} (moles/cc.)$^{-2}$ sec.$^{-1}$, then $k_2/k_1 \sim 10^{-9}$.

Several arguments may be applied which lead one to the conclusion that the stationary amino radical concentration cannot be greater than 10^{-12} mole per cc. Now if $k_3 = 10^{15}$ and $(NH_2) < 10^{-12}$ mole per cc., then in equation (12) the cubic term, $(NH_2)^3$, is less than 1/1000 as large as $(k_2/k_1)(NH_2)^2$, and the original assumption in which the cubic term is neglected is valid.

If one assumes the pre-exponential factor values of 10^{14} (moles/cc.)$^{-1}$ sec.$^{-1}$ and 10^{15} (moles/cc.)$^{-2}$ sec.$^{-1}$ for the second and third order reactions (8) and (7), respectively, and if $k_2/k_1 = 10^{-9}$, it may be calculated from the Arrhenius equation that at 27° the activation energy of step (8) is about 11 kcal. greater than for step (7).

In addition to accounting for the observed products, it is seen that this mechanism accounts for the dependence of the rate of hydrogen formation on the 3/2 power of the light intensity. It is true that only a few cases have been reported in which increasing the light intensity leads to an increasing quantum yield, yet some of the most recent mechanisms proposed for the photolysis of ammonia[11a,12,13] yield ane xpression in which the

(11) Hofmann and Kroll's reactions are

$$NH_2OH + NH_2OH \longrightarrow NH_2NHOH + H_2O \qquad (1)$$
$$NH_2NHOH + NH_2OH \longrightarrow (NH_2)_2NOH + H_2O \qquad (2)$$

and to account for the majority of the observed products they suggested that the diamide acid decomposes to give nitrogen, ammonia and water. Further possibilities are

$$2NH_2NHOH \begin{cases} \nearrow N_2O + 2NH_3 + H_2O & (3) \\ \searrow N_2 + N_2H_4 + 2H_2O & (4) \end{cases}$$
$$2(NH_2)_2NOH \longrightarrow 2NO + 2NH_3 + N_2H_4 \qquad (5)$$

(11a) Mund and van Tiggelen, *Bull. soc. chim. Belg.*, **46**, 104 (1937).

(12) Mund, Brenard and Kaertkemeyer, *ibid.*, **46**, 211 (1937).

(13) Kangro, *Z. physik. Chem.*, **42**, 783 (1938).

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quantum yield of ammonia decomposition increases with the cube root of the light intensity. Mund, Brenard and Kaertkemeyer[12] have pointed out that experiments performed by them, by Wiig and by Ogg, Leighton and Bergstrom are in accord with this relation.

The requirement that hydrogen and nitrogen should be formed in approximately equal amounts is satisfied by step (7).

Step (10) was shown to take place by mixing hydrogen peroxide and hydroxylamine vapors. The dry-ice fraction resulting from this mixture was shown to contain only nitrous oxide. The quantities of nitrous oxide thus obtained were much larger than resulted at any time from the simple thermal decomposition of hydroxylamine. It is postulated that this reaction could account for the small amount of nitrous oxide observed in the photolysis. It is probable that the reaction is not fourth order as shown, but takes place in a series of simple bimolecular collisions, quite possibly involving the intermediates postulated in the thermal decomposition of hydroxylamine [equations (1) and (2)]. It is unlikely that hydrogen peroxide remains as a final product in the photolysis, but it is possible that some of it decomposes to form water and oxygen. This is not obviated by the fact that no oxygen was ever observed, since any formed in this manner would react with nitric oxide formed in the thermal decomposition to produce nitrogen dioxide. This in turn would either be frozen out or would react with ammonia formed in the thermal decomposition. Nitrous oxide, if it is formed directly in the photolysis, might appear as the result of reaction (10), while ammonia might result from the decomposition of hydrazine.

The requirement that Φ_{NH_2OH} should increase with increasing light intensity is also satisfied, and values of greater than 2 are permitted by the proposed mechanism. The decrease in Φ_{NH_3CH} with exposure time already has been partially explained.

Other possibilities for the primary step should be noted. The two most probable ones require breaking either an N–H bond or an O–H bond. All other possibilities require the breaking of more than one bond. It may be calculated that at least 67 kcal. would be necessary to break the N–O bond in step (6). This is some 40 kcal. less than that required for the O–H or N–H bonds. So though 67 kcal. is a lower limit to step (6), it is in all probability more likely from an energetic standpoint than are the other two. The fact that no structure whatever was observed in the absorption spectrum, and that no fluorescence could be observed, is evidence against the formation of an activated complex or excited hydroxylamine molecule which by secondary reactions is caused to decompose.

It should be noted that step (8) might be replaced by

$$NH_2 + NH_2OH \longrightarrow N_2H_4 + OH \qquad (18)$$

and (9) by

$$OH + OH + M \longrightarrow H_2O_2 + M \qquad (19)$$

Such a replacement in no way alters either the form of the rate expression for hydrogen formation or the amounts of hydrogen peroxide or hydrazine and their rate of formation. However, (9) seems more likely than (19) because there is some evidence that the latter does not readily take place.

Summary

1. The ultraviolet absorption spectrum of hydroxylamine vapor is found to be experimentally continuous from its onset at about 2350 Å. down to at least 2000 Å.

2. Absorption in this region results in photolysis, the chief products being hydrogen, nitrogen and water. Some hydrazine is also produced, the amount increasing in a flow system. The chief products of the thermal decomposition at room temperature are nitrogen, nitric oxide, nitrous oxide, water and ammonia. Small amounts of nitrous oxide and ammonia may also result directly from the photolysis.

3. For equal amounts of light absorbed, the rate of hydrogen formation decreases with increasing hydroxylamine pressure, and increases with the 3/2 power of the incident light intensity.

4. A mechanism involving amino and hydroxyl radicals is found to fit the experimental data.

Stanford University, California

Received September 17, 1943

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[CONTRIBUTION FROM THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

The Solubility of Sodium Iodide in Sodium Hydroxide Solutions at 20°

BY RICHARD POMEROY AND H. DARWIN KIRSCHMAN

In a recent article[1] we have presented the results of a study of the solubility of potassium iodide in potassium hydroxide solutions at 20° over the range 0 to 14.35 *N* in alkali. The present paper extends the study to the iodide of sodium in solutions of sodium hydroxide from 0 to 15.21 *N*.

The results of our measurements are presented in Table I and Fig. 1.

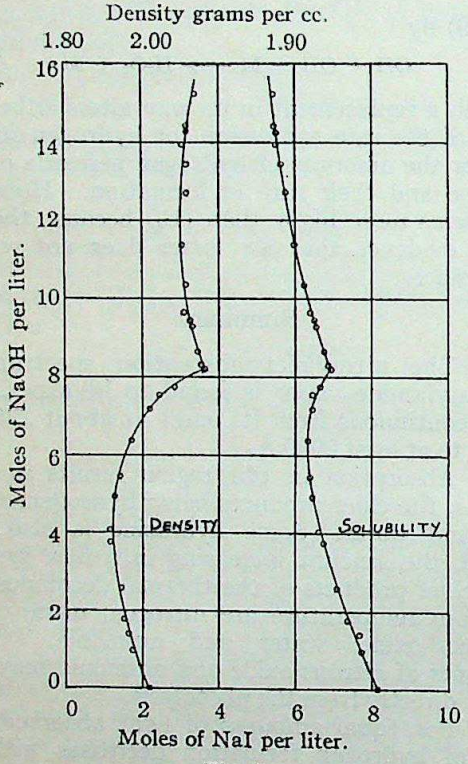

Fig. 1.

Experimental

Sodium iodide of C. P. grade was purified by recrystallization as the dihydrate. A highly concentrated solution of sodium hydroxide was prepared, filtered free from carbonate, and crystallized as the monohydrate by cooling. The bottle containing these crystals was warmed to produce a melt which was mixed with suitable amounts of water and sodium iodide crystals in the equilibrium bottles. These bottles were then immersed in a water-bath at 20° for from four to twelve days and shaken frequently. Portions were removed with pipets and diluted with water to suitable concentrations for analysis. The drainage error in the use of a pipet with these rather viscous solutions was corrected for by washing out and titrating the residual liquid in the pipet. The alkalinity was determined by titration with standard sulfuric acid solution using methyl orange indicator. The iodide content was determined gravimetrically as silver iodide. The density determination was made by weighing a 25-ml. sample of the saturated solution. These weighings were corrected for the buoyant effect of the air.

(1) Kirschman and Pomeroy, THIS JOURNAL, 65, 1605 (1943).

TABLE I

SOLUBILITY AND DENSITY DATA AT 20°

NaOH moles/liter	NaI moles/liter	Density, g./ml.
0.00	8.14	1.910
0.97	7.74	1.888
1.40	7.69	1.881
1.76	7.40	1.876
1.77	7.34	1.871
2.62	7.11	1.872
3.72	6.76	1.860
3.78	6.72	1.856
4.04	6.63	1.856
4.90	6.48	1.865
4.93	6.43	1.858
4.94	6.54	1.870
5.45	6.40	1.870
6.38	6.36	1.885
7.10	6.44	1.905
7.16	6.45	1.908
7.19	6.42	1.912
7.24	6.41	1.908
7.27	6.56	1.919
7.54	6.49	1.922
7.74	6.66	1.942
8.20	6.92	1.981
8.30	6.88	1.977
8.66	6.76	1.972
9.29	6.54	1.965
9.44	6.50	1.962
9.61	6.47	1.962
9.70	6.34	1.948
10.36	6.24	1.956
11.38	5.99	1.952
12.71	5.76	1.958
13.41	5.62	1.957
13.49	5.64	1.958
13.95	5.50	1.953
14.24	5.52	1.959
14.41	5.45	1.959
15.21	5.42	1.970

Equilibrium seemed to be somewhat more slowly attained than in the experiments with potassium iodide in potassium hydroxide but a few trials employing mechanical stirring of the mixture for several hours showed satisfactory agreement with other methods of saturation. The density and solubility curves show a discontinuity at a point corresponding to 8.20 *N* in sodium hydroxide and 6.92 *N* in sodium iodide. The solid phase in the mixtures with hydroxide concentrations above 8.20 was identified as anhydrous, cubic, sodium iodide.

The accuracy of results is estimated to be 1%.

Summary

The solubility of sodium iodide at 20° was determined in sodium hydroxide solutions from 0 to 15.21 *N* in alkali. The density and solubility curves show a discontinuity at a point correspond-

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ing to 8.20 *N* in sodium hydroxide and 6.92 *N* in sodium iodide, which point marks the transition from the dihydrate to anhydrous sodium iodide.

PASADENA, CALIF. RECEIVED OCTOBER 4, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF BRITISH COLUMBIA]

The Density and Transition Points of the *n*-Paraffin Hydrocarbons

BY WM. F. SEYER, RALPH F. PATTERSON[1] AND JOHN L. KEAYS[2]

The density and transition point of dicetyl ($C_{32}H_{66}$) formed the subject matter of a previous communication to this Journal.[3] Since then, all the even-numbered hydrocarbons, beginning with $C_{16}H_{34}$ and ending with $C_{34}H_{70}$, have been investigated, also $C_{29}H_{60}$ of the odd-numbered series.

Materials.—All of these hydrocarbons excepting $C_{16}H_{34}$ and $C_{29}H_{60}$ were synthesized in the laboratory. Samples of hexadecane were obtained from Messrs. Deanesly and Carelton of the Shell Oil Company, and Professor Parks of Stanford University. Both samples were from lots that had been carefully purified by the donors, but upon comparing the m. ps. of the two, it was found that the m. p. from the former had a slightly higher value than that from the latter. The m. p. of the best material was found to be 18.145 and its setting point 18.3.

The nonacosane was obtained from the Bureau of Standards through the efforts of Dr. B. J. Mair. It had an m. p. of 63.0° but as Piper and his co-workers[4] gave a value of 63.4–6° it was recrystallized until the m. p. rose to 63.5°.

The method employed for synthesizing the desired hydrocarbons depended upon the nature of the material available. Where alcohols served as a starting point the Kraft procedure was followed and where acids, the Peterson electrolytic method was utilized. After the usual preliminary purification the hydrocarbons were treated with sulfuric acid until no color formed upon the addition of the acid. To remove it, the hydrocarbons were washed with hot water. They were then dried and recrystallized from five to twenty times until a constant m. p. and t. p. were obtained.

Tetratriacontane, the highest member so far synthesized, was prepared by the electrolysis of the corresponding acid which in this case was stearic. Considerable difficulty was encountered in the purification of this compound. It could not be obtained completely colorless although it was drastically treated with sulfuric acid and recrystallized from glacial acetic acid over forty times. The reason for this failure may lie in the following statement of Oldham and Ubbelohde.[5] "Owing to the appreciable oxidation of certain liquid paraffins at 130°, it was advisable to hinder the circulation of air over the surface of the paraffin during the purification." It may be that this hydrocarbon was oxidized at the temperatures where purification was attempted.

Melting Points of the Normal Paraffin Hydrocarbons.—A knowledge of the melting points of the normal paraffin hydrocarbons was found to be essential for the present investigation. Piper,[4] *et al.*, claim that the transition point is a more reliable index of purity than the melting point.[4] This may be true for those hydrocarbons having more than twenty-six carbon atoms but for those below this in the series this cannot be so, because there is either no transition point or it is indistinct. As mentioned in the previous article, the melting points, even when done by the method outlined by Piper, *et al.*, were affected by the rate of heating and the personal equation, but experience showed that the setting point was not. It could be reproduced by any worker in the Laboratory to within 0.2 to 0.1° for any one sample by observing the temperature when the first crystal formed upon slow cooling (temperature dropping less than 0.5° per minute). Hence, the setting point has been used in this Laboratory for the purpose of establishing the purity of the compounds under investigation. The observed setting points along with the melting and transition points are given in Table II, where N denotes the number of carbon atoms in the chain.

Equations have been developed by Moullin,[6] Taskototos,[7] and Garner[8] for correlating the melting points with number of carbon atoms in the paraffin hydrocarbon chain. None of the equations was found to be satisfactory over the whole range of melting points. Moullin's equation, which is of the form $\log (N - 2) = a + bt$, could be made to fit the curve of melting point against carbon number, if one assumed discontinuities at about $N = 16$ and $N = 33$. N here represents the number of carbon atoms in the chain and a and b are constants. There is also up to $C_{16}H_{34}$ one curve for the odd numbers and one for the even numbers. Above this member, melting points of the odd and even numbered paraffins fall on the same straight line.

The values of the constants, a and b, obtained by the method of least squares for different sections of the curve are given in Table I. Members lower than C_6H_{14}, for both the odd and even numbered compounds, are not included, as the deviations of observed from calculated m. ps. are too great. The recorded m. p. of $C_{11}H_{24}$ is also out of line.

TABLE I

VALUES OF CONSTANTS *a* AND *b*

No. of carbon atoms range:		*a*	*b*
$C_6 \longrightarrow$	C_{16} (even)	1.051	0.00481
C_7	C_{15} (odd)	1.067	.00410
C_{16}	C_{34} (odd and even)	1.02	.0065
C_{33}	C_{70}	0.08	.0006

In correlating the melting points of the normal paraffin series with numbers of carbon atoms in the chain, it was attempted insofar as possible to select values obtained by one set of workers. For as has been mentioned above, the m. ps. obtained depend not only upon the purity of the product but also upon the m. p. technique. Further, workers interested in a set of values are sure to develop laboratory methods and gain experience much broader in scope that those who accidentally are led to make measurements only on one compound. Consequently, we have used the selected values of Deanesly and Carleton[9] for the range 6–18, and our own for the range 18–34.

For 40, 50, 60 and 70 we selected the melting point given by Carothers,[10] and for 36, 52, 62 and 64 those of Gascard.[11]

(1) Standard Oil Company of British Columbia Research Fellow, 1938–1939.

(2) Standard Oil Company of British Columbia Research Fellow, 1941–1942.

(3) Seyer and Morris, THIS JOURNAL, 61, 1114 (1939).

(4) Piper, *et al.*, *Biochem. J.*, 25, 2072 (1931).

(5) Oldham and Ubbelohde, *J. Chem. Soc.*, 200 (1938).

(6) Moullin, *Proc. Camb. Phil. Soc.*, 34, 459 (1938).

(7) Taskototos, *Compt. rend.*, 143, 1235 (1900).

(8) Garner, Van Bibber and King, *J. Chem. Soc.*, 1533 (1931).

(9) Deanesly and Carleton, *J. Phys. Chem.*, 45, 1104 (1941).

(10) Carothers, Hill, Kirby and Jacobson, THIS JOURNAL, 52, 5279 (1930).

(11) Gascard, *Ann. chim.*, 15, 332 (1921).

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From the foregoing data, curves were constructed. Then by means of the smoothed curves a new set of values for the melting points of the paraffin hydrocarbons, up to $N = 70$, was computed as shown in Table II.

Experimental Procedure

The experimental procedure was in general the same as that used in the former measurements with dicetyl. For this, a special dilatometer had to be constructed with a funnel-like opening at the filling end, and to prevent the solid hydrocarbon from working its way upward through the mercury the bulb had to be inverted. However, the difficulties encountered in the measurements of those hydrocarbons lying within the range C_{16} to C_{26} were so great that additional information on the experimental method seemed advisable.

The dilatometer tube, after having been filled, was placed in the constant temperature bath and the capillary heights noted. These heights were plotted against temperature immediately as found. This was done for two reasons. The capillary height–temperature curves resemble, in shape, the density–temperature curve, and therefore, any discrepancy in this, when height was plotted against temperature, would show up at once. Further, the capillary height–density curve shows at a glance the temperature at which any transition points occur and thus indicate what regions must be investigated. The general method of obtaining these curves follows:

The general form of the curve obtained is shown in Fig. 1, where B represents the first transition point and C the second transition or melting point.

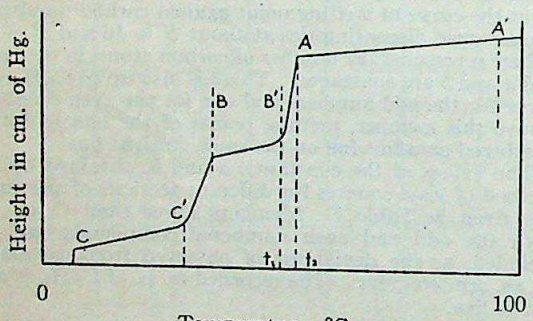

Fig. 1.

Readings were begun near 0°. The bath was kept at this temperature until a constant reading of the mercury level had been obtained. The temperature was then raised several degrees and held constant until equilibrium had been reached. The process was repeated at temperature intervals sufficiently close together to ensure a smooth and continuous curve. The curve given in Fig. 1 is an idealized form of the curve for all members of the aliphatic series greater than 18 and less than 44.

In the regions A–A′, B–B′, and C–C′, equilibrium was reached within a few minutes, but not so in the curve sections A′–B, and B′–C. As the regions of sharp transition were approached, the time required for the mercury level to reach a constant value increased rapidly. In the 0.1–0.2° interval between t_1 and t_2 (that is, at a temperature just below the setting point) it required from one to two weeks for equilibrium to be established. During this time it was necessary to control the temperature as closely as possible.

When the highest possible mercury level had been reached, the temperature was lowered by suitable increments, readings taken, and the values plotted in order to provide a check on the previous curve. It was found that on a descending temperature scale, the points A, B′, B or C′ for any given sample could be determined with an accuracy limited only by the rigidity of temperature control, the accuracy of temperature measurement, and the patience of the observer. In those regions where the densities were

TABLE II

N	M. p. computed, °C.	M. p. observed, °C.	Dev., °C.	S. p. observed, °C.	T. p. observed, °C.
6	−94.0	−95.4	−1.4		
7	−89.7	−90.6	−0.9		
8	−56.7	−56.9	+ .2		
9	−54.1	−53.7	+ .4		
10	−29.7	−29.7	.0		
11	−27.6	−25.6	+2.0		
12	−10.0	− 9.6	+0.4		
13	− 6.3	− 6.2	+ .1		
14	5.5	5.5	.0		
15	10.5	10.0	− .5		
16	18.0	18.3	+ .3	18.3	None
17	22.5	21.0	−1.5		
18	28.3	28.1	−0.2	28.1	26.8
19	32.0	31.4	− .6		
20	36.4	36.2	− .2	36.2	32.0
21	39.8	40.4	+ .6		
22	44.2	44.1	− .1	44.1	40.0
23	46.5	47.0	+ .5		
24	49.6	50.6	+1.0	50.7	47.9
25	52.5	53.3	+0.8		
26	55.6	55.8	+0.2	55.8	48.8
27	58.1	59.1	+1.0		
28	61.2	61.2	0.0	61.2	54.0
29	63.6	63.3	− .3	63.2	57.1
30	65.6	65.7	+ .1	65.4	60.0
31	68.7	68.0	− .7		
32	70.2	69.5	− .7	69.5	63.5
33	71.6	72.0	+ .4		
34	73.0	72.9	− .1	72.9	68.4
35	74.4	75.0	+ .6		
36	75.6	76.0	+ .4		
37	76.9	74.4	−2.5		
38	78.0	77.6	−0.4		
39	79.2	78.8	− .4		
40	80.4	80.7	+ .3		
41	81.5	81.7	+ .2		
42	82.6	82.9	+ .3		
43	83.6	83.8	+ .2		
44	84.8	86.4	+1.6		84.8
50	90.5	92.1	+1.6		
54	94.0	95.0	+1.0		
60	98.7	98.9	+0.2		
62	100.2	100.5	+ .3		
64	102.2	102.6	+ .4		
70	105.4	105.3	− .1		

TABLE III

n	Density at m. p.	Density at t. p.
16	0.774	
18	.774	0.839
20	.779	.867
22	.779	.869
24	.801	.867
26	.779	.872
28	.779	.878
30	.782	.880
32	.784	.878
34	.785	.883
29	.780	.796

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linear functions of the temperature, determinations were made in about five-degree intervals. Elsewhere, the intervals were much smaller varying from 1 to 0.1°, depending upon rate of change of density in that particular region. The densities at the melting and transition points are given in Table II. Here n denotes the number of carbon atoms in the compound.

Discussion of Results

When the densities are plotted against the temperatures, a family of curves is obtained such as shown in Fig. 2. It is at once evident that the dilatometer method yields information which both amplifies and substantiates results arrived at by X-ray examinations of some of these hydrocarbons.

The straight, approximately parallel lines sloping to the right at the bottom of the figure represent the change in density with temperature of the various hydrocarbons in the liquid state. For this group of lines the following equation has been determined

$$d_t = 0.7615 + 0.00205n - 0.0006368t$$

where d_t is the density at $t°$, n the number of carbon atoms in the chain and t the temperature. Values of the density near the m. p. calculated by means of this equation agree to within less than 1% of those given in Beilstein. From the fact that the lines are straight and all have the same slope, one must conclude that the molecules in the liquid state under these conditions are parallel to one another, and that there is thus some degree of order or arrangement. This type of order has been given the name, "cybotaxis." It appears then that in the liquid state the behavior of the n hydrocarbon molecule, with respect to temperature, is the same whether it be even or odd numbered, or whether the chain be long or short. From the observations of Mueller,[12] it would appear safe to assume that hexagonal packing occurs in the liquid just above the m. p. as it does in the solid phase, just below the m. p. The difference between the two phases would then be only that in the liquid phase the molecules would be farther apart than in the solid and that the terminal groups would no longer be in one plane. While movement in the liquid could take place by the molecules sliding over one another in a direction parallel to their long axis, it is more likely that movement occurs by a rolling of the molecules over one another at right angles to the long chain axis. It is this type of motion which probably gives these long chain hydrocarbons their characterisic property as lubricants.

This orderly arrangement must, however, show signs of disappearing as the temperature approaches the b. p. A few preliminary measurements made with hexadecane indicated that a noticeable departure from linearity begins to occur at 100°. At a temperature then somewhere near the b. p. molecular agitation will become so great as to disturb the orderly arrangement and one would then expect the expansions per degree for the different hydrocarbons to differ from one another. Their differences should be a function of molecular weight or chain length. Hence, in the orderly liquid state, expansion must be largely at right angles to the long axis rather than in the chain itself or in the gaps between the terminal atoms between the molecules just as was found to be the case in the different solid phases.

Upon cooling the liquid, the setting point is reached. It is apparent that there is a slight increase in density at this point in going from C_{16} to C_{34}. At the s. p., crystallization begins, and there is a large change in density with a relatively small change in temperature as this process takes place. It would appear, at first sight, that no change in temperature should take place during this change in phase but experience shows this not to be the case. Considerable pains were taken to measure the density in this region by successively lowering the temperature through intervals of 0.1° over periods of time, amounting to several days. It is worth while to note that

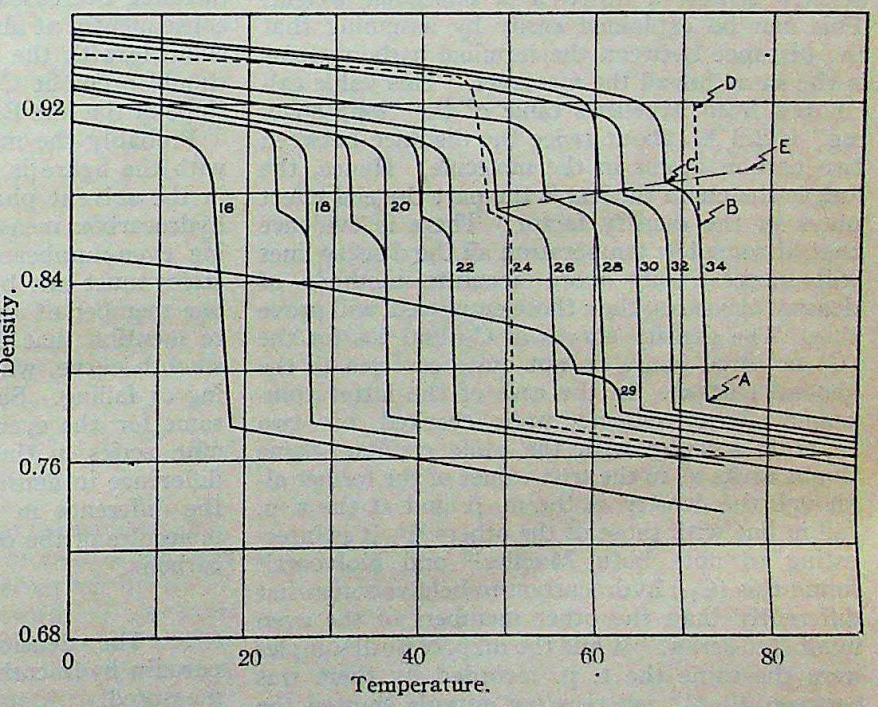

Fig. 2.

(12) A. Mueller, *Proc. Roy. Soc.* (London), **A138**, 515 (1932).

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the slope of the lines from the s. p. (A) to the point (B) is practically the same for all the even numbered hydrocarbons, except C_{16} which shows no transition point. At the point (B), crystallization can be said to be completed and the rate of change of density with respect to temperature begins to fall off rapidly until the transition point (C) is reached. The solid phase existing in the region BC corresponds to Mueller's A modification with the "long spacing." In this case, X-ray work shows the molecule to be standing at right angles to the basal plane, the 001 plane. Here at the point (C), a new solid phase appears and the difference between this and the previous one, according to the above-mentioned investigator, and Piper, *et al.*,[4] is that the molecule in the crystal cell is now tilted with respect to the basal plane.

The similarity of the shapes of the curves in this solid phase is obvious. This suggests that the manner of crystal packing must be the same for all the even numbered *n*-hydrocarbons, and that expansion or contraction must be largely in a plane at right angles to the long chain axis. Unlike the liquid state, however, the density is now a function of molecular weight. This can be explained easily by assuming that the distance between the terminal carbon atoms is the same for all the members. This value calculated from Mueller's table of the "long spacing" is 2.6 Å., about twice the distance between two carbon atoms in the molecule. Hence, the longer the chain the less is the part the end effect plays in the density factor. There is evidence that at some low temperature all the density lines will merge. Only more accurate methods of density measures, than those employed, will prove this. The density curves of C_{24} and C_{30} for the (C) or tilted phase do not quite conform to the general pattern. In the case of the latter compound, measurements were checked on two separate samples with the same results. Some doubt exists as to the true values of the former although the density at the m. p. and at the t. p. fall in line with those of the others.[13] It is interesting to note both Mueller[12] and Kolvoort[14] found this (C_{24}) hydrocarbon to behave somewhat differently than the other members of the even numbered series. While the m. p. of both samples were the same the t. p. recorded by them was between 40–41° whereas our sample showed the expected value of 47.9. It appears that C_{24} forms a kind of boundary between the set of hydrocarbons to the left and the set to the right.

The difference between the two groups lay in their behavior with ascending or descending temperatures. In the case of the group to the right, comprising the members C_{26}, C_{28}, C_{30}, C_{32} and C_{34}, points on the curves could be retraced either upon heating or cooling. This condition also applied to C_{24}, but not for C_{22}, C_{20} and C_{18}. Points on the curve for C_{16}, which has no t. p., could also be checked, irrespective of whether the temperature was going up or down. Those hydrocarbons to the left of C_{24} showed no t. p. upon heating but only upon cooling. The curves obtained upon cooling were of the same form as all the other members of the series and were reproducible. Upon heating these compounds the C phase did not convert to the B but melted directly, and the curves drawn represent limiting conditions. Indications were noted which implied that if the heating were done slowly enough some of the B modifications might be formed before melting took place. Density points would then lie somewhere within the enclosed region as shown in the figure.

If the line AB is produced to the point D and the distance from this line to the t. p. is measured along the temperature axis, it will be seen that this distance decreases as we pass from C_{26} to C_{34}. This indicates that at some higher member in the series than C_{34} the transition point will again disappear. Measured from the figure this distance decreases 0.03° per carbon atom, and consequently at about C_{45} or C_{46} the t. p. should coincide with the m. p. Mueller states that this should occur at C_{44}. This is also shown by the slope of the line EC.

Probably the most striking fact in connection with the figure is the great difference in density in the solvent phase between C_{29}, the only odd hydrocarbon measured and that of its neighboring even-numbered members. While too much stress must not be laid on the behavior of this one member at this time, nevertheless it is well to mention that the density points all fell on a smooth curve, whether the temperature was rising or falling. Since the type of packing is the same for the even and odd members of the paraffin series in this molecular weight range, the difference in density must be ascribed largely to the difference in the gap distance between the molecules of the odd- and even-numbered hydrocarbons.

Summary

1. The densities of the even-numbered *n*-paraffin hydrocarbons from C_{16} to C_{34} have been measured.

2. The density measurements indicate that the structure in the liquid and solid states is the same for all members of the series.

3. The odd numbered hydrocarbon C_{29} has a solid phase much less dense than the neighboring even-numbered members.

4. The transition points of hydrocarbons C_{24} to C_{34} could be observed with either heating or cooling, while the transition points of C_{18}, C_{20} and C_{22} were observed only on cooling.

(13) E. Yatabe, unpublished M.Sc. Thesis.

(14) Kolvoort, *J. Inst. Pet. Tech.*, **24**, 338 (1938).

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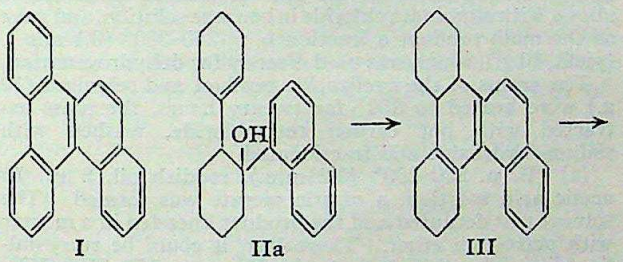
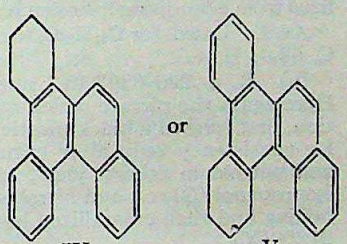
1,2,3,4-Dibenzphenanthrene and its Derivatives. II. Some New Synthetic Attempts[1]

BY FELIX BERGMANN AND H. EMILE ESCHINAZI

Amongst the several possible approaches to the synthesis of 1,2,3,4-dibenzphenanthrene (I) by cyclization, we have investigated more thoroughly the reaction of cyclohexenylcyclohexanone with α-naphthylmagnesium bromide, following the method of Rapson[2] for the synthesis of triphenylene. The carbinol II(a or b) could be cyclized by aluminum or stannic chloride in benzene rather than in carbon disulfide solution, but the reaction product, expected to correspond to III, was not homogeneous. This, however, is not surprising for a structure like III, which should be able to undergo a disproportionation. Dehydrogenation of III with selenium at 320–340° proceeded with extreme difficulty and yielded an oily product, which on the basis of the analytical results was considered to be one of the tetrahydro derivatives IV or V. No further aromatization



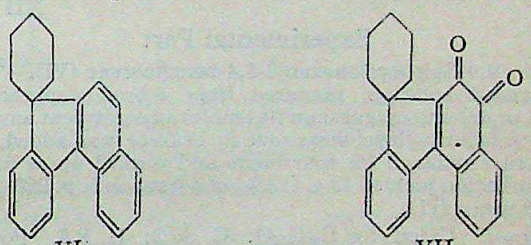
I IIa III



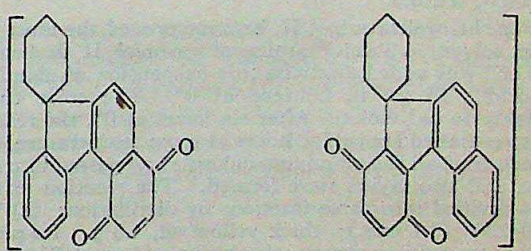
IV V

could be achieved by palladium asbestos at 350°. This resistance to complete aromatization was not understood, until it was observed by R. N. Jones,[3] that the ultraviolet absorption spectrum suggests that the product is a derivative of 3,4-benzfluorene and therefore must be represented by formula VI. The red quinone, which is obtained from it, probably is the *o*-quinone VII, although the two *p*-quinoid structures VIII and IX cannot be excluded. It is hoped that further experiments on model substances will decide this question.

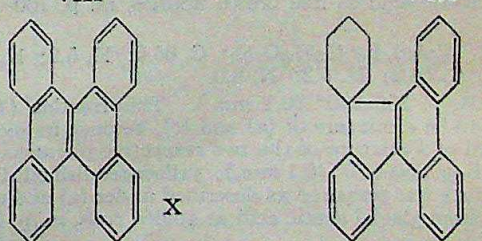
The formation of analogous spirane structures is probable also in the experiments of Rapson.[2] When he started with the oily portion of the cyclization product, he always found appreciable amounts of oily dehydrogenation products besides triphenylene, whereas in the case of crystalline octahydro-triphenylene, "an almost quantitative yield of triphenylene" was obtained with a palladium–charcoal catalyst. But it is strange that no trace of I was detected in our reaction mixture, especially in view of the results from the corresponding reaction of cyclohexenylcyclohexanone with 9-phenanthrylmagnesium bromide. In this case two products could be isolated after aromatization. A small amount of tetrabenznaphthalene (X) was identified as its black picrate. Besides that another picrate was obtained, differing from the former by four to six hydrogen atoms. In analogy with the above results the spirane structure XI is ascribed to it.



VI VII



VIII IX



X XI

It is usually supposed, that spirane formation competes with the cyclization to a six-membered ring in all those cases where dehydration may lead to isomeric olefins.[4] In the present case, a diene is formed during dehydration, which may have either of two structures, and, accordingly, may give rise to two different cyclization products. However, in view of the fact that there was no indication of a second product another mechanism must be considered: the cyclization catalyst as an electrophilic reagent liberates a carbonium ion from the carbinol, and this ion is a resonance hybrid and

(1) Part I. F. Bergmann and Eschinazi, THIS JOURNAL, 65, 1413 (1943).

(2) Rapson, *J. Chem. Soc.*, 15 (1941).

(3) See Jones, THIS JOURNAL, 66, 185 (1944).

(4) Perlmann, Davidson and Bogert, *J. Org. Chem.*, 1, 288 (1936).

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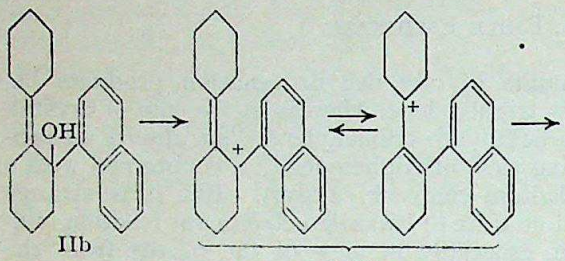
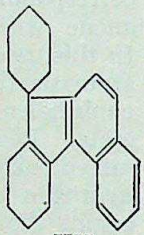
therefore able only to form a five-membered ring. This mechanism will be discussed in a future paper.



IIb XIII



XII

Experimental Part

1. **9,9-Spirocyclohexanyl-3,4-benzfluorene (VI).**—To a Grignard solution, prepared from α-bromonaphthalene (0.1 mole) and magnesium (0.1 mole) an equivalent amount of cyclohexenylcyclohexanone in benzene was added, the mixture refluxed for four hours and worked up as usual. Distillation yielded 13 g. (42%) of a fraction b. p. 225–230° (0.8 mm.) (II).

Anal. Calcd. for $C_{22}H_{26}O$: C, 86.2; H, 8.5. Found: C, 85.6; H, 8.2.

For the cyclization of II, benzene proved the most suitable solvent. Twelve grams of carbinol II in benzene (50 cc.) was added dropwise to a suspension of aluminum chloride (15 g.) in benzene at 0°. The color turned quickly to red-violet. After six hours at 0°, the reaction was continued for twelve hours at room temperature, after which time all the aluminum chloride had passed into solution and two layers were formed. The reaction product was divided into three fractions by distillation: (a) b. p. 210–230° (0.1 mm.); thick yellow oil, 4.5 g. Its picrate was prepared in isopropanol solution and crystallized from glacial acetic acid as fine brown needles, m. p. 160–161° (XII?).

Anal. Calcd. for $C_{28}H_{27}O_7N_3$: C, 65.0; H, 5.2; N, 8.1. Found: C, 64.9; H, 5.2; N, 8.0.

(b) B. p. 230–240° (0.1 mm.). This fraction (4 g.) proved to be a mixture of (a) and (c), because its picrate consisted of a mixture of the two respective picrates.

(c) B. p. 250–270° (0.1 mm.); yellow-reddish oil, 1.5 g. The picrate was prepared as described under (a) and crystallized from glacial acetic acid as golden rods, m. p. 169–170°.

Anal. Found: C, 65.3; H, 5.1; N, 8.2.

This substance, according to its analysis, is isomeric with the product, yielding the picrate of m. p. 160–161°. A mixture of both picrates melts at 150–152°.

Dehydrogenation was best attained with fraction (c); the other fractions gave essentially the same end-product, but less pure and in poorer yields.

15 g. of (c) and selenium (25 g.) were heated to 320° for thirty hours. The hot mixture was then stirred carefully into petroleum ether (80°), the solution washed with sodium hydroxide and distilled. The main fraction (9.5 g.) had b. p. 220–240° (0.1 mm.) and consisted of a reddish oil with green fluorescence. This product was purified via its picrate, which was prepared in glacial acetic acid with addition of a little petroleum ether, in order to obtain a homogeneous solution. The picrate crystallizes from glacial acetic acid in red rods, m. p. 141–142°; 7 g of crude hydrocarbon yielded about 8 g. of picrate.

Anal. Calcd. for $C_{28}H_{23}O_7N_3$: C, 65.5; H, 4.45; N, 8.2. Found: C, 65.8; H, 4.2; N, 8.0.

Five grams of this picrate yielded 2.5 g. of spirane VI, b. p. 225–230° (0.05 mm.) as a thick yellow oil with strong green fluorescence. It dissolves readily in petroleum ether or acetone, but sparingly in acetic acid. With concd. sulfuric acid a pink solution is obtained on gentle heating, which turns slowly to green. After long standing, the substance tends to crystallize, but because of its low melting point could not yet be recrystallized satisfactorily.

Anal. Calcd. for $C_{22}H_{20}$: C, 93.0; H, 7.0. Found: C, 93.4; H, 6.9.

Oxidation to the quinone (VII?): 0.25 g. of VI in acetic acid (5 cc.) was boiled with $K_2Cr_2O_7$ (0.5 g.) for five minutes and the quinone precipitated by water. After two crystallizations from high-boiling petroleum ether, it formed beautiful long red plates, m. p. 228° (VIII?). Concd. sulfuric acid dissolves it with cherry-red color.

Anal. Calcd. for $C_{22}H_{18}O_2$: C, 84.1; H, 5.7. Found: C, 84.0; H, 5.8.

Tetrabenznaphthalene (X) and Spirane XI.—The Grignard reaction between 9-bromophenanthrene (26 g.), magnesium (2.5 g.) and cyclohexanylcyclohexanone (18 g.) in benzene, after ten hours of boiling, gave a mixture which after decomposition and distillation yielded 17 g. of a bright yellow sirup, b. p. 270–290° (0.1 mm.). Cyclization of this carbinol (16 g.) was carried out as described above, with aluminum chloride in benzene solution, and gave as the main product a fraction b. p. 320–360° (0.1 mm.), (yield, 10 g.), which was used directly for dehydrogenation.

Ten grams of the cyclization product and selenium (12 g.) were heated to 350° for twenty hours, the mass extracted with hot carbon tetrachloride, washed with sodium hydroxide and fractionated.

(a) B. p. 230–260° (0.2 mm.), reddish oil, 3 g. In acetic acid solution, a plastic picrate was formed. The solvent was decanted and the product kneaded in a mortar with petroleum ether. Thereafter, it could be recrystallized from isopropanol; brown leaflets, m. p. 157–159° (XI).

Anal. Calcd. for $C_{32}H_{25}O_7N_3$: C, 68.2; H, 4.4. Found: C, 68.0; H, 4.0.

(b) B. p. 290–320° (0.1 mm.); dark-red resin, 1.5 g. Here again the picrate which was prepared in acetic solution, first formed a black plastic mass and acquired granular consistency only after trituration with butyl acetate and petroleum ether; yield, 1.8 g. It was dissolved in isopropanol (50 cc.) and nitrobenzene (2 cc.) by prolonged boiling and then crystallized in red-black rods, m. p. 210–212°[5] (X).

This procedure had to be repeated two or three times.

Anal. Calcd. for $C_{32}H_{19}O_7N_3$: C, 68.9; H, 3.4; N, 7.5. Found: C, 68.6; H, 3.2; N, 7.4.

Acknowledgment.—The authors wish to thank Prof. R. N. Jones for his kind coöperation and his help in the discussion of the theoretical problems met with in the present work.

Summary

Cyclization of 1-(α-naphthyl)-2-cyclohexenylcyclohexanol-1 yields a 9,9-spirane derivative of 3,4-benzfluorene instead of the expected 1,2,3,4-dibenzphenanthrene skeleton. The mechanism of this "cyclodehydration" is discussed.

The analogous reaction between cyclohexenylcyclohexanone and 9-phenanthrylmagnesium bromide yielded, besides the corresponding spirane, a small amount of tetrabenznaphthalene.

REHOVOTH, PALESTINE RECEIVED SEPTEMBER 10, 1943

(5) E. Bergmann and Fujise, *Ann.*, **483**, 65 (1930), report a m. p. of 200°.

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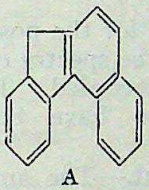
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY AND QUEEN'S UNIVERSITY]

The Spectrographic Characterization of a Hydrocarbon Synthesized by Bergmann and Eschinazi

BY R. NORMAN JONES

Selenium dehydrogenation of the cyclized condensation product of cyclohexenylcyclohexanone with α-naphthylmagnesium bromide yields a product which Bergmann and Eschinazi[1] believed to possess either structure IV or V as shown in their article.

The ultraviolet absorption spectrum provides a method of distinguishing between these two structures, since IV[1] is an alicyclic derivative of



A

3,4-benzphenanthrene and (V)[1] is an alicyclic derivative of chrysene. It is known that alicyclic rings do not alter significantly the spectrum characteristic of the polynuclear aromatic hydrocarbon to which they are attached.[2] The spectrum of (IV)[1] should resemble closely that of 3,4-benzphenanthrene, and the spectrum of (V)[1] should be similar to the spectrum of chrysene.

The spectrum of Bergmann and Eschinazi's hydrocarbon is compared with the spectra of chrysene[3] and 3,4-benzphenanthrene[4] in Fig. 1; but the resemblance to either of these spectra is so slight as to cast considerable doubt on the close relation of the compound to either hydrocarbon.

In Fig. 2 the spectrum of Bergmann and Eschinazi's hydrocarbon is compared with the spectrum of 3,4-benzfluorene[4] (A) which it resembles closely in the region from 2200 to 3600 Å. The low intensity structure between 3800 and 4600 Å., not observed in the spectrum of 3,4-benzfluorene, may be due to a trace of impurity. Assuming an intensity of log E_{molar} = 4.0–4.5 for a hypothetical component responsible for the 4360 Å. maximum, this would indicate a concentration of about 0.1% of impurity. Structure in this region of the spectrum was observed in early determinations of the spectrum of fluorene, but was later shown to be due to impurities.[5] It is also possible that corresponding low intensity structure might be present in the spectrum of 3,4-benzfluorene, but was not recorded by Mayneord and Roe,[4] whose measurements did not extend below log

(1) Bergmann and Eschinazi, THIS JOURNAL, 65, 183 (1944). With the exception of structure (A), reference should be made to this paper for structural formulas discussed in the current article.

(2) Jones, *Chem. Rev.*, 32, 1 (1943).

(3) Redrawn from the data of Mayneord and Roe, *Proc. Roy. Soc.* (London), A152, 299 (1935).

(4) Redrawn from the data of Mayneord and Roe, *ibid.*, A158, 634 (1937).

(5) Askew, *J. Chem. Soc.*, 512 (1935).

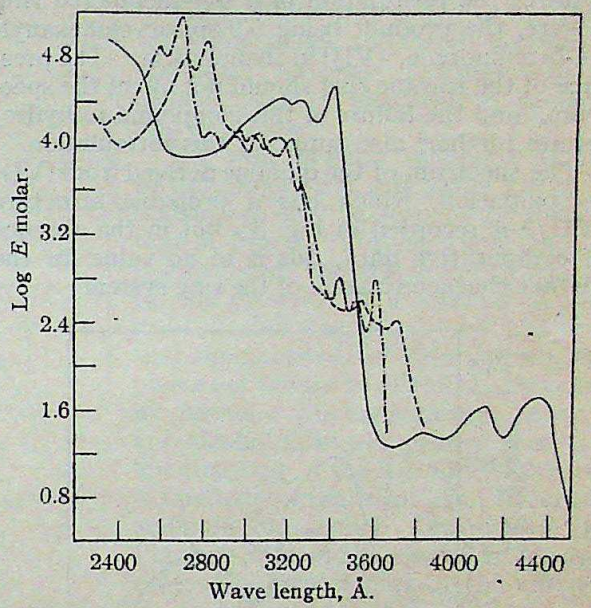


Fig. 1.———, Absorption spectrum of Bergmann and Eschinazi's hydrocarbon; -·-·-·, spectrum of chrysene; – – – – –, spectrum of 3,4-benzphenanthrene.

E_{molar} = 1.6. This explanation would seem more reasonable, as Bergmann and Eschinazi purified their compound through the picrate.

Over the region from 2400 to 3400 Å. the absorption of Bergmann and Eschinazi's hydrocarbon is everywhere more intense than that of 3,4-

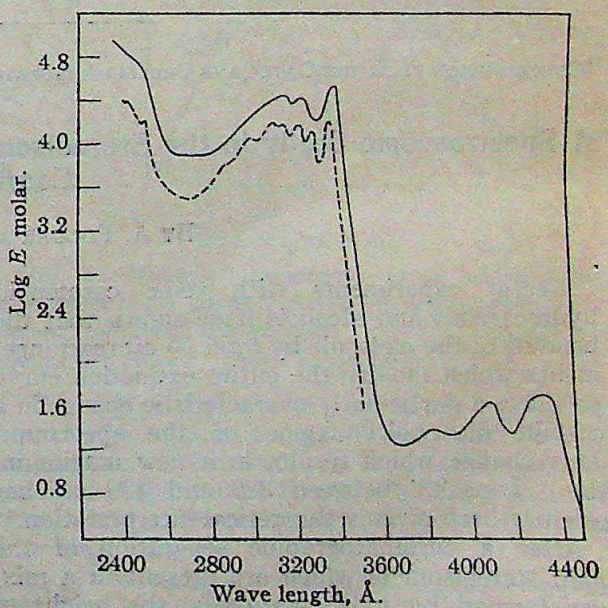


Fig. 2.———, Absorption spectrum of Bergmann and Eschinazi's hydrocarbon; – – – – –, spectrum of 3,4-benzfluorene.

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benzfluorene. This is unusual, but a similar effect has been recorded by Bachmann and Carmack,[6] who compared the spectra of 3,4-benzpyrene and its 4′,5-dimethylene derivative.

The formulation of Bergmann and Eschinazi's hydrocarbon as a derivative of 3,4-benzfluorene requires the postulation of a five-membered ring closure, the product being 9,9-spirocyclohexanyl-3,4-benzfluorene, (VI)[1] in their article. The presence of the spirane ring should not affect the spectrum,[7] and the failure of this compound to hydrogenate further[1] also supports this formulation.

The spectrum of the quinone derived from (VI)[1] by oxidation, which has a probable structure (VII),[1] is recorded in Fig. 3; but in the absence of comparative data, this is of no value for the further characterization of the ring system.

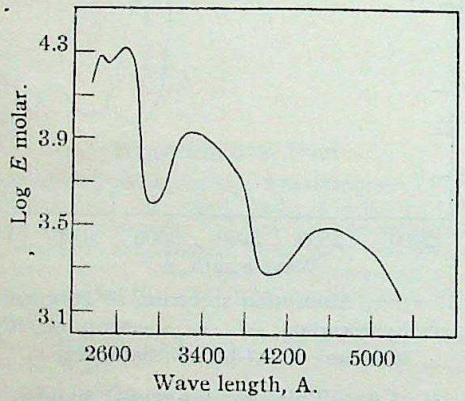

Fig. 3. ——, Absorption spectrum of quinone (probably VII[1]).

(6) Bachmann and Carmack, THIS JOURNAL, 63, 1685 (1941).

(7) Compare the spectra of 7,8-dihydrophenalyl-7-spirocyclopentane and naphthalene, in reference 5.

TABLE I

POSITION AND INTENSITY OF ABSORPTION MAXIMA

Wave length, Å.	Intensity (log E_{molar})
(a) Hydrocarbon (VI)[1] (solvent ethanol)	
3150	4.45
3250	4.43
3395	4.55
3845	1.38
4105	1.61
4360	1.69
(b) Quinone (VII)[1] (solvent ethanol)	
2470	4.28
2680	4.32
3330	3.94
4600	3.49

In Table I data for the position and intensity of the maxima of the spectra of compounds (VI)[1] and (VII)[1] are recorded. The spectrographic methods employed have been reported previously.[8]

Acknowledgment.—The author wishes to express his thanks to Professor L. F. Fieser, of Harvard University, in whose laboratory the spectra were determined, and to acknowledge the financial support of The International Cancer Research Foundation.

Summary

Comparison of the ultraviolet absorption spectrum of a hydrocarbon synthesized recently by Bergmann and Eschinazi, with the spectra of chrysene, 3,4-benzphenanthrene and 3,4-benzfluorene suggests that the new hydrocarbon is 9,9-spirocyclohexanyl-3,4-benzfluorene.

(8) Jones, THIS JOURNAL, 62, 148 (1940).

KINGSTON, CANADA RECEIVED SEPTEMBER 10, 1943

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY No. 939]

A Spectroscopic Study in the Stereoisomeric Capsanthin Set. *cis*-Peak Effect and Configuration

BY A. POLGÁR AND L. ZECHMEISTER

Recent experiments with some carotenoid hydrocarbons and alcohols have shown that the bending of the molecule by *trans* → *cis* rearrangements which modify the entire extinction curve produces a particularly characteristic change in a certain ultraviolet region of the spectrum.[1] This change which results in a new maximum, the "*cis*-peak," between 320 and 380 mμ has recently been given a theoretical interpretation.[2]

After a chromatographic separation of the main stereoisomers which are present in a mixture formed by iodine catalysis, the height of the *cis*-peak can be determined for each stereoisomer.[1,2,3] This procedure has been used recently to assign tentative configurations to the main observed members of the stereoisomeric sets of α-carotene, β-carotene, lycopene and lutein.[2,3]

In order to provide data for compounds of another type a carotenoid ketone, capsanthin, $C_{40}H_{58}O_3$, which is the main pigment of the red pepper (*Capsicum annuum*) has been investigated. Capsanthin was one of the first C_{40}-carotenoids in which stereochemical effects in the form of spontaneous isomerization were observed by Cholnoky and one of the authors.[4] This was

(1) L. Zechmeister and A. Polgár, THIS JOURNAL, 65, 1522 (1943).

(2) L. Zechmeister, A. L. LeRosen, W. A. Schroeder, A. Polgár and L. Pauling, *ibid.*, 65, 1940 (1943).

(3) L. Zechmeister and A. Polgár, *ibid.*, 65, 137 (1943).

(4) L. Zechmeister and L. Cholnoky, *Ann.*, 530, 291 (1937).

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followed by a more detailed study of the thermal and iodine catalyzed *cis–trans* isomerization of capsanthin, capsorubin, and some of their esters.[5]

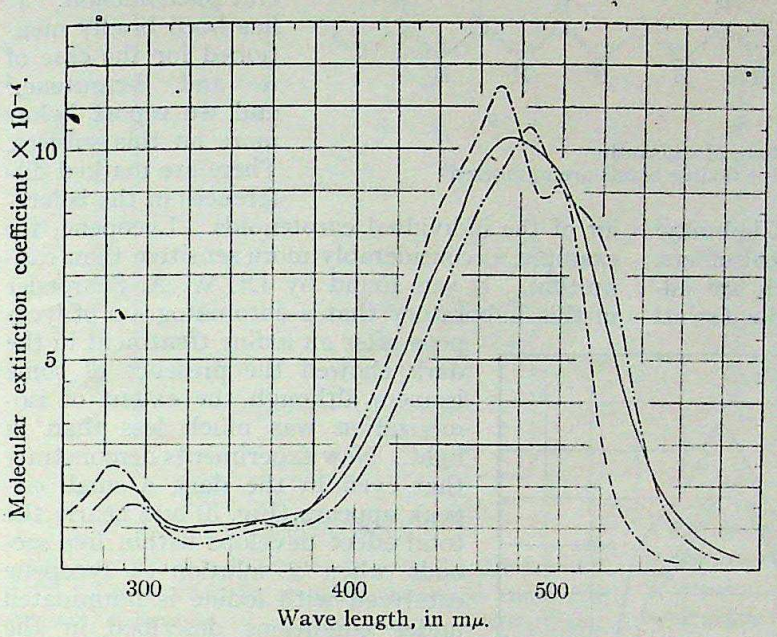

Fig. 1.—Molecular extinction curves of all-*trans*-capsanthin: —— in ethanol; –·– in benzene; and – – ·– – in hexane.

Recent experiments show that capsanthin also undergoes a partial stereoisomerization upon melting its crystals or short exposure of solutions to sunshine.

We shall consider first the general shape of the capsanthin extinction curves, before and after stereoisomerization, and shall then discuss the possibilities for assigning spatial structures to some members of this set.

The extinction curve of natural (all-*trans*)-capsanthin in benzene was determined by Kuhn[6] in the visible region, and by Karrer and Würgler[7] also in the ultraviolet region; however, the latter paper is not available to us.

As one of our goals, we wished to obtain some data concerning the influence of polar solvents upon the shape of the extinction curve, especially upon the fine structure of the fundamental band in the visible region. It has been reported by Cholnoky and one of us[8] that the color of a solution of one milligram of capsanthin in two hundred milliliters of petroleum ether is straw-yellow, but that in alcohol is wine-red. Furthermore, the spectrum in alcohol is so blurred that it was impossible to locate bands with a visual spectroscope. Kuhn and Brockmann[9] noted earlier the same behavior in the polyene diketone, rhodoxanthin, $C_{40}H_{52}O_2$. They correctly attributed this phenomenon to the interaction between polar carbonyls and polar alcohol molecules. According to Kuhn and Brockmann, the effect is displayed only if the carbonyl group stands in conjugation with the carbon–carbon conjugated system. When this conjugation was interrupted by the addition of two hydrogen atoms to rhodoxanthin, the visual maxima in non-polar solvents (hexane) and in alcohol became identical in position and sharpness.

The very definite influence of the solvent upon the extinction curve of capsanthin may be seen by an inspection of Fig. 1. The complete lack of fine structure, which is probably caused by the presence of a number of pigment-alcohol complexes and the mutual superposition of their curves, explains our failure to read visual spectra in alcohol. An examination in hexane–alcohol mixtures proved that the fine structure of the fundamental band is markedly diminished even by small amounts of alcohol. As shown by Fig. 2 as little as 2% alcohol in hexane causes the greater part of the change from the 0% alcohol curve to the 100% alcohol curve.[9a]

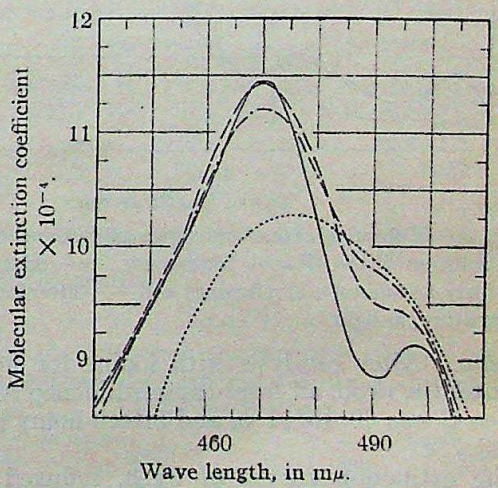

Fig. 2.—Molecular extinction curves of all-*trans*-capsanthin in the visible region: —— in hexane; – – – in hexane, containing 2% ethanol; – – ·– – in hexane, containing 5% ethanol; and ..... in ethanol.

The stereochemical situation in the capsanthin set may be summarized as follows. The number of possible stereoisomers is thirty-two, and the number of the double bonds, which can undergo *trans* → *cis* isomerization, is five[10] (see the formula).

(5) L. Zechmeister and L. Cholnoky, *Ann.*, **543**, 248 (1940).

(6) R. Kuhn, in L. Zechmeister, "Carotinoide," Julius Springer, Berlin, 1934, p. 235.

(7) P. Karrer and E. Würgler, *Helv. Chim. Acta*, **26**, 116 (1943).

(8) L. Zechmeister and L. Cholnoky, *Ann.*, **516**, 30 (1935).

(9) R. Kuhn and H. Brockmann, *Ber.*, **66**, 828 (1933); I. M. Heilbron and B. Lythgoe, *J. Chem. Soc.*, 1376 (1936) (with further references).

(9a) *Cf.* W. R. Brode, "Chemical Spectroscopy," 2nd ed., J. Wiley and Sons, Inc., New York, N. Y., 1943, pp. 185–188.

(10) L. Pauling, *Fortschr. Chem. organ. Naturstoffe*, **3**, 203 (1939); L. Zechmeister, A. L. LeRosen, F. W. Went and L. Pauling, *Proc. Natl. Acad. Sci.*, **27**, 468 (1941).

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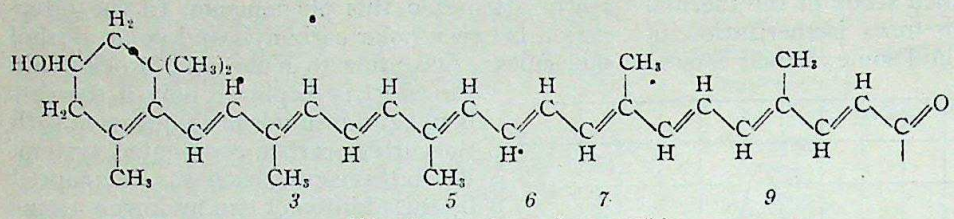

The chromophore of capsanthin
(The stereochemically effective double bonds are numbered)

It was shown in collaboration with Cholnoky[5] that capsanthin forms three main stereoisomers, the neo compounds A, B and C which are adsorbed above the all-*trans* pigment on the Tswett column. After catalysis with iodine for fifteen minutes the ratio, all-*trans*-capsanthin:neo A:neo B:neo C was 69:15:11:5, and fifteen hours later, 66:23:7:4.

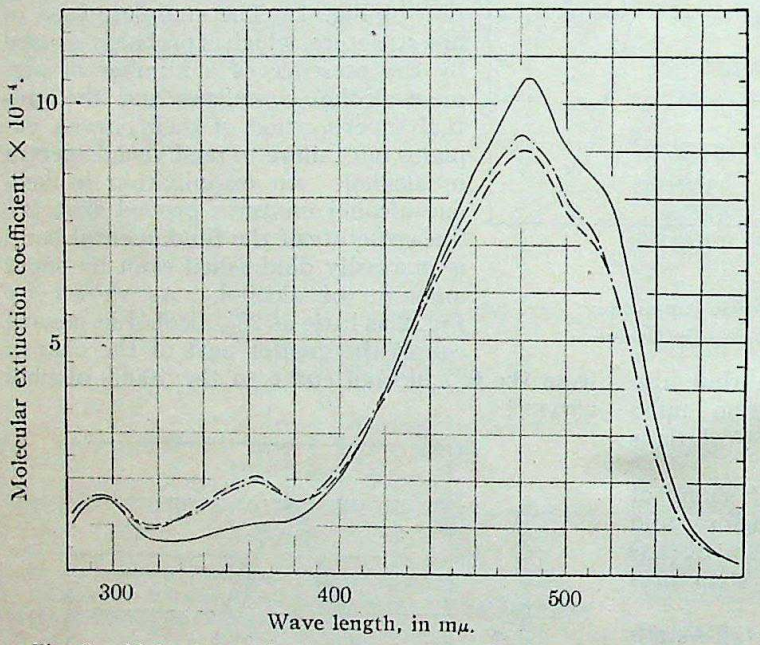

Fig. 3.—Molecular extinction curves of capsanthin in benzene: —— fresh solution of the all-*trans* compound; – – – mixture of stereoisomers after forty-five minutes of refluxing; and – · – · after iodine catalysis at room temperature, in light.

The extinction curves of fresh, refluxed and iodine catalyzed solutions of capsanthin show that the presence of a carbonyl group does not essentially alter the influence of stereoisomerization on the spectral properties. The extinction is diminished in the visible spectrum while in the ultraviolet region a considerable *cis*-peak appears, for example, in benzene at 363 mμ (Fig. 3).

Iodine does not cause the formation of a *cis*-peak in capsanthin solutions in the dark. Figure 4 shows, however, that an illumination as short as five seconds develops about a third of the ultimate effect. The photochemically excited iodine atoms are mainly responsible for this catalysis. As far as we know, the influence of light on the iodine catalysis of carotenoids is a general phenomenon. It has been briefly mentioned for the case of α- and β-carotene,[3] and we report below more on this subject. There are marked differences in the behavior of the individual carotenoids. Lycopene, for example, is considerably more sensitive than capsanthin. It was found by Dr. W. A. Schroeder in this Laboratory that a chromatogram of lycopene after an iodine treatment in the dark showed the presence of some isomers although the extent of isomerization was much less than in light. New experiments demonstrate that even in the dark a small *cis*-peak appears (Fig. 5) and nearly the total effect develops within five seconds when a solution of lycopene catalyzed with iodine is illuminated under conditions described in the Experimental Part.

The configurations of some neocapsanthins can be deduced tentatively from spectroscopic data. The longest wave length maximum of neocapsanthin A or B is shifted 6 mμ relative to that of the all-*trans* compound, and that of neo C is shifted 10.5 mμ. Our interpretation[2,3] demands that the molecules of neocapsanthin A and B contain one *cis* double bond but that the number of such bonds be two in neocapsanthin C.

Although the neocapsanthins A and B cannot be differentiated in the visual spectroscope, this is easily possible by a quantitative investigation of the *cis*-peak region. As shown in Fig. 6, the peak of neo A, which is comparable with the highest *cis*-peaks observed in the α- or β-carotene

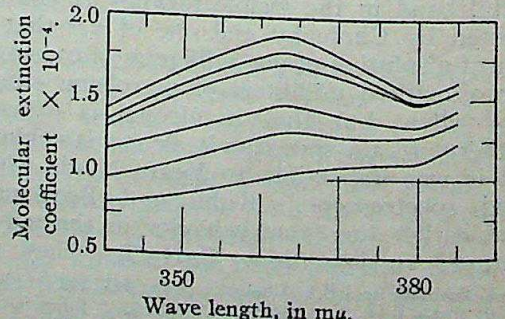

Fig. 4.—Influence of illumination on the development of the *cis*-peak effect in an iodine catalyzed solution of capsanthin, in benzene; curves from bottom to top: after 0 sec., 5 sec., 30 sec., 2½ min., 15 min., and 30 min. illumination.

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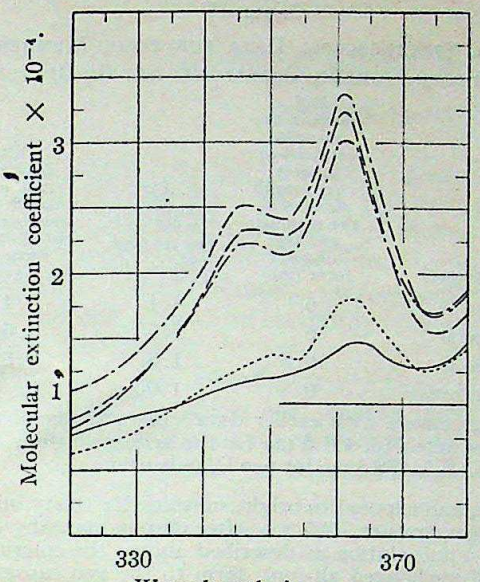

Fig. 5.—Influence of illumination on the development of the *cis*-peak effect in an iodine-catalyzed solution of lycopene, in hexane: ..... after 0 sec., – – – after 5 sec.; – – · – – after 30 sec., and – · – · after 15 min. illumination. The full line denotes the curve taken before the addition of iodine, and without illumination.

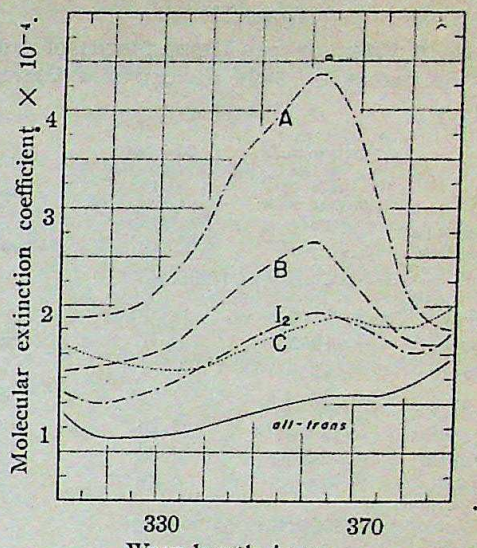

Fig. 6.—Molecular extinction curves of some members of the stereoisomeric capsanthin set in the *cis*-peak region, in benzene; I_2 indicates the equilibrium mixture obtained upon iodine catalysis.

set, is much higher than the peak of neocapsanthin B. Consequently, and in accordance with recent investigations in other stereoisomeric sets, the most probable configuration of neocapsanthin A is that of *6*-mono-*cis*-capsanthin, and of neo B that of *5*-mono-*cis*- or *7*-mono-*cis*-capsanthin.[11] The position of the two *cis* double bonds in neo C cannot be stated definitely. The models do not exclude the possibility that one of these *cis* bonds is located at or near the center of the chromophoric system.

Acknowledgment.—We wish to thank Dr. L. Cholnoky for the preparation of the capsanthin samples.

Experimental Part

Materials and Methods.—The following solvents were used in the optical experiments: benzene (thiophene-free, reagent, Baker and Adamson), purified by shaking with sodium thiosulfate and then distilling; absolute ethanol, distilled over sodium; and hexane (practical, from petroleum, Eastman Kodak Co.), purified by shaking first with fuming sulfuric acid, then with alkaline permanganate, and finally redistilled.

The extinction readings were taken with a Beckman photoelectric spectrophotometer.[12] The extinction curves of all-*trans* pigments drawn in Figs. 1, 2 and 3 are based on average values (Tables I–II) of several independent experiments. The greatest deviation at the visual maxima is ±2.4% in benzene, and ±1.1% in ethanol. Because capsanthin is sparingly soluble in cold hexane, the solution was prepared by shaking crystals with this solvent and then filtering. The concentration was established by the use of extinction values obtained by dissolving capsanthin in absolute alcohol and diluting with 98 volumes of hexane; the maximum in Fig. 2 represented by a full line is, therefore, only approximately correct.

(11) For nomenclature see reference 3.

(12) H. H. Cary and A. O. Beckman, *J. Optical Soc. Am.*, **31**, 682 (1941).

TABLE I

MOLECULAR EXTINCTION COEFFICIENTS OF CAPSANTHIN AND OF ITS STEREOISOMERIC EQUILIBRIA AT THE MAXIMA (*italicized*) AND MINIMA IN BENZENE

Fresh solution		After heat isomerization		After iodine isomerization	
mμ	$E^{mol.}_{1\,cm.} \times 10^{-4}$	mμ	$E^{mol.}_{1\,cm.} \times 10^{-4}$	mμ	$E^{mol.}_{1\,cm.} \times 10^{-4}$
508[a]	8.7	506[a]	7.4	506[a]	7.7
484	10.5	*481*	9.0	*481*	9.4
274–276[a]	1.08	382–385	1.52	382	1.52
		363	2.06	*362*	1.94
324–330	0.6(3)	315–318	0.9(1)	318	0.9(9)
295	1.56	*293–295*	1.56	*294*	1.63

[a] Point of inflection.

TABLE II

MOLECULAR EXTINCTION COEFFICIENTS OF CAPSANTHIN AT THE MAXIMA (*italicized*) AND MINIMA IN HEXANE AND ABSOLUTE ETHANOL

In hexane		In ethanol	
mμ	$E^{mol.}_{1\,cm.}$	mμ	$E^{mol.}_{1\,cm.}$
498	9.1	*476*	10.3
492	8.8	320	1.04
468–470	11.4	*290*	2.00
365	1.08		
355	1.14		
320–330	0.9(2)		
284	2.50		

Influence of Illumination on the Development of the *cis*-Peak Effect in Solutions Catalyzed with Iodine.—Fresh solutions were prepared and catalyzed in the dark. After the extinctions had been determined, the solutions which were in 25-ml. volumetric flasks (glass), were placed in horizontal position on white paper and irradiated by means of two fluorescent lamps (3500° white, Mazda, 40 W; length of tube, 120 cm.) from a distance of 60 cm. The gradual development of the peaks of α-carotene, β-carotene, lycopene, and capsanthin is characterized by the data in Table III.

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TABLE III

INFLUENCE OF LIGHT ON THE DEVELOPMENT OF THE *cis*-PEAK IN SOLUTIONS OF SOME CAROTENOIDS CATALYZED WITH IODINE

Duration of the illumination	Mol. extinction coeff. at the max. of longest wave length, $E^{mol.}_{1 cm.} \times 10^{-4}$	Mol. extinction coeff. at the wave length of the *cis*-peak $E^{mol.}_{1 cm.} \times 10^{-4}$	Increase in the *cis*-peak (% of the greatest change)
	α-Carotene (hexane)		
0 sec.	14.6	0.8(6)	0
5 sec.	14.2	1.51	45
30 sec.	13.7	1.94	75
2½ min.	13.4	2.11	87
15 min.	13.2	2.16	90
30 min.	12.7	2.30	100
60 min.	11.3	2.26	97
	β-Carotene (hexane)		
0 sec.	14.2	0.8(7)	0
5 sec.	13.9	1.49	40
30 sec.	13.2	1.95	69
2½ min.	13.0	2.04	75
15 min.	12.3	2.22	87
30 min.	10.9	2.22	87
60 min.	8.6	2.43	100
	Lycopene (hexane)		
0 sec.	18.6	1.47	0
5 sec.	15.5	3.2	92
30 sec.	15.6	3.4	100
2½ min.	15.4	3.2	92
15 min.	14.0	3.0	81
	Capsanthin (benzene)		
0 sec.	9.9	1.02	0
5 sec.	9.8	1.29	31
30 sec.	9.5	1.47	51
2½ min.	9.3	1.72	80
15 min.	9.0	1.80	89
30 min.	9.0	1.89	99
60 min.	8.9	1.90	100

Estimation of *cis*-Peaks of the Neocapsanthins.—The mixture obtained from capsanthin by iodine catalysis in benzene was chromatographed on calcium carbonate (Merck precipitated Heavy Powder) and developed with benzene which contained 1 to 2% acetone. Each neo zone was eluted with ice-cold alcohol, transferred into benzene, washed thoroughly with ice water, dried with sodium sulfate, and investigated spectrophotometrically. The concentrations were established by catalyzing an aliquot part of each solution with iodine, determining the extinction at the wave length of the highest maximum, and calculating the concentration from the corresponding value of the iodine equilibrium curve.[1,2,3] Table IV contains the averages of two independent experiments.

***cis–trans* Isomerization of Capsanthin by Insolation.**—A solution of 2.5 mg. of all-*trans* pigment in 25 ml. of benzene was placed in a transparent quartz test-tube (diameter, 22 mm.) from which the air was displaced with carbon dioxide, and exposed to bright sunshine for thirty minutes (final temperature, 33.5°). After chromatography (23 × 4.8 cm.) and elution as described above, the colorimetric ratio of unchanged all-*trans* form to the neo capsanthins was 65:35. No appreciable quantity of irreversibly formed pigments appeared on the column.

TABLE IV

TYPICAL SPECTROSCOPIC DATA FOR SOME MEMBERS OF THE STEREOISOMERIC CAPSANTHIN SET (in BENZENE)

Member	Diff. between the visually established longest wave length maxima of the member and the all-*trans* form (mμ)	Mol. extinction coeff. at the *cis*-peak $E^{mol.}_{1 cm.} \times 10^{-4}$	Diff. between mol. ext. coeff. of member and of all-*trans* form at *cis*-peak
Neo A	6	4.4	3.4
Neo B	6	2.65	1.60
Neo C	10.5	1.87	0.82
All-*trans*	0	1.05	0

In agreement with earlier data,[5] the visually observed maxima were 513, 481.5 mμ for the neocapsanthins A and B, and 508.5, 478.5 mμ for neo C, in benzene.

***cis–trans* Isomerization of Capsanthin by Melting.**—Five milligrams of pigment, in a sealed tube, filled with carbon dioxide, was melted in a bath of 180° (5° above the melting point) for one minute. The color intensity decreased by about one-third. After cooling in ice-water, the benzene solution of the melt was chromatographed on calcium carbonate as described. The colorimetric ratio of unchanged all-*trans* pigment to the neocapsanthins was 29:71. The neo fraction contained some uninvestigated new isomers; furthermore, a cherry-red zone (3% of the total recovered pigment) appeared below that of all-*trans*-capsanthin. The chromatographic filtrate was slightly colored.

Summary

The interaction of the carbonyl group of capsanthin, $C_{40}H_{58}O_3$, with a polar solvent such as ethanol can be demonstrated by extinction curves. In contrast to the behavior in hexane, no fine structure of the fundamental band is observed in alcoholic solution. As little as 2% alcohol in hexane causes the greater part of the change from the 0% alcohol curve to the 100% alcohol curve. The modification of the extinction curve upon stereoisomerization is similar to that observed with carotenoid hydrocarbons and alcohols. Upon iodine catalysis a marked *cis*-peak develops at 363 mμ (in benzene) for which process light is needed. It is probable on the basis of spectroscopic data that neocapsanthin A contains one *cis* bond which is located at the center of the chromophore. This isomer should be assigned the configuration of 6-mono-*cis*-capsanthin. Neocapsanthin B is probably either 5-mono-*cis*- or 7-mono-*cis*-capsanthin. Neocapsanthin C is a di-*cis*-compound.

PASADENA, CALIFORNIA RECEIVED SEPTEMBER 20, 1943

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF COLUMBIA UNIVERSITY]

Amidino Arsenicals. II. Some Trivalent Arsenicals

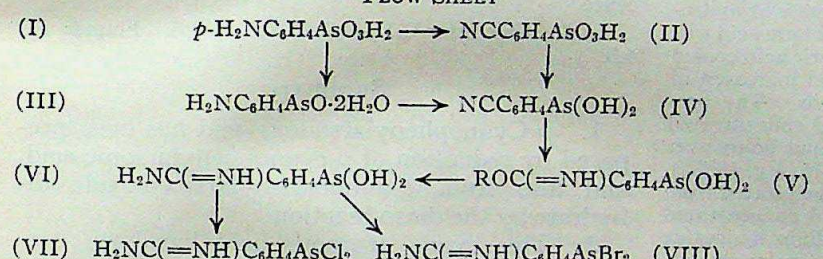
BY FRED LINSKER[1] AND MARSTON TAYLOR BOGERT

In a previous paper,[2] we have described the preparation and some of the properties of *p*-amidinophenylarsonic acid, 4,4′-diamidinoarsenobenzene, and a few intermediate or incidental compounds. The present communication records further progress in the study of the trivalent amidino arsenicals.

Mapharsen and Phenarsine are good examples of the generally recognized greater therapeutic efficiency of the trivalent as compared with the pentavalent arsenicals, the reasons for which need not be discussed here.

The Flow Sheet exhibits the various steps involved in this study.

FLOW SHEET



Acknowledgments.—This investigation, like its predecessor, was made possible by the generous action of Merck & Co., Inc., of Rahway, N. J., in establishing at Columbia University a research fellowship for the purpose of finding better medicaments for the treatment of various tropical diseases. The necessary microanalyses were carried out by Miss Frances E. Marx and Miss Lois E. May, of the Columbia University Department of Chemistry.

Experimental

p-Cyanophenylarsonous Acid (IV) (a) By Reduction of *p*-Cyanophenylarsonic Acid (II).—To a solution of 14 g. of *p*-cyanophenylarsonic acid[2] in 220 cc. of water and 32 cc. of 2 *N* sodium hydroxide, there was added 3.2 g. of potassium iodide. The clear solution was acidified with 84 cc. of dilute (16% by volume) sulfuric acid, cooled to below 10°, and sulfur dioxide passed through the solution for three hours at the rate of 3 bubbles per second, while the temperature was not permitted to rise above 10°. A yellow precipitate soon began to separate, and gradually increased in amount. When the reduction was complete, the flask was removed, stoppered tightly and left in the refrigerator overnight. The yellow-brown crystalline precipitate was filtered out, and consisted of 11 g. (85% yield) of quite pure *p*-cyanophenylarsonous acid. It was further purified by solution in *N* sodium hydroxide and reprecipitation with 5 *N* ammonium chloride solution, washing the precipitate with water until it gave no test for chlorine ion, and then drying in a desiccator over calcium chloride. It formed pale yellow-brown small prisms, which softened at 230° and melted with decomposition at 234° (cor.).

Anal. Calcd. for $C_7H_6O_2AsN$: As, 35.5; N, 6.6. Found: As, 35.3; N, 6.6.

This process is preferable to the succeeding one in that it gives a purer product.

(b) From *p*-Aminophenylarsine Oxide Dihydrate (III).—The arsine oxide dihydrate was prepared from *p*-arsanilic acid by reduction with sulfur dioxide, as described by Ehrlich and Bertheim[3]; yield, 71%; melts with decomposition at 98° (literature, yield, about 71%; m. p. with decomposition, 100°).

A solution of 11 g. of the arsine oxide dihydrate (III) in 120 cc. of water and 13 cc. of hydrochloric acid (sp. gr. 1.12) was cooled to 5° and diazotized with 17 cc. of a 3 *N* sodium nitrite solution. During the diazotization a pale yellow precipitate formed but was not removed. The diazotized mixture was poured slowly into a cuprous cyanide solution prepared from 12.5 g. of copper sulfate pentahydrate, 14 g. of potassium cyanide, and 75 cc. of water. The mixture was warmed until the evolution of nitrogen ceased. After cooling for three hours in the refrigerator, the brown solid which had precipitated was removed, washed with dilute hydrochloric acid and dried; yield, 13 g. Since this crude product was contaminated by considerable copper, it was dissolved in 170 cc. of *N* sodium hydroxide solution, filtered, and the product reprecipitated from the red filtrate by the addition of 45 cc. of 5 *N* ammonium chloride solution; yield, 9 g. (80%) of pale yellow-brown copper-free *p*-cyanophenylarsonous acid (IV); m. p. 230–240° with decomposition; soluble in caustic or carbonated alkali solutions, or in hot alcohol; insoluble in water, cold alcohol, ether, acetone, or ammonium hydroxide solution. It evolved ammonia when heated with caustic alkalies. The product was identical in all respects with that obtained by the reduction of *p*-cyanophenylarsonic acid.

p-Arsonosobenziminoether Hydrochloride (V).—The base of this compound appears in a list of amide-substituted phenylarsine oxides and their derivatives recently published by Eagle, Hogan, Doak and Steinman [as a note in THIS JOURNAL, 65, 1236 (1943)] where its analysis is given, as well as its toxicity and treponemicidal activity, and where it is stated that "Experimental details for the preparation of this compound will be published in a separate paper."

As these details have not yet appeared, so far as we are aware, the details of our own experiments were as follows.

To a suspension of 7 g. of dry finely pulverized *p*-cyanophenylarsonous acid (IV) in 40 cc. of dry ether, there was added 3 cc. of absolute alcohol, the mixture was cooled to 0° and dry hydrogen chloride passed through it for thirty minutes. The cyano acid dissolved and the solution assumed a dark red color. The flask was stoppered tightly and placed in the refrigerator. After several hours, crystallization of the imino ether hydrochloride began, and was complete in five days. The grayish crystals were removed, washed with dry ether and excess of hydrogen chloride eliminated in a vacuum desiccator over solid potassium hydroxide. Dissolved in a little cold absolute alcohol and precipitated by dry ether, the hydrochloride separated in colorless prisms; yield, 9.3 g. (95%). This hydrochloride softened at 150° and melted at 152°, with decomposition and foaming, to a dark liquid. It was easily soluble in water or alcohol, insoluble in ether or acetone. Its aqueous solution precipitated silver chloride from a silver nitrate solution, and liberated ammonia when heated with caustic alkali.

(1) Merck Research Fellow at Columbia University, New York.

(2) Linsker and Bogert, THIS JOURNAL, 65, 932 (1943).

(3) Ehrlich and Bertheim, *Ber.*, 43, 917 (1910).

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Anal. Calcd. for $C_9H_{13}O_3AsClN$: N, 4.7. Found: N, 4.7.

p-Amidinophenylarsonous Acid Hydrochloride (VI).—Six grams of finely pulverized iminoether hydrochloride (V) was suspended in 60 cc. of a 10% solution of dry ammonia in absolute alcohol. The suspension was warmed in a closed vessel for four hours at 60°, with frequent shaking. The mixture was filtered, and to the filtrate there was added five times its volume of absolute ether. This threw down the amidine hydrochloride as a white voluminous precipitate, which was filtered out rapidly, to avoid prolonged contact with moist air, and placed immediately in a vacuum desiccator over calcium chloride; yield, 4 g., or 80%. It crystallized in colorless needles when its absolute alcohol solution was concentrated. When heated to 210°, it decomposed with foaming. It was very hygroscopic, soluble in water or alcohol, insoluble in ether or acetone. The sample used for analysis was dried at 60° and 20 mm.

Anal. Calcd. for $C_7H_{10}O_2AsClN_2$: As, 28.3; N, 10.6. Found: As, 28.1; N, 10.7.

Due to its great solubility in water, this acid could not be prepared satisfactorily by the reduction of *p*-amidinophenylarsonic acid with sulfur dioxide.

p-Amidinophenyldichloroarsine Hydrochloride (VII).—A solution of 4 g. of *p*-amidinophenylarsonous acid hydrochloride (VI) in 12 cc. of ice-cold 2 *N* hydrochloric acid was filtered into 30 cc. of concentrated hydrochloric acid cooled to 0°. A crystalline precipitate formed and increased in amount on standing overnight in the icebox. The precipitate was collected, washed with ice-cold concentrated hydrochloric acid, and then left for twenty-four hours over solid sodium hydroxide in a desiccator; yield, 4 g. (89%). For further purification, the product was precipitated from its concentrated aqueous solution with cold concentrated hydrochloric acid, and dried over solid sodium hydroxide at 80° and 20 mm. It was easily soluble in water or alcohol, crystallizing from the latter in small colorless prisms. When heated, it sintered at 202°, and melted at 208° with decomposition.

Anal. Calcd. for $C_7H_8AsCl_3N_2$: N, 9.3. Found: N, 9.2.

p-Amidinophenyldibromoarsine Hydrobromide (VIII).—Two g. of *p*-amidinophenylarsonous acid hydrochloride (VI) was dissolved in 4 cc. of dilute cold hydrobromic acid (2 cc. of concentrated hydrobromic acid to 30 cc. of water). The filtered solution was added to 8 cc. of ice-cold concentrated hydrobromic acid. After the mixture had been standing for several hours at 0°, the pale yellow precipitate was collected and purified by a series of precipitations of its aqueous solution by concentrated hydrobromic acid. The pure salt formed starry clusters of elongated prisms, melting with decomposition at 219°; soluble in water, alcohol, or dilute mineral acids; yield, nearly that calculated. The sample for analysis was dried over solid sodium hydroxide at 80° and 20 mm., in an Abderhalden pistol.

Anal. Calcd. for $C_7H_8AsBr_3N_2$: N, 6.4. Found: N, 6.4.

The compound was soluble in water, alcohol, or dilute mineral acids, and was hygroscopic.

p-Arsonobenziminoether Hydrochloride, $R\acute{O}C(=NH)\text{-}C_6H_4AsO_3H_2$.—In our previous article,[2] the formation of this compound from *p*-cyanophenylarsonic acid was described, but the crude product was converted immediately into the corresponding amidino compound.

We have since purified this crude product by drying it *in vacuo* over solid caustic soda, and crystallizing it by concentration of its alcoholic solution. It formed colorless prisms which decomposed at 130° with strong effervescence.

Anal. Calcd. for $C_9H_{13}O_4AsClN$: N, 4.5. Found: N, 4.3.

Summary

1. *p*-Cyanophenylarsonous acid has been prepared by reduction of *p*-cyanophenylarsonic acid, and also from *p*-aminophenylarsine oxide dihydrate by the diazo reaction.

2. This cyano arsonous acid has been converted, through its imino ether, into the *p*-amidinophenylarsonous acid and, from the latter, the *p*-amidinophenyldihalo arsines have been prepared.

3. Certain of these new products are now being tested pharmacologically.

NEW YORK, N. Y. RECEIVED OCTOBER 15, 1943

[CONTRIBUTION FROM VENEREAL DISEASE RESEARCH AND POSTGRADUATE TRAINING CENTER, UNITED STATES PUBLIC HEALTH SERVICE, JOHNS HOPKINS HOSPITAL]

p-Arsenosobenzoylurea and Related Compounds[1]

BY H. G. STEINMAN, G. O. DOAK AND HARRY EAGLE

In previous papers of this series[2] we have described various amide-substituted aromatic arsenoso compounds.[3] Because of the interesting effect of the amide group in modifying the pharmacologic properties of arsenoso compounds we have extended the study to include compounds in which two or more amide groups were connected on a single side chain.

Two methods were used for the preparation of these compounds: namely, (1) the customary Bart reaction or the Scheller modification[4] with the corresponding amines and (2) the coupling of the appropriate dichloroarsinoacyl chlorides with the desired aliphatic amino acids or directly with the amino acid amides when available. All nitro compounds were reduced catalytically to the corresponding amines by the method of Stevinson and Hamilton.[5]

Experimental Part

p-Arsenosobenzoylurea.—*p*-Aminobenzoylurea[6] yielded *p*-arsonobenzoylurea with the customary Bart reaction. *p*-Arsenosobenzoylurea was obtained on reduction with

(1) Paper VI in the Series Entitled "The Preparation of Phenylarsenoxides."

(2) Doak, Steinman and Eagle, THIS JOURNAL, **62**, 3012 (1940); **63**, 99 (1941).

(3) In this and succeeding papers from this Laboratory, wherever practicable, new arsenicals will be named according to the system of nomenclature used in *Chemical Abstracts*.

(4) Scheller, French Patent 624,028, *Chem. Zentr.*, **93**, II, 2229 (1927); Doak, THIS JOURNAL, **62**, 167 (1940).

(5) Stevinson and Hamilton, *ibid.*, **57**, 1298 (1935).

(6) Jacobs and Heidelberger, *ibid.*, **39**, 2418 (1917).

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sulfur dioxide in the usual manner. Attempts to prepare the arsenoso compound directly by treating *p*-dichloroarsinobenzoyl chloride with either (a) urea in pyridine, (b) sodium urea in benzene, or (c) silver cyanate in benzene followed by ammonia, proved unsuccessful.

The action of sodium urethan upon *p*-dichloroarsinobenzoyl chloride in benzene or in pyridine gave products of indefinite composition. In ether a white solid which analyzed for the ethyl ester of bis-(*p*-arsenosobenzoyl)-carbamic acid was obtained.

Anal. Calcd. for $C_{17}H_{13}As_2NO_6$: As, 31.4; N, 2.94. Found: As, 31.2; N, 2.85.

p-Nitrobenzoyl Isocyanate.—This substance was prepared in 63% yield by refluxing *p*-nitrobenzoyl chloride with silver cyanate in benzene for seventy-two hours.[7] It was recrystallized from ethyl acetate under anhydrous conditions in rectangular prisms, m. p. 209–210°.

Anal. Calcd. for $C_8H_4N_2O_4$: N, 14.6. Found: N, 14.7.

1-(*p*-Arsenosobenzoyl)-3-(2-hydroxyethyl)-urea.—*p*-Nitrobenzoyl isocyanate condensed with 2-aminoethanol in benzene to give 1-(*p*-nitrobenzoyl)-3-(2-hydroxyethyl)-urea in 30% yield. On recrystallization from water needles melting at 186–187° were obtained.

Anal. Calcd. for $C_{10}H_{11}N_3O_5$: N, 16.6. Found: N, 16.3.

Catalytic reduction gave 1-(*p*-aminobenzoyl)-3-(2-hydroxyethyl)-urea in 70% yield. It crystallized from water in long colorless needles, m. p. 230.5–231.5°.[8]

Anal. Calcd. for $C_{10}H_{13}N_3O_3$: N, 18.8. Found: N, 18.7.

The amine derivative underwent the Bart reaction to give 1-(*p*-arsonobenzoyl)-3-(2-hydroxyethyl)-urea, from which the arsenoso compound was obtained on reduction with sulfur dioxide. An attempt to prepare this compound by heating *p*-arsonobenzoyl chloride[9] with silver cyanate and then treating the reaction mixture with 2-aminoethanol was unsuccessful.

Attempted Preparation of 1-(*p*-Arsenosobenzoyl)-3-(2,3-dihydroxypropyl)-urea.—3-Amino-1,2-propanediol was condensed with *p*-nitrobenzoyl isocyanate to give 1-(*p*-nitrobenzoyl)-3-(2,3-dihydroxypropyl)-urea. It was recrystallized first from alcohol and finally from water, m. p. 197–199°; yield 22%.

Anal. Calcd. for $C_{11}H_{13}N_3O_6$: N, 14.8. Found: N, 15.1.

In contrast to the behavior of the lower homolog, the nitro compound gave only *p*-aminobenzamide when reduced with Raney nickel and hydrogen.

1-(*p*-Arsenosobenzoyl)-biuret.—On refluxing *p*-nitrobenzoyl isocyanate with urea in benzene for twenty-four hours 1-(*p*-nitrobenzoyl)-biuret was obtained as a powder melting at 203–205°; yield 50%.

Anal. Calcd. for $C_9H_8N_4O_5$: N, 22.2. Found: N, 21.8.

Reduction in alcoholic suspension with Raney nickel gave 1-(*p*-aminobenzoyl)-biuret in 90% yield. It crystallized from alcohol in fine needles sintering about 270°.

Anal. Calcd. for $C_9H_{10}N_4O_3$: N, 25.2. Found: N, 24.4.

The Bart reaction with this amine yielded the desired 1-(*p*-arsonobenzoyl)-biuret which was readily reduced to the arsenoso derivative.

p-Arsenoso-α-toluylurea.—Urea was refluxed in benzene for eighteen hours with *p*-dichloroarsino-α-toluyl chloride. The resulting product upon hydrolysis yielded *p*-arsenoso-α-toluylurea. The Bart reaction with *p*-amino-α-toluylurea[6] did not yield any arsonic acid. An attempt to prepare the arsenoxide directly by coupling sodium urea with the methyl ester of *p*-arsenoso-α-toluic acid also failed.

N^{α}-(*p*-Arsenosophenyl)-glycylurea.—This compound was obtained from N^{α}-(*p*-arsonophenyl)-glycylurea[10] by reduction with sulfur dioxide.

α-(*p*-Arsonobenzamido)-acetamide.—*p*-Nitrobenzoyl chloride combined readily with glycinamide hydrochloride[11] in sodium bicarbonate solution to give α-(*p*-nitrobenzamido)-acetamide. It crystallized from alcohol in needles, m. p. 239–240° with decomposition.

Anal. Calcd. for $C_9H_9N_3O_4$: N, 18.8. Found: N, 18.5.

Reduction in alcoholic suspension with Raney nickel gave α-(*p*-aminobenzamido)-acetamide in 75% yield. It crystallized from alcohol in rectangular prisms, m. p. 228° with decomposition.

Anal. Calcd. for $C_9H_{11}N_3O_2$: N, 21.8. Found: N, 21.8.

The compound was best isolated as the sulfate by adding alcoholic sulfuric acid to the original alcohol solution of the amine. It separated in platelets charring above 250°.

Anal. Calcd. for $C_{18}H_{22}N_6O_4 \cdot H_2SO_4$: N, 17.4. Found: N, 17.5.

This salt yielded the desired arsonic acid with the Bart reaction.

α-(*p*-Arsenosobenzamido)-acetamide.—Although this arsenoxide could be produced by the reduction of α-(*p*-arsonobenzamido)-acetamide or by the direct ammonolysis of the methyl ester of *p*-arsenosohippuric acid,[12] it was more conveniently obtained by the direct condensation of *p*-dichloroarsinobenzoyl chloride (0.1 mole) with glycinamide hydrochloride (0.15 mole) in 10% sodium carbonate solution (500 cc.).

α-[α-(*p*-Arsenosobenzamido)-acetamido]-acetamide.—N-Glycylglycine coupled readily with *p*-dichloroarsinobenzoyl chloride in 1 *N* potassium hydroxide solution to give N-(*p*-arsenosohippuryl)-glycine. The methyl ester could not be prepared by esterification with methyl alcohol in the presence of anhydrous hydrogen chloride. It was prepared successfully, however, through the silver salt.

Anal. Calcd. for $C_{11}H_{10}AgAsN_2O_5 \cdot H_2O$: As, 16.6; N, 6.21. Found: As, 16.7; N, 6.17.

The desired amide was obtained on treating this ester with aqueous ammonia at −25° for several days and then allowing the ammoniacal solution to evaporate slowly.

β-(*p*-Arsenosobenzamido)-propionamide.—β-Alaninamide was prepared by the Raney nickel reduction of α-cyanoacetamide in absolute alcohol. The hydrochloride was isolated by acidifying the reaction mixture to *p*H 7.7 with alcoholic hydrogen chloride and cooling overnight at −25°. On recrystallization from methanol it was obtained in 70% yield, m. p. 149°.[13] When condensed with *p*-dichloroarsinobenzoyl chloride in the usual manner (sodium carbonate solution) the desired β-(*p*-arsenosobenzamido)-propionamide was formed.

α-Amino-N^{α}-(*p*-arsenoso-α-toluyl)-acetamide.—*p*-Dichloroarsino-α-toluyl chloride was added to glycinamide hydrochloride in sodium carbonate solution and the reaction mixture concentrated at 40° on the water pump to one-third the original volume. On standing overnight at 5° the desired amide precipitated out.

α-(*p*-Arsenosophenylsulfonamido)-acetamide.—Similarly, *p*-arsenosobenzenesulfonyl chloride prepared by the partial hydrolysis of *p*-dichloroarsinobenzenesulfonyl chloride yielded α-(*p*-arsenosophenylsulfonamido)-acetamide on coupling with glycinamide hydrochloride as above.

(7) *Cf.* Billeter, *Ber.*, **36**, 3218 (1903).

(8) Charlton and Day [*J. Org. Chem.*, **1**, 552 (1937)] prepared the isomeric β-*p*-nitrobenzoxyethylurea which melted at 183–183.4° (cor.). That this compound is different from the urea derivative reported here is shown by the fact that the amino derivative which Charlton and Day obtained melted at 203° (cor.).

(9) *p*-Dichloroarsinobenzoyl chloride in carbon tetrachloride was oxidized with chlorine to *p*-tetrachloroarsinobenzoyl chloride. This was converted to *p*-arsonobenzoyl chloride on partial hydrolysis with cold water. *Anal.* Calcd. for $C_7H_4AsClO_4$: As, 28.3; Cl, 13.4. Found: As, 28.4; Cl, 13.6.

(10) Jacobs and Heidelberger, THIS JOURNAL, **41**, 1600 (1919).

(11) Bergell and Wülfing, *Z. physiol. Chem.*, **64**, 348 (1910).

(12) Cohen, King and Strangeways, *J. Chem. Soc.*, 3236 (1931).

(13) *Cf.* Franchimont and Friedmann, *Rec. trav. chim.*, **25**, 75 (1906).

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Table I

Arsonic Acids and Arsenoso Compounds Derived from Benzoylurea and Related Compounds

Compound	Description	M. p., °C.	Yield, %	Formula	As analyses, % Calcd.	As analyses, % Found	N analyses, % Calcd.	N analyses, % Found
R = Arsono								
p-R-benzoylurea	Amorphous (W)	326.5	17	$C_8H_9AsN_2O_5$	26.0	25.6	9.73	9.78
1-(*p*-R-benzoyl)-3-(2-hydroxyethyl)-urea	Rectangular plates (W)	238–238.5 w. dec.	50	$C_{10}H_{13}AsN_2O_6$	22.6	22.5	8.44	8.50
1-(*p*-R-benzoyl)-biur t	Rectangular plates (W)	> 360	17	$C_9H_{10}AsN_3O_6$	22.6	22.7	12.7	12.9
α-(*p*-R-benzamido)-acetamide	Platelets (W)	211–213 w. dec.	5	$C_9H_{11}AsN_2O_5$	24.8	24.7	9.28	9.26
R = Arsenoso								
p-R-benzoylurea	Amorphous	270–271	75	$C_8H_7AsN_2O_3\cdot H_2O$	27.5	28.0	10.3	10.4
1-(*p*-R-benzoyl)-3-(2-hydroxyethyl)-urea	Amorphous	...	67	$C_{10}H_{11}AsN_2O_4$	25.1	25.2	9.40	9.15
1-(*p*-R-benzoyl)-biuret	Needles (W)	> 360	84	$C_9H_8AsN_3O_4\cdot 3H_2O$	21.3	21.5	12.0	12.0
p-R-α-toluylurea	Shiny plates (W)	Chars > 272	45	$C_9H_9AsN_2O_3$	28.0	27.5	10.5	9.86
N^{α}-(*p*-R-phenyl)-glycylurea	Amorphous	166–168 w. dec.	75	$C_9H_{10}AsN_3O_3\cdot 2H_2O$	23.5	23.5	13.2	13.6
α-(*p*-R-benzamido)-acetamide	Rectangular prisms (W)	Chars > 285	65	$C_9H_9AsN_2O_3$	28.0	28.1	10.5	10.5
N-(*p*-R-hippuryl)-glycine	Amorphous	Dec. > 220	75	$C_{11}H_{11}AsN_2O_5\cdot H_2O$	21.8	21.3	8.14	7.92
N-(*p*-R-hippuryl)-glycine, methyl ester	Amorphous	Chars > 240	30	$C_{12}H_{13}AsN_2O_5\cdot H_2O$	20.9	20.8	7.83	7.80
α-[α-(*p*-R-benzamido)-acetamido]-acetamide	Rectangular prisms (W)	Chars > 240	50	$C_{11}H_{12}AsN_3O_4\cdot H_2O$	21.8	21.9	12.3	12.0
β-(*p*-R-benzamido)-propionamide	Needles (W)	283–285 w. dec.	50	$C_{10}H_{11}AsN_2O_3$	26.6	26.6	9.94	9.94
α-Amino-N^{α}-(*p*-R-α-toluyl)-acetamide	Needles (W)	133 w. dec.	50	$C_{10}H_{11}AsN_2O_3\cdot 2H_2O$	23.6	23.5	8.81	8.40
α-(*p*-R-phenylsulfonamido)-acetamide	Amorphous	193–195 w. dec.	55	$C_8H_9AsN_2O_4S$	24.6	24.4	9.22	8.89

Attempted Preparation of Sulfur Ureas.—In contrast to the behavior of urea, sulfamide[14] did not condense with *p*-nitrobenzoyl chloride when refluxed in benzene for forty-eight hours or in ethyl acetate for twenty-four hours. Potassium sulfamide[15] also failed to condense with either *p*-nitrobenzoyl chloride or *p*-nitrobenzenesulfonyl chloride when refluxed in benzene for forty-eight hours.

The table lists the arsonic acids and arsenoso compounds which were prepared. Recrystallization was done from water (W). Melting points below 200° were taken in a double-walled sulfuric acid bath using Anschütz thermometers with a Bureau of Standards report; no stem correction was made. Melting points above 200° were made in a copper block with a thermometer standardized against the same set of Anschütz thermometers. All analytical results were the average of two or more determinations.

Acknowledgment.—The authors wish to acknowledge the assistance given by Leon D. Freedman throughout the course of the work.

Summary

A number of arsonic acids and arsenoso compounds containing two or more amide groups on a single side chain have been prepared.

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(14) Kindly supplied through the courtesy of Doctor E. F. Degering, Purdue University.

(15) Franklin and Stafford, *Am. Chem. J.*, **28**, 83 (1902).

[Contribution from the Venereal Disease Research and Postgraduate Training Center, United States Public Health Service, Johns Hopkins Hospital]

Arsenoso Compounds Containing Amide Groups[1]

By G. O. Doak, H. G. Steinman and Harry Eagle

Among the various types of aromatic arsenoso compounds which have been described in previous publications from this Laboratory, those containing amide groups have been of particular interest from the pharmacological viewpoint. The present paper gives the results of further research on this class of compounds.

For the oxidation of tolylarsonic acids and the esterification of the resulting arsonobenzoic acids the methods of Cohen, King and Strangeways[2] were used. The catalytic method of Stevinson and Hamilton[3] was used for the reduction of nitrobenzenearsonic acids to the corresponding amino compounds. Cyanobenzenearsonic acids were prepared and isolated by the method previously described,[4] except that cuprous cyanide was substituted for nickel cyanide. In contrast to the findings of Korczynski and Fandrich[5] with non-arsenated aromatic amines the use of cuprous cyanide gave a larger yield in this particular reaction. The Scheller–Bart reaction[6] was used for the preparation of **4-nitro-, and 5-nitro-*o*-toluenearsonic acids.** While the yields were larger by this procedure as compared to the

(1) Paper VII in the Series Entitled "The Preparation of Phenylarsenoxides."

(2) Cohen, King and Strangeways, *J. Chem. Soc.*, 3236 (1931).

(3) Stevinson and Hamilton, This Journal, **57**, 1298 (1935).

(4) Doak, Eagle and Steinman, *ibid.*, **62**, 3010 (1940).

(5) Korczynski and Fandrich, *Compt. rend.*, **183**, 421 (1926).

(6) Scheller, French Patent 624,028, *Chem. Zentr.*, **98**, II, 2229 (1927); Doak, This Journal, **62**, 167 (1940).

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customary Bart reaction,[7] considerable difficulty was experienced in removing inorganic arsenic. Contrary to the statement of Maschmann[7c] the preparation of 2-arsono-4-nitrobenzoic acid by the oxidation of 2-methyl-5-nitrobenzenearsonic acid did not proceed smoothly and repeated recrystallizations were necessary in order to obtain an analytically pure sample. For the preparation of 2-arsono-5-nitrobenzoic acid the method of Karrer[8] was found preferable to the oxidation of 2-methyl-4-nitrobenzenearsonic acid.

N-Substituted arsenosobenzamides were prepared by the condensation of dichloroarsinobenzoyl chlorides with the appropriate amine as described for the preparation of *p*-arsenoso-N-(2,3-dihydroxypropyl)-benzamide.

Experimental Part

5-Arsenosoisophthalamide.—The Bart reaction applied to 3,5-xylidine gave **3,5-xylenearsonic acid** which was then oxidized with potassium permanganate. An **acid potassium salt of 5-arsonoisophthalic acid,** with the composition $H_2O_3AsC_6H_3(COOH)_2 \cdot KHO_3AsC_6H_3(COOH)_2$, crystallized from solutions strongly acid to congo red. This acid salt, suspended in chloroform, was treated with phosphorus tri- and pentachloride and the reaction mixture added to cold aqueous ammonia. Instead of the expected amide we obtained **5-arsenosoisophthalic acid.** This compound was esterified to **5-arsenosoisophthalic acid, dimethyl ester,** which gave the desired compound when heated with ammonia in a sealed tube at 100° for six hours.

6-Arsenosoisophthalamic Acid.—2-Arsono-5-nitrobenzoic acid[8] on reduction gave **5-amino-2-arsonobenzoic acid.** The Sandmeyer reaction applied to this compound gave **2-arsono-5-cyanobenzoic acid** in impure form. We were unable to obtain an analytically pure sample by repeated recrystallization from either water or alcohol. Oxidation of the slightly impure nitrile with 30% hydrogen peroxide gave **6-arsonoisophthalamic acid.** Reduction gave the desired arsenoso compound.

6-Arsenosoterephthalamic Acid.—2-Arsono-4-nitrobenzoic acid was reduced catalytically to 4-amino-2-arsonobenzoic acid.[7c] By a series of reactions similar to those described above we obtained **2-arsono-4-cyanobenzoic acid, 2-arsonoterephthalamic acid** and finally the desired arsenoso compound.

2-Amino-4-arsenosobenzamide.—This compound has been previously described[9] but the following procedures offer some improvement. The acid potassium salt of 2-nitro-4-arsonobenzoic acid,[2] suspended in chloroform, was treated with phosphorus tri- and pentachlorides. The solvent was removed *in vacuo* and the residue added to cold aqueous ammonia. The resulting **4-arsenoso-2-nitrobenzamide** was oxidized to **4-carbamyl-3-nitrobenzenearsonic acid** with 30% hydrogen peroxide. Catalytic reduction gave 4-carbamyl-*m*-arsanilic acid which was reduced to the arsenoso compound with sulfur dioxide.

The compound was more satisfactorily prepared from the methyl ester of 4-arsenosoanthranilic acid[2] by heating in a sealed tube with aqueous ammonia for sixty hours at 90°.

2-Acetamido-4-arsenosobenzamide.—While this compound was prepared readily by acetylation of 2-amino-4-arsenosobenzamide, we were unable to prepare it by reduction of the corresponding arsonic acid. We were also unable to convert 2-acetamido-4-arsonobenzoic acid to the amide by treatment with phosphorus tri- and pentachlorides, and adding the mixture to ammonia.

4-Arsenososalicylamide.—This compound was obtained by reduction of the corresponding arsonic acid.[2]

5-Arsenososalicylamide.—5-Arsonosalicylic acid[10] esterified with methanol gave **5-arsonosalicylic acid, methyl ester,** which possessed a faint but definite wintergreen odor. Ammonolysis at 100° in a sealed tube resulted in splitting arsenic from the ring. Ammonolysis at 0° for several days gave **3-carbamyl-4-hydroxybenzenearsonic acid.** Reduction of this arsonic acid gave the desired compound.

3-Amino-5-dichloroarsinosalicylamide Hydrochloride.—Esterification of 3-amino-5-arsonosalicylic acid[9] gave 3-amino-5-arsonosalicylic acid, methyl ester. This compound was not purified but added directly at 0° to aqueous ammonia, especially prepared from oxygen free water. After standing for three days the ammonia was removed in a stream of nitrogen and the solution acidified. **5-Carbamyl-4-hydroxy-*m*-arsanilic acid** precipitated.

Anal. Calcd. for $C_7H_9AsN_2O_5$: N, 10.2. Found: N, 10.2.

Reduction in hydrochloric acid solution gave the dichloroarsino hydrochloride compound, m. p. 177–178°.

Anal. Calcd. for $C_7H_7AsCl_2N_2O_2 \cdot HCl \cdot H_2O$: As, 21.3; N, 7.97. Found: As, 21.8; N, 8.07.

As this compound was unstable in alkaline solution the arsenoso compound was not prepared.

***p*-Arsenosobenzimido Ethyl Ether.**—*p*-Cyanobenzenearsonic acid was reduced with sulfur dioxide and hydriodic acid in 12 *N* sulfuric acid and the precipitate treated with sodium bicarbonate solution. The resulting ***p*-arsenosobenzonitrile** (2.5 g.) was suspended in 10 ml. of ether, 0.7 ml. of 95% alcohol added, and the mixture saturated with hydrogen chloride at 0°. After standing two days at 10°, the ***p*-dichloroarsinobenzimido ethyl ether hydrochloride** was filtered off and thoroughly washed with ether. The yield was 53%, m. p. 141°.

Anal. Calcd. for $C_9H_{10}AsCl_2NO \cdot HCl \cdot H_2O$: As, 21.5; N, 4.02. Found: As, 21.3; N, 4.06.

This was hydrolyzed with sodium bicarbonate solution to the arsenoso derivative.

***p*-Arsenoso-N-(2,3-dihydroxypropyl)-benzamide.**—*p*-Dichloroarsinobenzoyl chloride (8.6 g.) in 20 ml. of acetone was added dropwise and with cooling to a solution of 2.8 g. of 3-amino-1,2-propanediol in 100 ml. of 10% sodium carbonate solution. After standing overnight the precipitated arsenoso compound was filtered, washed, and finally recrystallized from 0.1% sodium bicarbonate solution.

***p,p'*-Diarsenoso-1,2-dibenzoylhydrazine.**—Hydrazine hydrate was added to an excess of *p*-dichloroarsinobenzoyl chloride in pyridine and benzene. The compound was purified by dissolving in sodium hydroxide solution and precipitating with acid.

***p*-Arsenoso-N-(2-acetamidoethyl)-benzamide.**—*p*-Dichloroarsinobenzoyl chloride was condensed with glycinonitrile sulfate in sodium carbonate solution and the resulting ***p*-arsenoso-N-(cyanomethyl)-benzamide** recrystallized from 0.1% sodium bicarbonate solution. Oxidation with iodine in sodium bicarbonate solution gave ***p*-(cyanomethyl)-carbamylbenzenearsonic acid.** Neither the arsonic acid nor the arsenoso compound could be reduced to the amine. No reduction occurred with the method of Carothers and Jones.[11] Reduction of the arsonic acid by Hartung's method[12] gave *p*-arsonohippuric acid. Reduction of the arsonic acid employing Raney nickel gave a mixture of amines. When *p*-dichloroarsinobenzoyl chloride was coupled with an excess of ethylenediamine in sodium carbonate solution only ***p,p'*-diarsenoso-N,N'-dibenzoylethylenediamine** was obtained. The desired compound was finally prepared by coupling the acid chloride with N-(2-aminoethyl)-acetamide.[13] The crude material was recrystallized twice from acetic acid and finally from water.

(7) (a) Jacobs, Heidelberger and Rolf, THIS JOURNAL, **40**, 1580 (1918); (b) Karrer, *Ber.*, **48**, 311 (1915); (c) Maschmann, *ibid.*, **57**, 1759 (1924).

(8) Karrer, *ibid.*, **48**, 1058 (1915).

(9) Doak, Steinman and Eagle, THIS JOURNAL, **63**, 99 (1941).

(10) Newberry, Phillips and Stickings, *J. Chem. Soc.*, 3051 (1928).

(11) Carothers and Jones, THIS JOURNAL, **47**, 3051 (1925).

(12) Hartung, *ibid.*, **50**, 3370 (1928).

(13) Hill and Aspinall, *ibid.*, **61**, 822 (1939).

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TABLE I

ARSONIC ACIDS AND ARSENOSO COMPOUNDS CONTAINING AMIDE GROUPS

Compound	Description	M. p., °C.	Yield, %	Formula	As analyses, % Calcd.	As analyses, % Found	N analyses, % Calcd.	N analyses, % Found
Arsonic acids								
3,5-Xylenearsonic acid	Needles (W)	222–223	18	$C_8H_{11}AsO_3$	32.6	32.2	...	...
5-Arsonoisophthalic acid, potassium acid salt	Needles (W)	Chars > 300	75	$C_{16}H_{13}As_2KO_{14}$[a]	24.2	24.0	...	...
4-Nitro-*o*-toluenearsonic acid	Needles (W)	240	67[b]	$C_7H_8AsNO_5$	28.7	29.2	5.37	5.39
5-Amino-2-arsonobenzoic acid	Plates (W)	> 360	72	$C_7H_8AsNO_5$	28.7	28.9	5.37	5.36
2-Arsono-5-cyanobenzoic acid	Plates (W)	Dec. > 300	23	$C_8H_6AsNO_5$	27.6	26.0	5.16	5.57
6-Arsonoisophthalamic acid	Rectangular prisms (W)	347.5	57	$C_8H_8AsNO_6$	25.9	25.6	4.85	4.86
5-Nitro-*o*-toluenearsonic acid	Needles (W)	235–236	52[b]	$C_7H_8AsNO_6$	28.7	29.2	5.37	5.38
4-Amino-2-arsonobenzoic acid	Needles (W)	Dec. > 220	94	$C_7H_8AsNO_5 \cdot H_2O$[c]	26.9	26.4	5.02	5.10
2-Arsono-4-cyanobenzoic acid	Needles (W)	Dec. > 351	41	$C_8H_6AsNO_5$	27.6	28.0	5.16	5.18
2-Arsonoterephthalamic acid	Plates (W)	> 360	63	$C_8H_8AsNO_6$	25.9	26.0	4.85	4.95
5-Arsonosalicylic acid, methyl ester	Needles (M)	Softens 193	59	$C_8H_9AsO_6$	27.0	26.8	...	...
3-Carbamyl-4-hydroxybenzenearsonic acid	Needles (W)	Chars > 330	90	$C_7H_8AsNO_6$	28.7	28.6	5.37	5.70
4-Carbamyl-3-nitrobenzenearsonic acid	Rectangular prisms (W)	Chars > 270	60	$C_7H_7AsN_2O_6$	25.8	26.2	9.66	9.72
4-Carbamyl-*m*-arsanilic acid	Plates (W)	Dec. > 230	60	$C_7H_9AsN_2O_4$	28.8	28.5	10.8	10.4
p-[(Cyanomethyl)-carbamyl]-benzenearsonic acid	Rectangular prisms (W)	251–252 w. dec.	100	$C_9H_9AsN_2O_4$	26.4	26.7	9.87	9.91
N-*p*-toluylarsanilic acid	Needles (AA)	> 360	100	$C_{14}H_{14}AsNO_4$	22.3	22.4	4.18	4.32
p-Arsonoterephthalanilic acid	Rosets (AA)	> 360	5	$C_{14}H_{12}AsNO_6$	20.5	20.5	3.84	3.79
N,N′-Terephthaloyldiarsanilic acid	Amorphous	Chars > 250	25	$C_{20}H_{18}As_2N_2O_8$	26.6	26.8	4.96	4.81
N-(*p*-Cyanobenzoyl)-arsanilic acid	Amorphous	> 360	35	$C_{14}H_{11}AsN_2O_4$	21.6	21.7	8.10	8.13
N-(*p*-Carbamylbenzoyl)-arsanilic acid	Needles (W)	> 360	95	$C_{14}H_{13}AsN_2O_5$	20.6	20.6	7.70	7.63
p-(*p*-Nitrophenylthio)-benzenearsonic acid	Yellow needles (A)	291–292	39	$C_{12}H_{10}AsNO_5S$	21.1	21.5	3.95	3.92
p-(*p*-Aminophenylthio)-benzenearsonic acid	Needles (A)	Dec. > 190	67	$C_{12}H_{12}AsNO_3S$	23.1	23.2	4.31	4.00
p-(*p*-Cyanophenylthio)-benzenearsonic acid	Yellow needles (W)	Dec. > 200	32	$C_{13}H_{10}AsNO_3S$	22.4	21.9	4.18	4.25
p-(*p*-Carbamylphenylsulfonyl)-benzenearsonic acid	Needles (W)	310.5	28	$C_{13}H_{12}AsNO_6S$	19.4	19.7	3.64	3.62
R = Arsenoso								
5-R-isophthalic acid	Amorphous (W)	224–225	39	$C_8H_6AsO_5 \cdot 2H_2O$	25.7	25.7	...	...
5-R-isophthalic acid, dimethyl ester	Rectangular prisms (M)	255	86	$C_{10}H_9AsO_5$	26.4	26.6	...	...
5-R-isophthalamide	Glass (W)	Sinters at 75	81	$C_8H_7AsN_2O_3 \cdot H_2O$	27.5	27.7	10.3	9.60
6-R-isophthalamic acid	Hexagonal needles (W)	236.5–237.5	43	$C_8H_6AsNO_4 \cdot H_2O$	27.4	27.6	5.13	5.16
6-R-terephthalamic acid	Rectangular prisms (W)	221.5–222.5	67	$C_8H_6AsNO_4$	29.4	29.5	5.49	5.67
4-R-2-nitrobenzamide	Hexagonal prisms (W)	162–163 w. dec.	60	$C_7H_5AsN_2O_4$	29.3	28.8	10.9	10.9
2-Amino-4-R-benzamide	Hexagonal prisms (W)	177–178	40[d]	$C_7H_7AsN_2O_3 \cdot 1^1/_2H_2O$	29.6	29.6	11.1	10.9
2-Acetamido-4-R-benzamide	Amorphous	263–264 w. dec.	35	$C_9H_9AsN_2O_3 \cdot H_2O$	26.2	26.2	9.80	9.40
4-R-salicylamide	Cubes (A)	> 360	72	$C_7H_6AsNO_3 \cdot H_2O$	30.6	30.1	5.72	5.64
5-R-salicylamide	Needles (W)	222–223	72	$C_7H_6AsNO_3 \cdot {}^1/_2H_2O$	31.7	31.5	5.94	5.87
p-R-benzonitrile	Amorphous	195.5–197.5	52	C_7H_4AsNO	38.8	38.7	7.25	7.03
p-R-benzimido ethyl ether	Amorphous	184.5–185	65	$C_9H_{10}AsNO_2 \cdot H_2O$	29.2	29.8	5.45	5.61
p-R-N-(2,3-dihydroxypropyl)-benzamide	Amorphous (W)	Chars > 250	50	$C_{10}H_{12}AsNO_4$	26.3	26.6	4.92	4.56
p,*p*′-Di-R-1,2-dibenzoylhydrazine	Amorphous	> 360	60	$C_{14}H_{10}As_2N_2O_4 \cdot 2H_2O$	32.9	33.0	6.14	5.94[e]
p-R-N-(cyanomethyl)-benzamide	Amorphous (W)	Chars > 265	87	$C_9H_7AsN_2O_2$	30.0	30.0	11.2	11.1
p,*p*′-Di-R-N,N′-dibenzoylethylenediamine	Amorphous	Chars > 320	80	$C_{16}H_{14}As_2N_2O_4 \cdot 2H_2O$	31.0	31.5	5.79	5.62[e]
p-R-N-(2-acetamidoethyl)-benzamide	Amorphous (W)	270–272 w. dec.	85	$C_{11}H_{13}AsN_2O_3$	25.3	25.2	9.47	9.76
p′-R-*p*-carbamylbenzanilide	Amorphous	319	100	$C_{14}H_{11}AsN_2O_3$	22.7	22.7	8.50	8.07

[a] Calcd.: K, 6.31. Found: K, 6.06. [b] These yields are for the Scheller–Bart reaction. For the yields by the customary Bart reaction see ref. 7. [c] Maschmann reports the unhydrated acid; m. p. 120° with dec. The hydrated acid, reported here, was converted to the anhydride on heating. Calcd.: H_2O, 12.9. Loss at 100°, 13.3. [d] Yield by ammonolysis of the corresponding ester. [e] Nitrogen determinations by a micro Dumas procedure.

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α-Amino-p-dichloroarsinoacetanilide Hydrochloride.—Reduction of the corresponding arsonic acid[14] in hydrochloric acid gave this dichloroarsine. It could not be successfully hydrolyzed to the arsenoso derivative.

Anal. Calcd. for $C_8H_9AsCl_2N_2O \cdot HCl$: As, 22.6; N, 8.45. Found: As, 22.3; N, 8.45.

p'-Arsenoso-p-carbamylbenzanilide.—By means of the Schotten–Baumann reaction *p*-toluyl chloride was condensed with atoxyl to give **N-p-toluylarsanilic acid.** This compound was oxidized with potassium permanganate in neutral solution, in the presence of magnesium sulfate. From the reaction mixture terephthalic acid was isolated in quantitative yield. According to German Patent 191,548[15] terephthalyl chloride condenses with arsanilic acid to give *p*-arsonoterephthalanilic acid. In several experiments, using various experimental conditions, we obtained a mixture of this compound and N,N'-terephthaloyldiarsanilic acid. It was found that the two compounds could be separated by the differential solubilities of their magnesium salts, as described for the separation of a similar mixture in the biphenyl series,[16] but the yield was poor. The desired compound was finally obtained by the following synthesis. *p*-Cyanobenzoic acid (14.7 g.) and 7.9 g. of pyridine were dissolved in 1 liter of absolute ether and the mixture treated with 11.9 g. of thionyl chloride according to the directions of Carré and Libermann.[17] While the resulting *p*-cyanobenzoyl chloride could not be readily separated from pyridine hydrochloride, this was found unnecessary. After removing the solvent the residue was triturated with 43 g. of arsanilic acid and then warmed on the water-bath for one hour. An excess of 10% hydrochloric acid was added and the mixture stirred for one hour to dissolve any unchanged arsanilic acid. The resulting **N-(p-cyanobenzoyl)-arsanilic acid** was purified through its magnesium salt. Oxidation with 30% hydrogen peroxide gave **N-(p-carbamylbenzoyl)-arsanilic acid,** which was reduced to the desired arsenoso derivative.

p-(p-Carbamylphenylsulfonyl)-benzenearsonic Acid.—The Scheller–Bart reaction, applied to *p*-amino-*p'*-nitrodiphenyl sulfide,[18] gave **p-(p-nitrophenylthio)-benzenearsonic acid** which was reduced catalytically to **p-(p-aminophenylthio)-benzenearsonic acid.** The Sandmeyer reaction applied to this amine gave **p-(p-cyanophenylthio)-benzenearsonic acid.** This nitrile was then oxidized with an excess of 30% hydrogen peroxide in alkaline solution. **p-(p-Carbamylphenylsulfonyl)-benzenearsonic acid** precipitated when the alkaline solution was acidified. Unfortunately all attempts to reduce this compound to the corresponding arsenoso derivative resulted in partial hydrolysis of the amide group.

The table lists the arsonic acids and arsenoso compounds which are new compounds or are known compounds prepared by a new procedure. Under "description," the letters in parentheses refer to the solvent used for crystallizing: W = water, A = ethyl alcohol, M = methanol and AA = acetic acid. Melting points were taken by the procedure described in paper VI. All analytical results are the average of two or more determinations.

Acknowledgment.—The authors wish to acknowledge the assistance given by Leon D. Freedman throughout the course of the work.

Summary

A number of arsonic acids and arsenoso compounds containing amide groups have been prepared.

(14) Jacobs and Heidelberger, THIS JOURNAL, **41** 1809 (1919).
(15) German Patent 191,548; *Chem. Zentr.*, **79**, I, 779 (1908).
(16) Doak, Eagle and Steinman, THIS JOURNAL, **64**, 1064 (1942).
(17) Carré and Libermann, *Compt. rend.*, **199**, 1422 (1934).
(18) Raiziss, Clemence, Severac and Moetsch, THIS JOURNAL, **61**, 2763 (1939).

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[CONTRIBUTION FROM VENEREAL DISEASE RESEARCH AND POSTGRADUATE TRAINING CENTER, UNITED STATES PUBLIC HEALTH SERVICE, JOHNS HOPKINS HOSPITAL]

Arsonic Acids and Arsenoso Compounds Containing the Azo Linkage[1]

BY G. O. DOAK, H. G. STEINMAN AND HARRY EAGLE

The customary preparation of arsonic acids containing the azo linkage consists in the coupling of diazotized aminoarylarsonic acids with phenols and amines. We have also prepared such compounds by coupling diazo compounds with hydroxyarylarsonic acids and by the application of the Scheller–Bart reaction[2] to aminoazo compounds.

While it has been stated that *o*- and *m*-hydroxybenzenearsonic acids[3] and *m*-arsanilic acid[4] couple with diazo compounds, the only evidence for such a reaction was color formation. Benda[5] obtained only arsenic acid and the corresponding phenylazophenol from *p*-hydroxybenzenearsonic acid and diazo compounds. Lawrence and Hamilton,[6] however, have successfully coupled aminonaphthalenearsonic acids.

In this Laboratory it has been found that diazo compounds couple with *o*- and *m*-hydroxybenzenearsonic acids, the coupling occurring in *para* position to the hydroxy group. Where the para position is blocked, *e. g.*, *p*-hydroxybenzenearsonic acid, the arsonic acid group is partially replaced by the phenylazo group. In addition, however, some coupling occurs in *ortho* position to the hydroxy group. The resulting azoarsonic acid then reacts further with the diazo compound to give the *bis*-(phenylazo)-phenol. The extent to which each of these three reactions occurs depends not only upon the strength of the reactants as coupling agents but is also influenced by the *p*H of the reaction mixture. The results of a series of experiments are given in Table I.

Experimental Part

A. The Coupling of Diazo Compounds with Hydroxyarylarsonic Acids.—The following description illustrates the general procedure that was followed.

(1) Paper VIII in the Series Entitled "The Preparation of Phenylarsenoxides."
(2) Scheller, French Patent 624,028, *Chem. Zentr.*, **98**, II, 2229 (1927); Doak, THIS JOURNAL, **62**, 167 (1940).
(3) Jacobs and Heidelberger, *ibid.*, **41**, 1440 (1919).
(4) Bertheim, *Ber.*, **41**, 1655 (1908).
(5) Benda, *ibid.*, **44**, 3449 (1911).
(6) Personal communication from Dr. Hamilton.

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TABLE I

THE COUPLING OF DIAZO COMPOUNDS WITH HYDROXYARYLARSONIC ACIDS IN RELATION TO *p*H

Arsonic acid	Diazo compound from	*p*H	% Yield of products: Phenylazophenol	Phenylazoaryl-arsonic acid	*bis*-(Phenylazo) phenol
p-HOC_6H_4-	Aniline	5.8–6.6[a]	36.9	0.5	4.6
		7.3–7.4[b]	39.4	5.9	12.2
		8.5–9.5[c]	9.4	0	27.8
4-$HOC_{10}H_6$-1-	Aniline	7.1–7.4[b]	34.4	20.0	33.8
p-HOC_6H_4-	Sulfanilamide	5.4–6.5[a]	[e]	0	
		7.1–7.5[b]	[e]	0	
p-HOC_6H_4-	*m*-Toluidine	7.4–7.5[b]	No coupling		
m-HOC_6H_4-	Aniline	7.0–7.1[b]	0	95	0
		8.9–9.1[d]	0	98	0
o-HOC_6H_4-	Aniline	8.9–9.1[d]	0	88	0
2,4-$(HO)_2C_6H_3$-	Aniline	7.6–7.9[b]		84[f]	
		8.5–9.5[c]	[g]	5.6[f]	[g]

[a] Phosphate buffer. [b] Sodium bicarbonate buffer. [c] In sodium carbonate solution. [d] In sodium hydroxide solution. [e] Analysis indicated that a mixture of phenylazophenols was obtained, which could not be readily separated. [f] This compound was 3,5-*bis*-(phenylazo)-2,4-dihydroxybenzenearsonic acid, obtained with an excess of the diazo solution. We were unable to obtain a phenylazo-2,4-dihydroxybenzenearsonic acid free from the *bis* compound. [g] A mixture was obtained from which only 2,4-*bis*-(phenylazo)-resorcinol could be obtained in a pure state.

4-Hydroxy-3-phenylazobenzenearsonic Acid.—The diazo solution, prepared from 0.93 g. (0.01 mole) of aniline and 0.03 mole of hydrochloric acid was added slowly to a solution of sodium *p*-hydroxyphenylarsonate (2.94 g. of the trihydrate, 0.01 mole) and 2.52 g. of sodium bicarbonate in 50 ml. of water, maintaining the temperature at 10°. The initial and final *p*H values were 7.4 and 7.3 (glass electrode). The reaction mixture was stirred for one hour, filtered and the residue washed with 100 ml. of warm 10% sodium carbonate solution. The insoluble fraction (0.37 g.) was recrystallized from alcohol. Analysis and melting point (131°) identified this substance as 2,4-*bis*-(phenylazo)-phenol. The combined filtrate and washings were acidified to congo red and cooled in the icebox for twenty-four hours. The mixture was filtered, the precipitate washed with 10 ml. of cold water and dried. Arsenic acid was determined in the filtrate as magnesium pyroarsenate. The dry precipitate was extracted with ether and the ether insoluble fraction (0.174 g.) recrystallized several times from water. This substance was identical with the 4-hydroxy-3-phenylazobenzenearsonic acid later prepared by the Scheller–Bart reaction. The ether soluble fraction gave *p*-phenylazophenol (0.78 g.) and 2,4-*bis*-(phenylazo)-phenol (0.15 g.) on fractional crystallization from alcohol. In subsequent reactions it was found advantageous to partially neutralize the diazo solution before coupling.

4-Hydroxy-3-phenylazo-1-naphthalenearsonic Acid.—4-Hydroxy-1-naphthalenearsonic acid has been previously described.[7] The yield has been increased considerably by the following modification. 4-Amino-1-naphthyl benzoate hydrochloride was treated with ammonia to give the free base. It was also obtained by reducing 4-nitro-1-naphthyl benzoate in alcohol, employing Raney catalyst. **4-Amino-1-naphthyl benzoate** crystallized from aqueous alcohol in plates, m. p. 107.2–107.6°. The yield was 95% by either procedure.

Anal. Calcd. for $C_{17}H_{13}NO_2$: N, 5.32. Found: N, 5.40.

The Scheller–Bart reaction applied to this amine gave **4-arsono-1-naphthyl benzoate** in 19% yield. It crystallized from aqueous alcohol in plates; m. p. 199.8–200°.

Anal. Calcd. for $C_{17}H_{13}AsO_5$: As, 20.1. Found: As, 19.8.

4-Hydroxy-1-naphthalenearsonic acid was prepared from this ester by hydrolyzing in methanol solution with dry hydrogen chloride in the cold. The solution was diluted with water, the methyl benzoate extracted with ether and the arsonic acid recrystallized from water. The yield was 57%.

Anal. Calcd. for $C_{10}H_9AsO_4$: As, 28.0. Found: As, 28.0.

The above arsonic acid (9 g.) was coupled with benzenediazonium chloride at *p*H 7.1–7.4. After standing for two hours at 10° the mixture was acidified to congo red. The precipitate which formed was dried and extracted with benzene. The benzene insoluble fraction was then extracted with boiling 10% sodium bicarbonate solution. This solution when cooled deposited a small amount of solid which was added to the bicarbonate insoluble fraction. When the bicarbonate solution was acidified to congo red 4-hydroxy-3-phenylazo-1-naphthalenearsonic acid precipitated (2.51 g.). It was recrystallized from aqueous alcohol.

The benzene soluble fraction (4.0 g.), after recrystallizing first from benzene and finally from amyl alcohol, was identified as 2,4-*bis*-(phenylazo)-1-naphthol by analysis and melting point (190–191°). The bicarbonate insoluble fraction (2.87 g.), after recrystallizing several times from amyl alcohol was similarly identified as 4-phenylazo-1-naphthol, m. p. 206°.

3-Amino-4-hydroxy-1-naphthalenearsonic Acid.—The preceding azoarsonic acid was converted to the monosodium salt and reduced catalytically, employing Raney nickel. The solution was filtered directly into dilute hydrochloric acid and the arsonic acid which precipitated purified by the method of Christiansen.[8] It was obtained as white needles which colored rapidly in the air and slowly when preserved in an atmosphere of hydrogen. It decomposed on heating. The yield was 52%.

Anal. Calcd. for $C_{10}H_{10}AsNO_4 \cdot H_2O$: As, 24.9. Found: As, 24.4.

3-Hydroxy-1,4,α-naphthisoöxazine-6-arsonic Acid.—This compound was prepared by the method of Newberry, Phillips and Stickings[9] for the corresponding benzene analog, employing chloroacetyl chloride. It crystallized from water in clusters of needles.

Anal. Calcd. for $C_{12}H_{10}AsNO_5$: As, 23.2. Found: As, 22.7.

The formation of the cyclic arsonic acid offers considerable evidence for the coupling of 4-hydroxy-1-naphthalenearsonic acid in the 3-position.

2-Hydroxy-5-phenylazobenzenearsonic Acid.—The crude product from the coupling of *o*-hydroxybenzenearsonic acid and benzenediazonium chloride was purified through the magnesium salt and finally by recrystallizing from water. It was reduced catalytically, employing

(7) Doak, Steinman and Eagle, THIS JOURNAL, 64, 1064 (1942).

(8) Christiansen, *ibid.*, 42, 2402 (1920).

(9) Newberry, Phillips and Stickings, *J. Chem. Soc.*, 3051 (1928).

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TABLE II

ARSONIC ACIDS AND ARSENOSO COMPOUNDS CONTAINING THE AZO LINKAGE

Compound	Description	M. p., °C.	Yield, %	Formula	As analyses, % Calcd.	As analyses, % Found	N analyses, % Calcd.	N analyses, % Found
R = Phenylazo, R′ = Benzene-arsonic acid								
4-Hydroxy-3-R-R′	Orange needles	290	40,[a] 5.9[b]	$C_{12}H_{11}AsN_2O_4$	23.2	22.9	8.70	8.70
2-Hydroxy-5-R-R′	Orange needles	257.3	45	$C_{12}C_{11}AsN_2O_4$	23.2	22.7	8.70	8.59
5-Hydroxy-2-R-R′	Golden plates	237.5	65	$C_{12}H_{11}AsN_2O_4$	23.2	23.0	8.70	8.64
4-Hydroxy-3-R-1-naphthalene arsonic acid	Red needles	245	20	$C_{16}H_{13}AsN_2O_4$	20.1	19.4		[c]
3,5-Bis-(R)-2,4-dihydroxy-R′	Orange powder	268	84	$C_{18}H_{16}AsN_4O_8$	17.0	16.2	12.7	12.5
p-R-R′	Orange plates	332.5–333.5	24	$C_{12}H_{11}AsN_2O_3$	24.5	24.2	9.16	9.30
p-(*p*-Tolylazo)-R′	Orange needles	> 360	41	$C_{13}H_{13}AsN_2O_3$	23.4	23.5	8.76	8.25
p-(*p*-Arsono-R)-benzoic acid	Orange needles	> 360	68	$C_{13}H_{11}AsN_2O_5$	21.4	21.5	8.01	8.41
p-(3-Acetamido-4-hydroxy-R)-R′	Red powder	224.8–225.2	75	$C_{14}H_{14}AsN_2O_5$	19.8	19.6	11.1	11.1
p-(3-Amino-4-hydroxy-R)-R′ hydrochloride	Red powder	Dec.	70	$C_{12}H_{13}AsClN_3O_4$	20.1	19.9	11.3	11.1
R = Phenylazo, R′ = Arsenoso								
p-R′-R-benzene	Orange powder	214–214.5	74	$C_{12}H_9AsN_2O$	27.5	27.6	10.3	10.4
p-(*p*-R′-R)-phenol[d]	Orange powder	> 360	100	$C_{12}H_9AsN_2O_2$	26.0	26.0	9.73	9.73
p-R′-2-R-phenol	Orange powder	215	94	$C_{12}H_9AsN_2O_2$	26.0	25.9	9.73	9.66
p-(*p*-R′-R)-benzamide	Orange powder	Chars > 260	88	$C_{13}H_{10}AsN_3O_2$	23.8	24.8	13.3	13.7
p-(*p*-R′-R)-(N-2-hydroxyethyl)-benzamide	Orange powder	Chars > 275	74	$C_{15}H_{14}AsN_3O_2 \cdot H_2O$	19.9	19.4	11.1	11.1
8-Amino-2-(*p*-R′-R)-1-naphthol-3,6-disulfonic acid[e]	Red powder	> 360	34	$C_{16}H_{12}AsN_3O_8S_2 \cdot 2H_2O$	13.6	13.5	7.65	7.72

[a] By the Scheller–Bart reaction. [b] By coupling. [c] Doak, Eagle and Steinman, THIS JOURNAL, 64, 1064 (1942), footnote[c] to Table I. [d] The corresponding arsonic acid was prepared by the method of Barrowcliff, Pyman and Remfry, *J. Chem. Soc.*, 93, 1893 (1908). [e] The corresponding arsonic acid was prepared according to German Patent 212,018, Raiziss and Gavron, "Organic Arsenical Compounds," Chemical Catalog Co., 1923, p. 286.

Raney nickel, and the resulting 6-hydroxy-*m*-arsanilic acid reduced in hydrochloric acid solution to 4-amino-2-dichloroarsinophenol hydrochloride, m. p. 183–183.4°.

Anal. Calcd. for $C_6H_7AsCl_3NO \cdot H_2O$: As, 24.3; N, 4.54. Found: As, 24.3; N, 4.61.

This compound was identical with the compound prepared by the reduction of an authentic sample of 6-hydroxy-*m*-arsanilic acid, thus establishing that *o*-hydroxybenzenearsonic acid coupled in the 5-position.

5-Hydroxy-2-phenylazobenzenearsonic Acid.—The crude reaction product from the coupling of *m*-hydroxybenzenearsonic acid and benzenediazonium chloride was purified by dissolving in warm sodium bicarbonate solution and precipitating with acid. It was finally recrystallized several times from water. This was similarly reduced to 5-hydroxy-*o*-arsanilic acid which gave **5-amino-4-dichloroarsinophenol hydrochloride**, m. p. 128–128.2°, on reduction in hydrochloric acid.

Anal. Calcd. for $C_6H_7AsCl_3NO \cdot H_2O$: As, 24.3; N, 4.54. Found: As, 24.1; N, 4.73.

This compound depressed the melting points of authentic samples of 2-amino-3-dichloroarsino- and 4-amino-5-dichloroarsinophenol hydrochlorides.[10] The structure of the coupled product as 5-hydroxy-2-phenylazobenzenearsonic acid was thus established.

B. The Scheller–Bart Reaction with Aminoazo Compounds

***p*-Phenylazobenzenearsonic Acid.**[11]—This compound was prepared by both the customary Bart reaction and the Scheller modification, but the latter method gave a somewhat larger yield. The compound was reduced catalytically, employing Raney nickel, to arsanilic acid and aniline which were identified by converting to *p*-dichloroarsinoaniline hydrochloride and acetanilide, respectively, and comparing with authentic samples of these two substances.

***p*-(*p*-Tolylazo)-benzenearsonic Acid.**—This was prepared from *p*-(*p*-tolylazo)-aniline which was obtained by a modification of the method of Nietzki.[12] *p*-(*p*-Tolylazo)-benzenearsonic acid, when oxidized with potassium permanganate gave ***p*-(*p*-arsonophenylazo)-benzoic acid.** The recrystallized compound, suspended in chloroform, was treated with phosphorus tri- and pentachlorides and the clear orange solution added to aqueous ammonia. ***p*-(*p*-Arsenosophenylazo)-benzamide** precipitated from this solution. No satisfactory means of purifying this compound was found.

***p*-(*p*-Arsenosophenylazo)-(N-2-hydroxyethyl)-benzamide** was obtained in a similar manner by using an aqueous solution of 2-aminoethanol instead of ammonia.

4-Hydroxy-3-phenylazobenzenearsonic Acid.[13]—This compound was prepared from the Scheller–Bart reaction applied to 4-amino-2-phenylazophenol. This latter compound was obtained by a slight modification of the method of Woroshzow.[14] The Scheller–Bart reaction was unsuccessful with the two following other amines which together with the two corresponding intermediate acetyl derivatives were prepared by the method of Woroshzow.[14]

***p*-(5-Amino-2-hydroxyphenylazo)-benzenesulfonic Acid.**—*Anal.* Calcd. for $C_{12}H_{11}N_3O_4S$: N, 14.3; S, 10.9. Found: N, 14.1; S, 11.5.

***p*-(5-Amino-2-hydroxyphenylazo)-benzenesulfonamide.**—*Anal.* Calcd. for $C_{12}H_{12}N_4O_3S$: N, 19.2. Found: N, 18.5.

Sodium Salt of *p*-(5-Acetamido-2-hydroxyphenylazo)-benzenesulfonic Acid.—*Anal.* Calcd. for $C_{14}H_{12}N_3NaO_5S$: N, 11.8; Na, 6.44. Found: N, 11.7; Na, 5.78.

***p*-(5-Acetamido-2-hydroxyphenylazo)-benzenesulfonamide.**—*Anal.* Calcd. for $C_{14}H_{14}N_4O_4S$: N, 16.8; S, 9.6. Found: N, 16.5; S, 10.1.

2-Amino-4-(*p*-arsenosophenylazo)-phenol.—*p*-Arsonobenzenediazonium chloride by coupling with *o*-acetamidophenol gave ***p*-(3-acetamido-4-hydroxyphenylazo)-benzenearsonic acid.** This was hydrolyzed with hydrogen chloride in methanol solution to give *p*-(3-amino-4-hy-

(10) Doak, Steinman and Eagle, THIS JOURNAL, 63, 99 (1941).

(11) Karrer, *Ber.*, 45, 2359 (1912).

(12) Nietzki, *ibid.*, 10, 662 (1877). *p,p*-Diazoaminotoluene, 10 g., 20 g. of aniline and 5 g. of aniline hydrochloride were heated at 36° for two hours, allowed to stand overnight and acidified with dilute acetic acid. The resulting compound was recrystallized twice from alcohol; yield 65%, m. p. 146–148°.

(13) Bart, *Ann.*, 429, 55 (1922).

(14) Woroshzow, *J. Russ. Phys.-Chem. Soc.*, 43, 787 (1911); *Chem. Zentr.*, 82, II, 1218 (1911).

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droxyphenylazo)benzenearsonic acid hydrochloride. The last traces of methanol were removed *in vacuo* at 100°. The compound showed the typical properties of an *o*-aminophenol. When this was reduced with sulfur dioxide a red insoluble product was obtained, the structure of which could not be determined.

Table II lists the arsonic acids and arsenoso compounds which were prepared. Melting points were taken by the procedure described in paper VI. All analytical results are the average of two or more determinations. The crystalline arsonic acids were recrystallized from either water or alcohol. The yields given are for the purified compounds.

Acknowledgment.—The authors wish to acknowledge the assistance given by Leon D. Freedman throughout the course of the work.

Summary

Arsonic acids containing the azo linkage have been prepared by coupling diazo compounds with hydroxyarylarsonic acids and by the Scheller–Bart reaction applied to aminoazo compounds. A number of these arsonic acids have been reduced to the corresponding arsenoso derivatives.

BALTIMORE, MD. RECEIVED OCTOBER 12, 1943

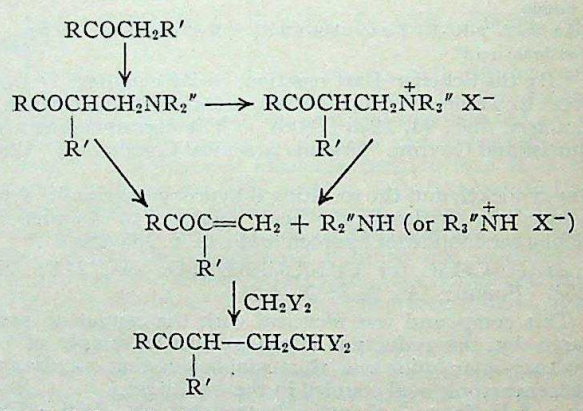
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Carbon-Alkylation with Quaternary Ammonium Salts. A New Approach to the Synthesis of Compounds Containing the β-Indolemethylene Group

BY H. R. SNYDER, CURTIS W. SMITH AND JOHN M. STEWART

Although simple quaternary ammonium salts have been used as alkylating agents in the preparation of numerous sulfur-,[1] oxygen-[2,3,4,5] and nitrogen-[6,7] alkylated substances, they have not appeared promising as reagents for the preparation of carbon-alkyl derivatives. For example, benzyldimethylphenylammonium chloride has been found not to yield phenacetonitrile by reaction with sodium cyanide in water,[1] and certain salts containing allyl groups attached to the nitrogen atom have been found not to produce allylphenols by reaction with phenolic substances.[3]

Successful reactions of quaternary salts derived from Mannich bases with active methylene compounds have been reported,[8,9] but these reactions have been interpreted as consisting not in simple alkylation but in Michael condensations of the active methylene compounds with vinyl ketones formed by decomposition of the quaternary salts of the Mannich bases.[10] The Mannich bases themselves react similarly in the presence of catalytic amounts of sodium, presumably also by decomposition to the vinyl ketones and the amines. The reactions are summarized in the following scheme.



In a study of the action of quaternary ammonium salts containing a benzyl group on sodium derivatives of acetoacetic ester and malonic ester it now has been found that carbon-alkylation occurs. Sodio acetoacetic ester reacts with benzyldimethylphenylammonium chloride in boiling ethanol to produce about 60% yields of crude ethyl α-benzylacetoacetate. Under the same conditions the sodium derivative of malonic ester reacts with the salt to give a yield of about 40% of diethyl benzylmalonate. The reactions probably proceed by an ionic path.

$$C_6H_5CH_2N^+(CH_3)_2C_6H_5 \longrightarrow$$

$$C_6H_5N(CH_3)_2 + [C_6H_5CH_2^+] \xrightarrow{CH(CO_2C_2H_5)_2^-} C_6H_5CH_2CH(CO_2C_2H_5)_2$$

There is no possibility of decomposition of this quaternary salt to an olefinic substance, according to the mechanism indicated above for reactions of the salts obtained from Mannich bases. As might have been expected, the amine, benzylmethylaniline, was found ineffective in these alkylations.

When benzylmethylpiperidinium chloride was allowed to react with the sodium derivative of malonic ester in ethanol solution the yield of diethyl benzylmalonate was only 5%. When the reaction was carried out in boiling 1-butanol the yield of crude ester (*ca.* 50%) was much improved, but the product apparently consisted of a mixture of ethyl and *n*-butyl esters. In order to effect the reaction at temperatures

(1) Snyder and Speck, THIS JOURNAL, **61**, 668, 2895 (1939).
(2) Hla Baw, *Quart. J. Indian Chem. Soc.*, **3**, 101 (1926).
(3) Tarbell and Vaughan, THIS JOURNAL, **65**, 231 (1943).
(4) Willstätter, *Ber.*, **35**, 584 (1902).
(5) Griess, *ibid.*, **6**, 585 (1873); **13**, 246 (1880).
(6) Rodionov, *Bull. soc. chim.*, **39**, 305 (1926); **45**, 109 (1929).
(7) *Frdl.*, **10**, 1215 (1910–1912); German Patent 247,180.
(8) Du Feu, McQuillin and Robinson, *J. Chem. Soc.*, 53 (1937).
(9) Harradence and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **72**, 239, 288 (1938); **73**, 233 (1939).
(10) Blicke, "The Mannich Reaction," in "Organic Reactions," John Wiley and Sons, Inc., New York, 1942, Vol. I, pp. 320–322.

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above the boiling point of ethanol, but without the risk of transesterification of the product, the reaction mixture in ethanol was heated in an autoclave at temperatures between 110 and 130°. The best yield obtained by this procedure was about 35%. The residue from the distillation of diethyl benzylmalonate was shown to contain diethyl dibenzylmalonate.

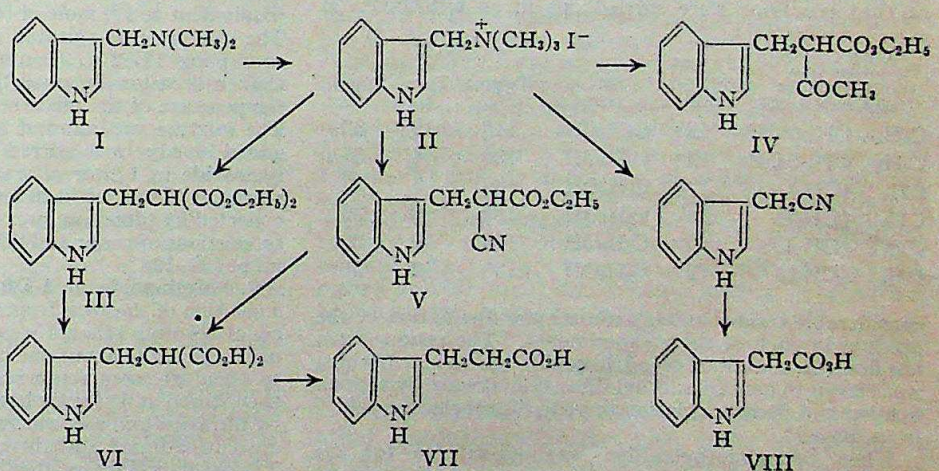
The occurrence of the ester of dibenzylmalonic acid is not surprising. Other side-reactions which might be expected in alkylations with benzylmethylpiperidinium chloride are the decomposition of the salt to an olefin, and the reaction with the alcohol used as solvent to form benzyl ethyl ether.[10a] That olefin formation is impossible with benzyldimethylphenylammonium chloride may account for the higher yields of diethyl benzylmalonate obtained with this salt.

Experimental conditions chosen with the view to the suppression of dialkylation and ether formation have resulted in further improvement of the yield of diethyl benzylmalonate. For example, when an ethanol solution of equivalent amounts of benzyldimethylphenylammonium ethoxide and malonic ester was added dropwise to an equivalent quantity of hot malonic ester with provision for removal of ethanol by distillation as rapidly as it entered the reaction mixture, the yield of diethyl benzylmalonate was slightly above 50%. When the chloride was added to a mixture of the sodium derivative of malonic ester and excess malonic ester, prepared by adding sodium ethoxide to an excess of malonic ester and removing most of the ethanol by distillation under diminished pressure, the yield was a little over 70%. When the reaction was carried out by adding the salt to the sodium derivative prepared from metallic sodium and excess malonic ester the yield was about 80%. These are the best conditions so far discovered. Substitution of benzylmethylpiperidinium iodide and benzyltriethylammonium iodide for the benzyldimethylphenylammonium chloride resulted in yields of 43 and 62%, respectively.

Alkylations of the type studied will be most useful in synthesis when the quaternary ammonium salts are more accessible than the alkyl halides. Gramine [3-dimethylaminomethylindole, (I)] can be prepared readily from indole[11] and it is converted easily to quaternary ammonium salts, such as the methiodide (II), which contain a radical of the benzyl type.

In a preliminary study of the use of gramine methiodide as an alkylating agent it has been found that this salt is more reactive than those containing a simple benzyl group. Reaction of II with the sodium derivative of malonic ester produced the substituted malonic ester (III) in 85% yields. Condensations with acetoacetic ester and cyanoacetic ester also were successful, although the products (IV and V) were oils which were not purified. The malonic ester condensation product was saponified and the malonic acid (VI) was decarboxylated to β-indolepropionic acid (VII). Hydrolysis of the crude cyanoacetic ester condensation product (V) gave the same malonic acid (VI). β-Indoleacetic acid (VIII) was prepared from the salt (II) and potassium cyanide in water solution, but in better yields from the salt (II) and potassium silver cyanide; the intermediate nitrile was not isolated in the pure state.

The greater reactivity of gramine methiodide, as compared to benzyltrimethylammonium salts, suggested that the possibility of alkylation with the free tertiary amine be reëxamined. Reaction occurred when gramine was heated with malonic ester containing a trace of the sodium derivative. The reaction, which could be followed by noting the evolution of dimethylamine, was very slow, however; the yield of ethyl α-carbethoxy-β-(3-indole)-propionate (III) obtained from a reaction carried out for fifty-three hours at temperatures between 120 and 150° was only about 40%.



I II IV III V VI VII VIII

Further studies of the application of these and similar reactions in the synthesis of indole derivatives are in progress.

Experimental

1. Benzyldimethylphenylammonium Chloride and the Sodium Derivative of Acetoacetic Ester in Ethanol.—To a solution of 1.15 g. (0.05 mole) of sodium in 100 cc. of absolute ethanol were added 7.15 g. (0.055 mole) of acetoacetic ester and 10.6 g. (0.05 mole) of benzyldimethylphenylammonium chloride. The mixture was heated under

(10a) Ingold and Patel [*J. Chem. Soc.*, 68 (1933)] obtained 65% yield of the ether from benzyltrimethylammonium iodide and sodium ethoxide in ethanol.

(11) Kuhn and Stein, *Ber.*, **70**, 567 (1937).

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reflux for a total of three and one-half hours (heating was interrupted after the first half hour to permit the removal of sodium chloride by filtration). About half of the ethanol was removed by evaporation and the residual solution was poured into a cold solution of 15 cc. of concentrated hydrochloric acid and 250 cc. of water. The aqueous phase was separated and extracted with three 50-cc. portions of ether. The ether extracts were combined with the organic layer and dried over sodium sulfate. Distillation yielded 6.6 g. (60%) of ethyl α-benzylacetoacetate boiling at 140–150 (2–3 mm.). The dinitrophenylhydrazone melted at 71.5°.

Anal. Calcd. for $C_{19}H_{20}N_4O_6$: C, 57.00; H, 5.04. Found: C, 57.19; H, 5.04.

2. Benzyldimethylphenylammoniuum Chloride and the Sodium Derivative of Malonic Ester in Ethanol.—To a solution of 2.3 g. (0.10 mole) of sodium in 80 cc. of absolute ethanol were added 17 g. (0.11 mole) of malonic ester and 28 g. (0.12 mole) of the quaternary chloride. The mixture was refluxed for ten hours. The ethanol was removed by evaporation and the residue was worked up in a manner similar to that described in 1. The diethyl benzylmalonate, b. p. 128–133° (6 mm.), weighed 9.4 g. (37.6%). The diamide[12] melted at 225°.

3. Benzylmethylpiperidinium Chloride and the Sodium Derivative of Malonic Ester in Ethanol and in Butanol.—The reaction in ethanol, run as in (2) gave a 5% yield of diethyl benzylmalonate. From the reaction in boiling *n*-butanol 52% yield of an oil boiling at 163–173 (4 mm.) was obtained. This product reacted very slowly with concentrated aqueous ammonia to give benzylmalonamide, m. p. 225°. The oil was probably a mixture of the ethyl butyl and dibutyl esters.

4. Various Quaternary Ammonium Salts and the Sodium Derivative of Malonic Ester.—The procedure used in the following experiments differed from that of (2) only in that reactions were carried out in an autoclave. A

Organic residues other than $C_6H_5CH_2$ in $C_6H_5CH_2NR_3^+X^-$	Anion	Solvent	Temp., °C.	Time, hr.	Yield, %
C_6H_5-, CH_3-, CH_2-	Cl^-	C_2H_5OH	115	12	32
C_6H_5-, CH_3-, CH_3-	Cl^-	C_2H_5OH	130	4	36
CH_3-, -$(CH_2)_5$-	I^-	C_2H_5OH	120	6	22
CH_3-, -$(CH_2)_5$-	I^-	C_2H_5OH	135	9	36
CH_3-, -$(CH_2)_5$-	Cl^-	C_2H_5OH	135	10	20
CH_3-, -$(CH_2)_5$-	Cl^-	C_2H_5OH	130	12	26

considerable residue remained after the distillation of the product in each of these experiments. The residue from the first run contained an oil, b. p. 170–183 (3 mm.), which was shown to contain diethyl dibenzylmalonate by saponification and decarboxylation to yield dibenzylacetic acid,[12] m. p. 88–89°.

When benzylmethylaniline was substituted for the quaternary salt in the second experiment, no diethyl benzylmalonate was obtained.

5. Benzyldimethylphenylammonium Ethoxide and the Sodium Derivative of Malonic Ester, with Removal of ethanal by Distillation.—The quaternary ethoxide was prepared by adding 25 g. (0.10 mole) of the quaternary chloride to 2.3 g. (0.10 mole) of sodium in 165 cc. of absolute ethanol and filtering from precipitated sodium chloride. The resulting solution was mixed with 16 g. (0.10 mole) of malonic ester and added over a period of about one hour to 16 g. (0.10 mole) of malonic ester in a distilling apparatus. During this period, and for two hours after the addition was complete, the oil-bath surrounding the flask containing the malonic ester was maintained at 150°. The bath temperature was then reduced to 110° for ten hours. The diethyl benzylmalonate, isolated essentially as described in (2), weighed 12.8 g. (51.3%).

6. Benzyldimethylphenylammonium Chloride and the Sodium Derivative of Malonic Ester without Solvent.—(a) A mixture of the sodium derivative of malonic ester and free malonic ester was prepared from 2.3 g. (0.10 mole) of sodium dissolved in 40 cc. of ethanol and 40 g. (0.25 mole) of malonic ester and removal of the ethanol by heating the mixture under 30 mm. pressure in an oil-bath at 50°. To the residue was added 27 g. (0.12 mole) of the quaternary chloride and the stirred mixture was suspended in an oil-bath which was heated to 110° over a period of two hours and then maintained at this temperature for six hours. The diethyl benzylmalonate, isolated essentially as in (2), weighed 18.2 g. (73%).

(b) The sodium derivative of malonic ester was prepared from 2.3 g. (0.10 mole) of powdered sodium and 40 g. (0.25 mole) of malonic ester in the presence of 100 cc. of anhydrous ether by stirring the mixture for six hours. To this mixture was added 27 g. (0.12 mole) of the finely ground quaternary chloride. The ether was removed by raising the temperature of the oil-bath to 110° over a period of about two hours. The stirred mixture was then heated at 140° for three hours. The yield of diethyl benzylmalonate was 19.7 g. (79%).

7. Other Quaternary Ammonium Salts Under the Approximate Conditions of Experiment 6-b.—In these experiments dibutyl ether (*ca.* 50 cc.) was added to facilitate stirring. N-Benzylmethylpiperidinium iodide gave a 43% yield of diethyl benzylmalonate, although the period of heating was extended by two hours. Benzyltriethylammonium iodide gave a 62.5% yield of the ester. With benzyltrimethylammonium bromide, evolution of trimethylamine began at 90°, continued for two hours with the oil-bath at 110–120°, and was completed after an additional half-hour at 140°. The yield of the ester was 77%.

8. 3-Dimethylaminomethylindole (Gramine).—The procedure was a modification of that of Kuhn and Stein.[11] To 135 g. of 35% dimethylamine (equivalent to 1.05 mole) at 5° was added 140 g. (2.33 moles) of glacial acetic acid. The mixture was cooled to 5° and 76 g. of 40% formalin (equivalent to 1.0 mole of formaldehyde) at 5° was added. The mixture was agitated mildly and poured into a flask containing 117.2 g. (1 mole) of indole. The flask was shaken occasionally until the indole had dissolved. The temperature of the mixture rose to 56° during this period. The mixture was allowed to stand for ten hours and was added slowly to a stirred solution of 140 g. of sodium hydroxide in 1 liter of water. The resulting suspension was cooled in an ice-bath for two hours. The gramine was collected by filtration, pressed dry, washed with three 100-cc. portions of water and dried in an oven at 50° overnight; m. p. 127–128°.

9. Methiodide of 3-Dimethylaminomethylindole.—To a solution of the base from the previous experiment in 750 cc. of absolute ethanol was added 156 g. of methyl iodide over a period of about one hour. The mixture was allowed to stand at room temperature for twelve hours and was then stored at 0° for six hours. The product was collected by filtration and was washed with three 100-cc. portions of absolute ethanol and three 100-cc. portions of dry ether. The dried product weighed 248.4 g. (80%, based on indole).

10. Ethyl α-Carbethoxy-β-(3-indole)-propionate.—The sodium derivative of malonic ester was prepared by stirring for twelve hours a mixture of 1.15 g. (0.05 mole) of powdered sodium, 75 cc. of butyl ether and 20 g. (0.125 mole) of malonic ester. To the resulting paste was added 17.5 g. of gramine methiodide. This mixture was heated, with stirring, for two hours with the oil-bath at 110° and for four hours with the oil-bath at 145°. The cooled mixture was stirred with three 100-cc. portions of water. The combined aqueous washings were extracted with three 100-cc. portions of ether and the ether extracts were added to the organic layer from the first extractions. The solution was dried and the solvents and excess malonic ester were removed by distillation, first from a steam-bath and finally at 5 mm. pressure with an oil-bath at 90°. The residual red liquid was poured slowly into 75 cc. of high-boiling petroleum ether, with cooling and stirring. The solid which soon formed was triturated with the cold solvent and collected by filtration; it weighed 16 g. (calcd. 14.5 g.) and melted at 60°.

(12) Bischoff and Siebert, *Ann.*, **239**, 96 (1887).

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The crude material was recrystallized by dissolving 13 g. in 30 cc. of hot ethanol and 15 cc. of hot water. After decolorization of the hot solution the filtrate was cooled to 50° and an additional 5 cc. of water was added. Crystallization was induced by careful cooling and stirring. After drying in a vacuum desiccator the product weighed 10 g. (85%, based on sodium) and melted at 61°. The analytical sample, prepared by a second recrystallization, melted at 62°. Ethyl α-carbethoxy-β-(3-indole)-propionate is soluble in benzene, toluene, chloroform and ethanol, and substantially insoluble in water, petroleum ether and carbon tetrachloride.

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62. Found: C, 65.93; H, 6.53.

11. α-Carboxy-β-(3-indole)-propionic Acid.—The ester was saponified by heating under reflux with 30% aqueous sodium hydroxide for six hours. The acid, after recrystallization from water, was obtained in 87% yield; m. p. 178° (dec.). The acid is very soluble in ethanol, and quite insoluble in chloroform and benzene.

Anal. Calcd. for $C_{12}H_{11}NO_4$: C, 61.77; H, 4.75. Found: C, 61.51; H, 4.88.

The diamide, prepared by allowing a mixture of the ester with ten times its weight of concentrated aqueous ammonia to stand for two weeks, crystallized from aqueous ethanol or acetone; m. p. 206°.

Anal. Calcd. for $C_{12}H_{13}N_3O_2$: C, 62.32; H, 5.66. Found: C, 62.53; H, 5.59.

12. β-(3-Indole)-propionic acid was prepared by heating the dibasic acid in an oil-bath at 180–190° for about fifteen minutes (until frothing stopped). The crude material, obtained by decolorizing a solution in 5% aqueous sodium hydroxide and reprecipitation by treatment with acid, melted at 120–123° (yield 75%). One recrystallization from water raised the melting point to 132–133°.

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.82; H, 5.86. Found: C, 68.96; H, 6.06.

The nitroso derivative melted at 135° (lit.,[13] 135°).

13. Ethyl α-cyano-β-(3-indole)-propionate was prepared by a procedure similar to that of (10). The crude material, obtained in 87% yield, was an oil which could not be crystallized. However, saponification with alcoholic potassium hydroxide gave α-carboxy-β-(3-indole)-propionic acid, m. p. 176°, which was shown by mixed melting point to be identical with the acid obtained in (11).

14. Ethyl α-Aceto-β-(3-indole)-propionate was obtained as an oil when acetoacetic ester was used in the procedure of (10). The dinitrophenylhydrazone prepared from the oil melted at 133.5°.

Anal. Calcd. for $C_{21}H_{21}N_5O_6$: C, 57.39; H, 4.82. Found: C, 57.51; H, 5.02.

15. 3-Indoleacetic Acid.—To a solution of potassium silver cyanide, prepared from 4.25 g. (0.025 mole) of silver nitrate and 3.2 g. (0.05 mole) of potassium cyanide in 28 cc. of water, was added 8 g. (0.025 mole) of gramine methiodide. The solution was heated under reflux for one and one-half hours, during which period trimethylamine was steadily evolved. The cooled solution was extracted with three 30-cc. portions of ether. Removal of the ether from the dried extracts gave a light red oil (4.8 g.). This oil was added to 75 cc. of 20% aqueous potassium hydroxide and the mixture was heated under reflux for ten hours. The acid, recovered by acidification of the cold mixture, was dissolved in 75 cc. of hot water and, after decolorization, was allowed to crystallize. The pure acid weighed 2 g. (46%), m. p. 164.5–165.5°.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18. Found: C, 68.57; H, 5.20.

In an experiment in which gramine methiodide was treated with twice the theoretical amount of potassium cyanide in boiling water for four hours, 3-indoleacetic acid was obtained in only 11.4% yield.

(13) Beilstein, "Handbuch der organische Chemie," Julius Springer, Berlin, 1935, ed. 4, Vol. XXII, p. 69.

16. 3-Dimethylaminomethylindole and Malonic Ester.—A mixture of 17.4 g. (0.1 mole) of 3-dimethylaminomethylindole and 49 g. (0.3 mole) of malonic ester was warmed until complete solution resulted and then approximately 0.05 g. (0.002 mole) of sodium was added. This mixture was heated in an oil-bath at 120° for five hours, during which time a slow evolution of dimethylamine occurred. At the end of five hours another 0.05 g. of sodium was added and the mixture was heated at 130° for nineteen hours. Another 0.05 g. of sodium was added and the mixture was heated at 150° for seventeen hours. The evolution of amine had become almost imperceptible. After the addition of another 0.05 g. of sodium and heating at 150° for twelve hours, heating of the now slightly amber solution was discontinued.

The reaction mixture was poured into 100 cc. of water containing 10 cc. of concentrated hydrochloric acid and extracted with three 150-cc. portions of ether. The combined ether extracts were washed with two 150-cc. portions of 10% sodium bicarbonate solution and dried over anhydrous sodium sulfate. After removal of the ether on a steam-cone the residue was heated under reduced pressure (140° (3 mm.)) to remove the excess malonic ester. The residue, 22 g. (76%) of a red viscous oil, did not crystallize on standing in the icebox overnight. About 0.5 cc. of this oil was extracted with low-boiling petroleum ether and allowed to stand for two days. This partly crystalline mixture was transferred to a clay plate which absorbed the oil; the solid melted at 59–61.5°. After two recrystallizations from ethanol and water the ethyl α-carbethoxy-β-(3-indole)-propionate melted at 62°; a mixture with a known sample also melted at 62°.

The remaining oil (about 21.5 g.) was extracted with 50 cc. of low-boiling petroleum ether and added to a solution of 22 g. of potassium hydroxide in 220 cc. of 90% ethanol. The solution was refluxed for three hours. Most of the ethanol was removed by distillation from the steam-bath and steam was passed into the residue until about 500 cc. of distillate had collected. The residual solution (volume, 250 cc.) was separated from a small amount of insoluble material, cooled, and acidified with 60 cc. of concentrated hydrochloric acid. The red solid which separated when the acidified mixture was stored in an icebox for twenty-four hours was collected and dissolved in 100 cc. of water containing 3 g. of sodium hydroxide and about 0.01 g. of sodium hydrosulfite. The solution was decolorized with charcoal and acidified. The crude α-carboxy-β-(3-indole)-propionic acid, m. p. 172–175° (dec.), weighed 9.6 g. (41%). A sample recrystallized from water melted at 178° (dec.) and a mixed melting point with a known sample showed no depression.

Summary

Benzyldimethylphenylammonium chloride and other quaternary ammonium salts containing a benzyl group are shown to react with the sodium derivatives of malonic ester and acetoacetic ester to yield C-benzyl derivatives. Diethyl benzylmalonate is obtained in approximately 80% yields by this method.

The method of C-alkylation is applied to the synthesis of a number of substances containing the β-indolemethylene group; the methiodide of gramine (β-dimethylaminomethylindole), easily prepared from indole, formaldehyde, dimethylamine and methyl iodide, is used as the alkylating agent. Malonic, acetoacetic and cyanoacetic esters are alkylated in this way. The products from malonic and cyanoacetic esters, by hydrolysis and decarboxylation, are converted to β-indolepropionic acid. β-Indoleacetic acid is prepared by hydrolysis of the nitrile obtained

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from gramine methiodide and potassium silver cyanide.

The tertiary amine (gramine) reacts with malonic ester in the presence of a small amount of the sodium derivative of the ester to yield ethyl α-carbethoxy-β-(3-indole)-propionate. However, the yield of alkylation product obtained from the amine is inferior to that obtained from the amine methiodide.

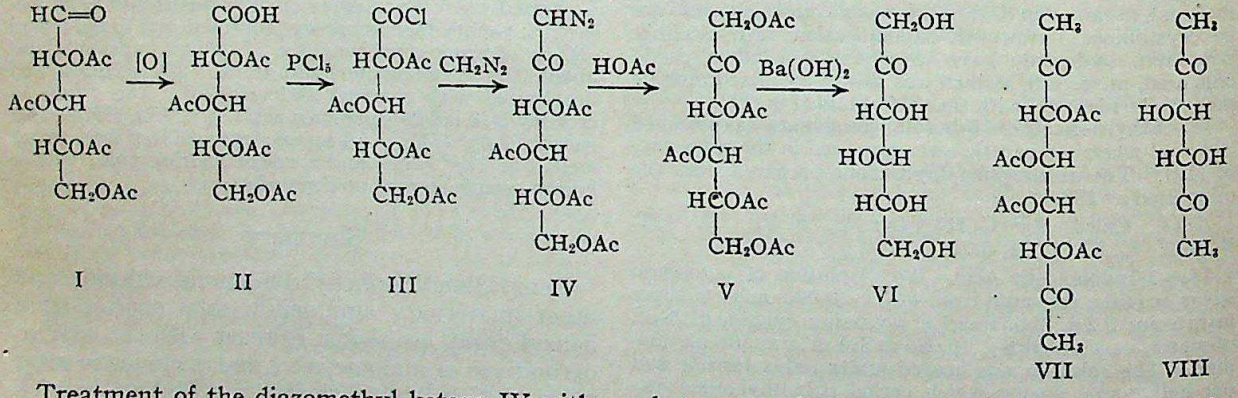
URBANA, ILLINOIS RECEIVED OCTOBER 2, 1943

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Action of Diazomethane upon Acyclic Sugar Derivatives. VI.[1] D-Sorbose[2]

BY M. L. WOLFROM, S. M. OLIN AND EVAN F. EVANS[3]

In continuation of our work upon the action of diazomethane upon acyclic sugar derivatives, we have synthesized 1-desoxy-1-diazo-*keto*-D-sorbose tetraacetate (IV) from D-xylonyl chloride tetraacetate (III). D-Xylonic acid tetraacetate (II) was prepared by the oxidation of *aldehydo*-D-xylose tetraacetate (I) according to the procedure reported by Major and Cook.[4] We describe an improved preparation of *aldehydo*-D-xylose tetraacetate[5] from D-xylose diethyl mercaptal tetraacetate, utilizing the general techniques of Wolfrom and Konigsberg.[6] The constants of Major and Cook[4] for I (m. p. 90–91°, spec. rot. +22.5° in absolute chloroform, for the L-form) have been verified. The rotation value differs appreciably from that previously reported[5] (m. p. 87–89°, spec. rot. −16° in chloroform, for the D-form). D-Xylonyl chloride tetraacetate has apparently not been recorded, although Major and Cook[7] described the D,L form.



Treatment of the diazomethyl ketone IV with acetic acid yielded *keto*-D-sorbose pentaacetate, enantiomorphic with the substance prepared by Arragon[8] and, nearly simultaneously, by Schlubach and Vorwerk[9] through the direct acetylation of L-sorbose. The acyclic nature of *keto*-L-sorbose pentaacetate was demonstrated by Cramer and Pacsu[10] and shortly later by Arragon.[11] We report herein a crystalline oxime of *keto*-L-sorbose pentaacetate. To our knowledge, this is the first nitrogen condensation product obtained for an acyclic or *keto* form of a ketohexose pentaacetate, previous attempts[10,12] having been unsuccessful. We record also the D,L form of *keto*-sorbose pentaacetate.

Careful saponification of *keto*-D-sorbose pentaacetate led to the synthesis of D-sorbose. Previous saponifications of the enantiomorphic derivative have been recorded by Schlubach and Vorwerk[9] and by Arragon.[11] This synthesis of D-sorbose from D-xylose compares with the synthesis of L-sorbose reported by Gätzi and Reichstein.[13] These workers oxidized diethylidene-(*levo*)-sorbitol to diethylidene-L-xylonic acid. From the crystalline acid chloride of the latter substance a sirupy diazomethyl ketone was obtained which on acid hydrolysis yielded crystalline L-sorbose. D-Sorbose (earlier psuedo-tagatose, *l*-sorbose) was first synthesized by Lobry de Bruyn and Alberda van Ekenstein[14] by the action of dilute aqueous alkali upon D-galactose. It was later formed from D-gulose and D-idose

(1) Previous publication in this series: M. L. Wolfrom and Robert L. Brown, THIS JOURNAL, **65**, 1516 (1943).

(2) Presented before the Division of Sugar Chemistry and Technology at the 106th meeting of the American Chemical Society, Pittsburgh, Pennsylvania, September 7, 1943.

(3) Allied Chemical and Dye Corporation Fellow, 1942–1943.

(4) R. T. Major and E. W. Cook, THIS JOURNAL, **58**, 2474 (1936).

(5) M. L. Wolfrom and Mildred R. Newlin, *ibid.*, **58**, 4379 (1931).

(6) M. L. Wolfrom and M. Konigsberg, *ibid.*, **61**, 574 (1939).

(7) R. T. Major and E. W. Cook, *ibid.*, **58**, 2477 (1936).

(8) G. Arragon, *Compt. rend.*, **196**, 1733 (1933).

(9) H. H. Schlubach and J. Vorwerk, *Ber.*, **66B**, 1251 (1933).

(10) F. B. Cramer and E. Pacsu, THIS JOURNAL, **59**, 1467 (1937).

(11) G. Arragon, *Compt. rend.*, **205**, 735 (1937).

(12) M. L. Wolfrom and A. Thompson, THIS JOURNAL, **56**, 880 (1934).

(13) K. Gätzi and T. Reichstein, *Helv. Chim. Acta*, **21**, 186 (1938).

(14) C. A. Lobry de Bruyn and W. Alberda van Ekenstein, *Rec. trav. chim.*, **16**, 262 (1897); **19**, 1 (1900); J. U. Nef, *Ann.*, **403**, 342 (1914).

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by aqueous alkali[15] and by pyridine.[16] Fischer and Baer[17] have demonstrated the formation of D-sorbose (and D-fructose) by the action of dilute alkali upon D-glyceraldehyde.

We include herein the synthesis of a derivative of a dicarbonyl-octose. The diazomethyl ketone obtained[18] from mucyl dichloride tetraacetate and designated 1,8-bisdiazomucyldimethane tetraacetate, was reduced with hydriodic acid according to the procedure of Wolfrom and Brown,[19] yielding the crystalline substance VII, designated mucyldimethane tetraacetate. In the C_6 series, a dicarbonyl hexose of a similar type has been isolated in crystalline form by Micheel,[20] who employed an entirely different method of synthesis. In this excellent work, the long-known 1,6-dichloro-D-mannitol[21] was converted through a series of crystalline intermediates into D-(*levo*)-tartaryldimethane, VIII, designated 1,4-dimethyl-1,4-diketo-tetrose by Micheel and Horn.

All compounds described herein were obtained in crystalline form.

Experimental

Improved Preparation of *aldehydo*-D-Xylose Tetraacetate (I).[22]—To a solution of 40 g. of mercuric chloride in 100 cc. of acetone in a 1-liter 3-necked flask was added 5 cc. of water and 25 g. of powdered cadmium carbonate and the mixture was stirred vigorously for ten minutes. To this was added a solution of 15 g. of D-xylose diethyl mercaptal tetraacetate[5] in 100 cc. of acetone and the resulting mixture was maintained at room temperature and under vigorous mechanical stirring for twelve hours, whereupon it was filtered and the solvent removed from the filtrate under reduced pressure and in the presence of a little fresh cadmium carbonate. The residual cake was extracted thrice with 75-cc. portions of warm chloroform and the combined extracts washed with 10% aqueous potassium iodide (to the disappearance of the red complex first formed) and then with water (to a negligible halide test with silver nitrate). The sirup obtained on solvent removal (reduced pressure) from the washed and dried extract was crystallized from anhydrous ether; yield 6 g. (3 crops), m. p.[23] 87–89°, spec. rot. −22.5° (20°, *c* 2.5, abs. $CHCl_3$, D line). Further purification from anhydrous ether yielded pure *aldeydo*-D-xylose tetraacetate; m. p. 90–91°, spec. rot. −23.3° (22°, *c* 4, abs. $CHCl_3$, D line). These constants are in agreement with those reported by Major and Cook[4] (m. p. 90–91°, spec. rot. +22.5° in abs. $CHCl_3$ for the enantiomorph) but differ in rotation from those reported[5] previously from this Laboratory (m. p. 88–89°, spec. rot. −16° in $CHCl_3$). The melting point of 90–91° and the specific rotation of −23° ($CHCl_3$) may then be accepted for *aldehydo*-D-xylose tetraacetate.

Anal. Calcd. for $C_5H_6O_5(CH_3CO)_4$: CH_3CO, 12.6 cc. 0.1 *N* NaOH per 100 mg. Found: CH_3CO, 12.5 cc.

(15) W. Alberda van Ekenstein and J. J. Blanksma, *Rec. trav chim.*, **27**, 1 (1908).
(16) K. Gätzi and T. Reichstein, *Helv. Chim. Acta*, **21**, 456 (1938).
(17) H. O. L. Fischer and E. Baer, *ibid.*, **19**, 519 (1936).
(18) M. L. Wolfrom, S. W. Waisbrot and R. L. Brown, THIS JOURNAL, **64**, 2329 (1942).
(19) M. L. Wolfrom and Robert L. Brown, *ibid.*, **65**, 1516 (1943).
(20) F. Micheel, *Ann.*, **496**, 77 (1932); F. Micheel and K. Horn, *ibid.*, **515**, 1 (1934).
(21) G. Bouchardat, *Ann. chim. phys.*, [5] **6**, 100 (1875).
(22) Experimental work by Mr. Robert L. Brown of this Laboratory.
(23) All melting points herein reported were taken in Pyrex melting point tubes.

D-Xylonyl Chloride Tetraacetate (III).[24]—D-Xylonic acid tetraacetate (3.0 g.), prepared by the oxidation of *aldehydo*-D-xylose tetraacetate according to the procedure of Major and Cook,[4] was shaken for one hour in ether (160 cc.) and phosphorus pentachloride (2.0 g.). The product (2.0 g.) crystallized from the filtered reaction mixture on standing overnight at icebox temperature and a further quantity (0.6 g.) was obtained from the mother liquor on addition of petroleum ether; total yield 2.6 g. (89%). Pure material was obtained on recrystallization from anhydrous ether; m. p. 72–73°, spec. rot. −14° (25°, *c* 5, abs. $CHCl_3$, D line). The substance crystallized in prismatic crystals.

Anal. Calcd. for $C_5H_6O_5Cl(CH_3CO)_4$: Cl, 10.05; saponification value (5 equiv.), 14.2 cc. 0.1 *N* NaOH per 100 mg. Found: Cl, 9.80; saponification value, 14.0 cc.

1-Desoxy-1-diazo-*keto*-D-sorbose Tetraacetate (IV).[24]—The diazomethane used in this work was prepared by the method of Werner[25] as modified by Arndt.[26] The ethereal solution of diazomethane was dried over potassium hydroxide pellets and was used at concentrations of 0.015–0.025 g. of diazomethane per cc. of solution. The concentration was determined by titration against benzoic acid.[27]

A solution of D-xylonyl chloride tetraacetate (8.3 g.) in sodium-dried ether (30 cc.) was poured slowly with stirring into 100 cc. of a dry, ether solution of diazomethane containing 2.3 g. of diazomethane. There was a vigorous evolution of nitrogen gas during the addition, and the crystallization of the reaction product, which began almost immediately after the addition of the acid chloride was complete, was allowed to complete itself at icebox temperature; yield 7.7 g. (92%), m. p. 122–124°, spec. rot. +43° (25°, *c* 5, abs. $CHCl_3$, D line). Pure material was obtained on recrystallization from five parts of acetone by the addition of like volumes each of ether and petroleum ether; m. p. 124.5–125.5°, spec. rot. +44.5° (25°, *c* 5, abs. $CHCl_3$, D line).

This diazomethyl ketone formed individual canary-yellow crystals that were insoluble in ether and petroleum ether but were very soluble in acetone, chloroform and alcohol.

Anal. Calcd. for $C_{14}H_{18}O_8N_2$: C, 46.93; H, 5.06; N, 7.82. Found: C, 46.94; H, 5.09; N, 7.33.

***keto*-D-Sorbose Pentaacetate (V).**[24]—A solution of 1-desoxy-1-diazo-*keto*-D-sorbose pentaacetate (2.0 g.) in glacial acetic acid (25 cc.) was refluxed until the cessation of nitrogen evolution (*ca.* twenty minutes). The crystalline solid obtained on pouring the cooled solution onto a mixture of ice and water and partially neutralizing the acetic acid with sodium bicarbonate, was removed by filtration and washed with water; yield 1.6 g. (73%), m. p. 91–94°, spec. rot. −1.9° (25°, *c* 4, abs. $CHCl_3$, D line). Pure material (elongated prisms) was obtained on recrystallization from methanol (decolorizing carbon)–water; m. p. 97.5–98.5°, spec. rot. −2.5° (25°, *c* 4, abs. $CHCl_3$, D line). For the enantiomorph, the following constants are reported: m. p. 99°, spec. rot. +2.8° (20°, $CHCl_3$, 5780 Å.)[8,11]; m. p. 96.5–97.5°, spec. rot. +2.9° (20°, *c* 2, $CHCl_3$, D line).[9]

Anal. Calcd. for $C_6H_7O_6(CH_3CO)_5$: C, 49.23; H, 5.68; CH_3CO, 12.8 cc. 0.1 *N* NaOH per 100 mg. Found: C, 49.16; H, 5.66; CH_3CO, 12.8 cc.

***keto*-D,L-Sorbose Pentaacetate.**[24]—Equal weights (1.0 g. of each) of *keto*-D-sorbose pentaacetate and *keto*-L-sorbose pentaacetate[8,9] were crystallized from methanol (15 cc.) and water (25 cc.); yield 1.8 g. (90%), m. p. 83–84° (unchanged on further crystallization), spec. rot. 0° (25°, *c* 2, abs. $CHCl_3$, D line).

Anal. Calcd. for $C_6H_7O_6(CH_3CO)_5$: C, 49.23; H, 5.68; CH_3CO, 12.8 cc. 0.1 *N* NaOH per 100 mg. Found: C, 49.16; H, 5.70; CH_3CO, 12.9 cc.

(24) Experimental work by Mr. S. M. Olin.
(25) E. A. Werner, *J. Chem. Soc.*, **115**, 1093 (1919).
(26) F. Arndt, *Org. Syntheses*, **15**, 3, 48 (1935).
(27) E. K. Marshall, Jr., and S. F. Acree, *Ber.*, **43**, 2323 (1910).

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Oxime of *keto*-L-Sorbose Pentaacetate.[28]—An amount of 5 g. of *keto*-L-sorbose pentaacetate[8,9] was dissolved in 250 cc. of boiling water. Hydroxylamine hydrochloride (2.5 g.) and potassium acetate (5 g.) were added to the hot solution which was then allowed to cool slowly to room temperature. Upon cooling to 0° and scratching the sides of the flask, the product crystallized; yield 1.3 g., m. p. 113–114°, spec. rot. −42° (23°, *c* 3, abs. $CHCl_3$, D line). An additional 0.4 g. was obtained by extraction of the mother liquor with chloroform. The constants were unaltered after recrystallization from solution in acetone–ether by the addition of petroleum ether.

Anal. Calcd. for $C_6H_8O_6N(CH_3CO)_5$: C, 47.41; H, 5.72; N, 3.46; CH_3CO, 12.3 cc. 0.1 *N* NaOH per 100 mg. Calcd. for $C_6H_9O_6N(CH_3CO)_4$: C, 46.28; H, 5.83; N, 3.86; CH_3CO, 11.0 cc. Found: C, 47.40; H, 5.88; N, 3.68; CH_3CO (O-acetyl[29]), 12.1 cc.

D-Sorbose (VI) from *keto*-D-Sorbose Pentaacetate.[28]—An amount of 2.43 g. of *keto*-D-sorbose pentaacetate was added to 100 cc. of 0.6 *N* barium hydroxide solution, previously cooled to *ca.* 5°. With occasional shaking, the crystals dissolved in about thirty minutes. The solution was kept for one hour longer at *ca.* 5° and then was saturated with carbon dioxide and the precipitated barium carbonate was removed by filtration. A slight excess of 2 *N* sulfuric acid was added slowly and the barium sulfate removed by filtration through a bed of Super-Cel (Johns-Manville). The excess sulfuric acid was then removed exactly with barium hydrate and the filtered solution was concentrated under reduced pressure at 40° to a sirup which crystallized spontaneously. The crystalline mass was stirred with 10 cc. of ethanol for filtration; yield 0.90 g. (80%), m. p. 158–160°, spec. rot. +40.5° (26°, *c* 3, H_2O, D line). Pure material was obtained on one recrystallization from water by the addition of absolute ethanol; m. p. 160–162°, spec. rot. +43 (24°, *c* 3, H_2O, D line, no significant mutarotation). For D-sorbose, Alberda van Ekenstein and Blanksma[15] reported the constants: m. p. 165°, spec. rot. +43° (*c* 1, H_2O, D line). For the enantiomorphic L-sorbose, Schlubach and Vorwerk[9] have recorded the constants: m. p. 159–161°, spec. rot. −43° (20°, *c* 2, H_2O, D line). Pigman and Isbell[30] record a small, complex mutarotation for L-sorbose.

Mucyldimethane Tetraacetate (VII).[24]—To a chloroform (40 cc.) solution of 1,8-bisdiazomucyldimethane tetraacetate[18] (2.00 g.), in a separatory funnel, was added 8 cc. of 47% hydriodic acid. The mixture was shaken until cessation of nitrogen evolution, diluted with water (40 cc.) and the chloroform layer removed and washed successively with water, aqueous sodium thiosulfate and water. A white crystalline solid was obtained on solvent removal from the dried chloroform solution; yield 1.60 g., m. p. 200–204°. Pure material was obtained on recrystallization from acetone by the addition of absolute ethanol; yield 1.35 g. (78%), m. p. 204–206°. The substance gave a positive iodoform test (iodoform identified by m. p. and mixed m. p.).

Anal. Calcd. for $C_{16}H_{22}O_{10}$: C, 51.21; H, 5.91. Found: C, 51.25; H, 5.85.

Summary

1. An improved demercaptalation procedure for *aldehydo*-D-xylose tetraacetate (I) is described.

2. The tetraacetates of D-xylonyl chloride (III) and of 1-desoxy-1-diazo-*keto*-D-sorbose (IV) have been synthesized. Reaction of the latter with acetic acid led to the synthesis of *keto*-D-sorbose pentaacetate (V), from which D-sorbose (VI) was obtained on saponification.

3. An oxime of *keto*-L-sorbose pentaacetate has been obtained.

4. *keto*-D,L-Sorbose pentaacetate is described.

5. Hydriodic acid reduction of 1,8-bisdiazomucyldimethane tetraacetate yielded mucyldimethane tetraacetate (VII).

(28) Experimental work by Mr. Evan F. Evans.

(29) M. L. Wolfrom, M. Konsgberg and S. Soltzberg, THIS JOURNAL, **58**, 490 (1936).

(30) W. W. Pigman and H. S. Isbell, *J. Research Natl. Bur. Standards*, **19**, 443 (1937).

COLUMBUS, OHIO RECEIVED SEPTEMBER 29, 1943

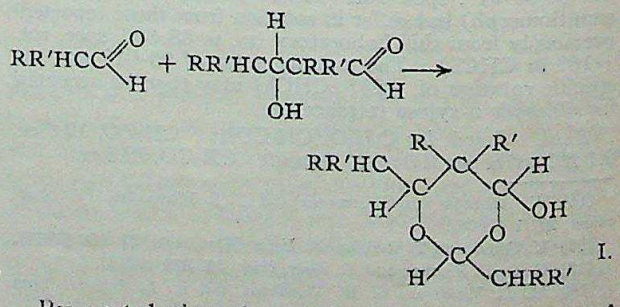
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF ILLINOIS INSTITUTE OF TECHNOLOGY]

The Aldol Condensation. III. Aldol-aldehyde Addition Products and their Derivatives

BY ROBERT H. SAUNDERS AND M. J. MURRAY

Späth, Lorenz and Freund[1] and Hanschke[2] have recently independently reported the isolation of an addition product of acetaldehyde to aldol, together with the acetate and benzoate of this compound. While this work was still unknown to us, we reported an analogous compound formed by the reaction of isobutyraldehyde with its aldol.[3] Under the circumstances we are reporting the results of our research to date and are concluding our work on this phase of the problem.

The following equation shows the addition of aldehyde to its aldol to form a 1,3-dioxane derivative



I.

By acetylating the crude reaction mixtures of aldolized aldehydes related to acetaldehyde, propionaldehyde, *n*- and isobutyraldehydes we obtained the 6-acetoxy-1,3-dioxanes in about 70% yields. In one instance, namely, that from isobutyraldehyde, we also prepared the 6-methoxy-1,3-dioxane. Physical properties for

(1) Späth, Lorenz and Freund, *Ber.*, **76B**, 57–68 (1943); *C. A.*, **37**, 4695 (1943).

(2) Hanschke, *Ber.*, **76B**, 180 (1943); *C. A.*, **37**, 5374 (1943).

(3) Saunders, Murray and Cleveland, THIS JOURNAL, **65**, 1714 (1943).

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TABLE I

PROPERTIES OF SOME 1,3-DIOXANES

Notation	R	R′	X	B. p., °C.	Mm.	$n^{25}D$	d^{25}_4	Mol. ref. Calcd.	Mol. ref. Obs.	Mol. wt. Calcd.	Mol. wt. Obs.[d]
A	H	H	H			1.4380	1.067	32.52	32.50		
B	Me	H	H	91.5	7	1.4408	1.001	46.38	46.21		
C	H[a]	H	Ac	85.5	10	1.4278	1.068	41.89	41.97	174	166
D	Me	H	Ac	100	7	1.4328	1.009	55.75	55.64		
E	Et	H	Ac	114	3	1.4378	0.9758	69.61	69.50	258	253
F	Me[b]	Me	Ac	93.5	2	1.4355	0.9726	69.61	69.44	258	255
G	Me[c]	Me	Me	110	20	1.4310	0.9220	64.98	64.70	230	225

[a] *Anal.* Calcd. for $C_8H_{14}O_4$: C, 55.2; H, 8.0. Found: C, 55.26; H, 7.83. [b] *Anal.* Calcd. for $C_{14}H_{26}O_4$: C, 65.1; H, 10.1. Found: C, 64.80; H, 9.76. [c] *Anal.* Calcd. for $C_{13}H_{26}O_3$: C, 67.7; H, 11.3. Found: C, 67.59; H, 11.04. Microanalyses performed by Dr. T. S. Ma, University of Chicago. [d] Cryoscopic in benzene.

seven of these compounds are listed in Table I. The R, R′ substituents refer to groups in formula I, and X refers to the group attached to oxygen on position 6.

It is interesting to observe the action of aldolizing conditions on the aldol from isobutyraldehyde: namely, 2,2,4,4-tetramethylaldol. This aldol, of course, is incapable of further aldol condensation and in the presence of cold, dilute alkali immediately begins to dissociate into the aldehyde-aldol equilibrium mixture. However, also catalyzed by base, the isobutyraldehyde formed in this dissociation rapidly reacts with the aldol to produce 2,4-diisopropyl-5,5-dimethyl-6-hydroxy-1,3-dioxane (H) whose properties were described in a previous communication.[3] This reaction is accompanied by 1,3-dioxane formation between two molecules of the aldol, forming a white solid which is apparently the same material as the paraldol that deposits slowly from 2,2,4,4-tetramethylaldol samples.

The Raman spectra of the 1,3-dioxanes which we have prepared are shown in Table II. The dioxane from *n*-butyraldehyde was the only one encountered that could not be distilled without dissociation. Its spectrum is rather incomplete since the fluorescent material present, most of which was removed with charcoal, did not permit the long exposures needed to obtain good spectrograms of this compound. For the Raman spectrum of H see reference 3. The spectra of A and B will be found listed under the headings "acetaldol" and "propionaldol" in a previous communication.[4]

There are several interesting features of these spectra which it will be well to point out, the first of which concerns the symmetrical breathing frequency of a flexible ring structure such as is found in 1,3-dioxane. This frequency in 1,3-dioxane itself lies at 834 cm.$^{-1}$ and is very intense, certainly the strongest line in the spectrum.[5] As the symmetry of the ring is destroyed by the substitution of different groups, the intensity of this line decreases and finally in highly unsymmetrical compounds ceases to be significant for identification purposes. In the present group of compounds the ring frequency produces a fairly strong line only for the 1,3-dioxane from acetaldehyde and for its acetate.

The compounds which were made from isobutyraldehyde contain neopentyl skeletons. A neopentyl group will produce a highly symmetrical vibration, somewhat similar to the breathing frequency of a ring structure, which gives rise to an intense Raman line in the region from 750 to 800 cm.$^{-1}$. The neopentyl vibration in H, F and G produces a strong line at about 790 cm.$^{-1}$ in

TABLE II[a]

RAMAN SPECTRA OF SOME SUBSTITUTED 1,3-DIOXANES

G $\Delta\nu$ I	F $\Delta\nu$ I	K[b] $\Delta\nu$ I	E $\Delta\nu$ I	D $\Delta\nu$ I	C $\Delta\nu$ I
132(1b)					
	223(1b)		226(0)		227(1)
	263(1b)				255(1)
303(1vb)		287(2)	291(3)	298(1)	
				337(1b)	
				374(1)	380(1b)
				434(1)	450(2)
476(2)	481(1)			474(3)	481(3)
				512(1)	
	536(1)			542(1)	539(4)
591(1)					
623(1)	643(1/2)		620(0)	629(1)	627(2)
791(4)	791(3)				
					815(5)
832(1)	838(1)		826(0)	825(1)	834(1)
871(2)	869(2)				
				895(2)	
923(1)	925(3)	906(2)	900(5)	914(3)	
953(3)	962(3)	956(1)	956(1)	947(3)	938(1)
		1019(2)			983(0)
1035(1)		1043(2)	1033(3)	1030(1)	
				1064(3)	
1122(1vb)	1118(0)			1119(1)	1105(1)
1176(3)	1185(2)	1152(2)	1161(3)	1176(3)	1161(3b)
1219(1b)	1208(0)				1220(1)
1248(2)	1248(1)				
			1273(0)		
1300(2)	1308(2)	1303(2)	1300(2)	1290(1b)	1327(1)
					1344(2)
1354(3)	1350(2b)		1382(2)	1368(3b)	1377(2)
		1436(3)	1438(4)	1441(6)	
1453(6)	1460(6)	1455(6)	1457(6)	1464(6)	1450(5)
	1761(2)		1751(2)	1752(2)	1754(2)
2712(1)	2724(1)	2726(1)	2735(1)	2741(1)	
2832(3)					2813(1)
2872(9)	2876(7)	2876(10)	2876(9)	2880(7)	2876(3)
2911(10)			2917(8)		
2958(8)	2939(9)	2928(9b)	2941(10)	2939(10)	2937(10)
2986(7)	2978(9)	2961(5)	2969(6)	2978(6)	2987(6b)

[a] $\Delta\nu$ = Raman displacement in cm.$^{-1}$, I = estimated intensity, b and vb = broad and very broad, respectively. [b] 2,4-Dipropyl-5-ethyl-6-hydroxy-1,3-dioxane.

(4) Saunders, Murray, Cleveland and Komarewsky, THIS JOURNAL, 65, 1309 (1943).

(5) Unpublished results from this Laboratory.

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each case; while this vibration for 2,2,4,4-tetramethylaldol, where the neopentyl group is not part of a ring system, drops to 770 cm.$^{-1}$. These two neopentyl lines were extremely useful in following the formation of H in the mixtures of isobutyraldehyde and 2,2,4,4-tetramethylaldol.[3]

The Raman lines in the 1750 cm.$^{-1}$ region for the acetates are due, of course, to the vibrations of the ester carbonyl group. It is interesting to note the similarity of the spectra of these acetates to the spectra of the parent 6-hydroxy-1,3-dioxanes.

Experimental

Preparation of the 6-Acetoxy-1,3-dioxanes.—The parent aldehyde was aldolized as described previously,[3] and the ether separated from the dried reaction product at the water pump. Equal volumes of this crude 1,3-dioxane, anhydrous pyridine, and acetic anhydride were mixed, and the reaction mixture allowed to stand overnight at room temperature. The acetic acid, pyridine, and excess acetic anhydride were then distilled off and the product fractionated under reduced pressure.

Preparation of G.—To 300 g. of 1% anhydrous methyl alcoholic hydrochloric acid was added 60 g. of H. This reaction mixture was sealed up in a 500-cc. flask for eighteen days. At the end of this time the reaction mixture was neutralized, diluted with water, and the organic layer fractionated under reduced pressure. Nineteen grams of the methyl ether was obtained; for physical properties see Table I.

The Aldolization of 2,2,4,4-Tetramethylaldol.—The aldolization of 14.4 g. of 2,2,4,4-tetramethylaldol was performed by the method previously described.[3] The crude product was washed well with water, dried, and freed of ether at the water pump. Distillation of this material produced 8.7 g. of H, and 3.5 g. of a white solid remained in the distilling flask. This white solid after two recrystallizations from petroleum ether melted at 105–107° which is the melting point found for the paraldol of 2,2,4,4-tetramethylaldol after recrystallization from the same solvent. This paraldol does not melt sharply and has a different melting point (within a range of 15°) when recrystallized from different solvents. This is probably due to the presence of several isomeric forms.

The apparatus and experimental technique for obtaining the Raman spectra are the same as were used in previous work.[3] The compounds studied gave very weak spectra so that long exposures were necessary.

Summary

1. The acetates of 2,4-diethyl-5-methyl-6-hydroxy-1,3-dioxane and 2,4-dipropyl-5-ethyl-6-hydroxy-1,3-dioxane, and the acetate and methyl ether of 2,4-diisopropyl-5,5-dimethyl-6-hydroxy-1,3-dioxane have been prepared and characterized.

2. The Raman spectra of the above compounds, of 2,4-dipropyl-5-ethyl-6-hydroxy-1,3-dioxane, and of 2,4-dimethyl-6-acetoxy-1,3-dioxane are reported.

3. It has been shown that the main product from the aldolization of 2,2,4,4-tetramethylaldol is 2,4-diisopropyl-5,5-dimethyl-6-hydroxy-1,3-dioxane.

CHICAGO, ILL. RECEIVED OCTOBER 8, 1943

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

A Study of the Haloform Reaction

BY RICHARD T. ARNOLD, ROBERT BUCKLES[1] AND JANET STOLTENBERG

Except for halogen-containing intermediates,[2,3] no neutral compounds have been isolated as products from the haloform reaction. In order to establish the structure of the methyl ketone (I) obtained from 5-methoxytetralin by means of the Friedel–Crafts reaction, the substance was treated with an aqueous methanol hypochlorite solution. To our surprise there was obtained, in addition to the small amount of expected carboxylic acid (II), a considerable quantity of a neutral, halogen-free solid whose analysis and molecular weight indicated the formula $C_{13}H_{16}O_3$. An 83% yield of this same compound was obtained if hypobromite solutions were employed. The method of preparation and the constitution of the starting materials permit only two reaonable structures for this formula, namely, III and IV.

It was at first supposed that the neutral substance was the ketol (IV) formed by hydrolysis of the phenacyl chloride which is presumably the first intermediate in the haloform reaction.[2] That this supposition was incorrect was indicated by the stability of the substance toward potassium permanganate, lead tetraacetate and periodic acid. Furthermore, no methane was liberated in the Zerewitinoff test.

Proof of the ester structure III was established by saponification to the acid II and the reconversion of II into III by treatment with diazomethane.

It seems surprising that methyl esters have not been reported previously as products of the haloform reaction since the procedure employed above is a typical one. We now believe that in aqueous methanol solution methyl esters are always formed but are so readily hydrolyzed that their isolation is difficult. In the experiment reported here, the temperature of the reaction mixture was not permitted to rise and the insoluble methyl ester crystallized from the solution as it was formed.

When the haloform reaction was carried out in aqueous dioxane solution (to prevent ester formation), a chlorine-containing acid (V) was formed as the sole product. That this substance was not formed during the haloform reaction but in-

(1) du Pont Postdoctorate Fellow, 1942–1943.

(2) Fuson and Bull, *Chem. Rev.*, **15**, 275 (1934).

(3) Aston, Newkirk, Dorsky and Jenkins, THIS JOURNAL, **64**, 1413 (1942).

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stead resulted from a rapid chlorination of the expected acid II (by excess hypochlorite) during the isolation process was shown in two ways. First, only compound II resulted if the excess hypochlorite were destroyed with acetone before acidification of the reaction mixture, and, second, an independent experiment proved that II was chlorinated (to give V) at an exceedingly rapid rate in acidic hypochlorite solutions.

Molecules having the $-\overset{O}{\overset{\|}{C}}-CCl_3$ group often react in a manner analogous to that of acid chlorides. The work of Houben and Fischer[4] indicates that trichloromethyl ketones react more rapidly with alcohols than with water in the presence of an alkaline catalyst. This difference in reaction

$$R-\overset{O}{\overset{\|}{C}}-CCl_3 + R'OH \longrightarrow R-\overset{O}{\overset{\|}{C}}-OR' + CHCl_3$$

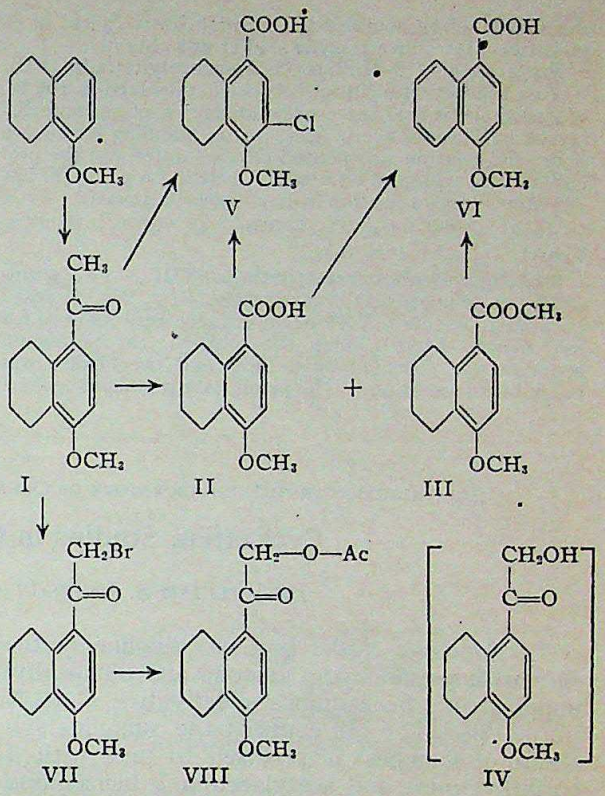
rate is remarkably similar to that observed in the Schotten–Baumann reaction of acid chlorides.[5]

The pseudo-halogen nature of the $-C-Cl_3$ group is also shown by the transformation of trichloroacetic acid esters into carbonates by reaction with alcohols.[6]

$$Cl_3-C\overset{O}{\overset{\|}{C}}-OR + R'OH \longrightarrow R'-O-\overset{O}{\overset{\|}{C}}-O-R + CHCl_3$$

An attempt to prepare IV was unsuccessful because of our inability to isolate a pure product from the hydrolysis of the acetate VIII.

The structure of the starting ketone employed in the haloform reaction was established by the dehydrogenation of III to 4-methoxy-1-naphthoic acid (VI). A reaction diagram is given below.



Experimental

5-Acetyl-8-methoxytetralin (I).—Into a 500-cc. three necked flask fitted with stirrer and reflux condenser there was placed a mixture of 200 cc. of redistilled nitrobenzene and 90 g. of aluminum chloride. While the temperature of this mixture was held at 0–5° by means of an ice-bath, 26 g. of acetic anhydride and 39 g. of 5-methoxytetralin were added at such a rate that the temperature did not exceed 5°. After four hours the reaction mixture was decomposed with ice and hydrochloric acid. The nitrobenzene was removed by steam distillation, and from the residue there was obtained 33.3 g. of ketone; b. p. 164–166° (8 mm.). The oxime prepared in the usual manner melted at 136–139° with decomposition.

Anal. Calcd. for $C_{13}H_{17}O_2N$: C, 71.2; H, 8.7. Found: C, 71.5; H, 7.8.

Preparation of 5-Carbomethoxy-8-methoxytetralin (III).—To a solution of 15 g. of calcium hypochlorate in 60 cc. of hot water was added a warm solution of 10.5 g. of potassium carbonate and 2 g. of potassium hydroxide in 30 cc. of water. After stirring thoroughly the mixture was filtered and the precipitate was washed with 12 cc. of water. One gram of the above-mentioned ketone was dissolved in 30 cc. of methanol and transferred to a separatory funnel. The hypochlorite solution was added slowly in small portions and following each addition the mixture was thoroughly shaken and cooled from time to time in an ice-bath. As soon as the hypochlorite addition was complete an oily solid formed. The solution was extracted with ether and the ether layer was evaporated. Crystallization of the residue first from aqueous methanol and finally from dilute acetic acid gave the methyl ester; m. p. 63–64°; yield 0.87 g. (80%).

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.90; H, 7.26. Found: C, 70.96; H, 7.09.

From the basic solution there was obtained 0.1 g. of 8-methoxy-5-tetralincarboxylic acid; m. p. 215.5–216° after recrystallization from methanol.

Anal. Calcd. for $C_{12}H_{14}O_3$: C, 69.9; H, 6.8. Found: C, 70.5; H, 7.2.

This acid was also formed quantitatively by the saponification of the methyl ester.

4-Methoxy-1-naphthoic Acid.—Eight-tenths of a gram of 8-methoxy-5-tetralin-carboxylic acid was treated with excess diazomethane in ether and when the evolution of nitrogen ceased the ether was evaporated. The residue was heated with 0.25 g. of sulfur for two hours at 250°. Extraction of the residue with ether, filtration and evaporation of the ether produced a residue which was readily saponified with aqueous-alcoholic sodium hydroxide. Acidification of the basic solution gave 4-methoxy-1-naphthoic acid; m. p. 243.5–244° (after recrystallization from ethanol). This sample was identical with an authentic specimen.[7]

7-Chloro-8-methoxy-5-tetralincarboxylic Acid (V).—The hypochlorite solution was prepared as described above except that 6 g. of potassium hydroxide was used. The hypochlorite was added to a solution of 1 g. of the ketone (I) dissolved in 30 cc. of dioxane. The mixture was shaken continuously for ten minutes and extracted with ether. Acidification of the aqueous layer resulted in the precipitation of an acid which melted at 154–156° after recrystallization from aqueous ethanol. A qualitative test for chlorine was positive.

Anal. Calcd. $C_{12}H_{13}O_3Cl$: C, 59.9; H, 5.4. Found: C, 60.08; H, 5.44.

If in the above experiment the excess hypochlorite were

(4) Houben and Fischer, *Ber.*, **64**, 240 (1931).
(5) Menalda, *Rec. trav. chim.*, **49**, 967 (1930).
(6) Meerwein and Sönke, *Ber.*, **64**, 2379 (1931).
(7) Danilov and Venus-Danilova, *ibid.*, **67**, 24 (1934).

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destroyed before acidification, a quantitative yield of 8-methoxy-3-tetralincarboxylic acid II was obtained.

Preparation of 8-Methoxy-5-bromoacetyltetralin (VII).—To a solution of 6.5 g. of ketone (I) dissolved in 100 cc. of glacial acetic acid there was added 5.1 g. of bromine dissolved in 25 cc. of acetic acid. After standing for twelve hours the solution was poured into ice-water and the precipitate was collected on a filter; weight 4.5 g.; m. p. 73–74° after recrystallization from aqueous acetic acid.

Anal. Calcd. for $C_{13}H_{15}O_2Br$: C, 55.1; H, 5.3. Found: C, 55.15; H, 5.51.

8-Methoxy-5-acetoxyacetyltetralin (VIII).—Two grams of the aforementioned bromoketone (VII), 2 g. of fused potassium acetate and 15 cc. of ethanol were refluxed for five hours. After cooling the solution, the potassium bromide was collected on a filter and the filtrate was poured into ice-water. The precipitate was dried and recrystallized first from petroleum ether (90–100°) and finally from dilute alcohol; m. p. 91–92°; yield 90%.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.7; H, 6.87. Found: C, 68.88; H, 6.79.

This compound reduced Fehling solution but could not be hydrolyzed to give a pure compound.

Summary

1. It has been shown that methyl esters may be obtained directly as products of the haloform reaction.

2. These esters probably result from the action of methanol on the trihalomethyl ketones which are intermediates in this reaction.

MINNEAPOLIS, MINNESOTA RECEIVED SEPTEMBER 25, 1943

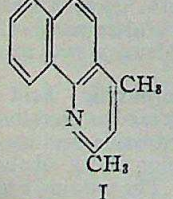
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Cyclization Studies in the Benzoquinoline Series

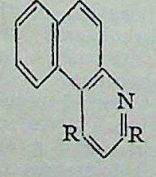
BY WILLIAM S. JOHNSON AND FREDERICK J. MATHEWS[1]

The Doebner–Miller type of quinoline synthesis[2a] with paraldehyde, acetone and β-naphthylamine gives a benzoquinoline derivative, $C_{15}H_{13}N$, m. p. 126–127°.[3] In contrast the quinoline synthesis of Combes[4] is reported to give with β-naphthylamine and acetylacetone a benzoquinoline of the same molecular formula, but m. p. 66–67°.[5] Both syntheses are known to be quite general for the production of quinoline derivatives. Thus from α-naphthylamine the Doebner–Miller and Combes' methods give bases[3,5] which are shown in the present work to be identical (formula I). The discrepancy regarding the benzoquinolines derived from β-naphthylamine presents a problem in proof of structures which is considered in this communication.

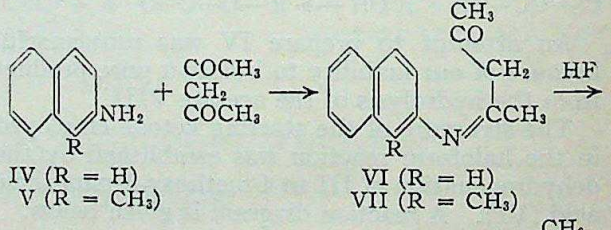
Previous studies suggest a similarity in mechanism—particularly at the cyclization step—between the Doebner–Miller and Skraup syntheses.[2] Since the latter is known[6] to give the angular base, benzo[f]quinoline (II) from β-naphthylamine, it would seem reasonable for Reed's 127° base to be 1,3-dimethylbenzo[f]quinoline (III). If the 127° base is III, the base reported by Combes could be 2,4-dimethylbenzo[g]quinoline (VIII) arising from the alternate—and indeed unexpected[7]—linear cyclization into the 3-position of the naphthalene nucleus. That these postulates are correct is shown below.



I

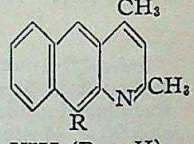


II (R = H)
III (R = CH_3)



IV (R = H)
V (R = CH_3)

VI (R = H)
VII (R = CH_3)



VIII (R = H)
IX (R = CH_3)

When the anil VI, which could be obtained in excellent yield from β-naphthylamine and acetylacetone, was treated with warm concentrated sulfuric acid according to the procedure of Combes,[5] only a small yield (4%) of basic material, m. p. 128.5–129° cor. (pure), was obtained. This substance proved to be identical with material which was prepared by the procedure of Reed.[3] The main product of the reaction was the monosulfonic acid (91% yield) of the expected base of Combes. The sulfonic acid (position of acid group unknown) could be hydrolyzed with dilute sulfuric acid at 220° to give the desired benzoquinoline. It was found, however, that under

(1) Present address: Röhm and Haas, Philadelphia, Pa.

(2) (a) Sidgwick, "Organic Chemistry of Nitrogen," Oxford University Press, 2nd ed., 1937, pp. 546–547; (b) *idem.*, pp. 544–546.

(3) Reed, *J. prakt. Chem.*, [2] **35**, 298 (1887).

(4) Hollins, "Synthesis of Nitrogen Ring Compounds," D. Van Nostrand Company, New York, N. Y., 1924, pp. 266–270.

(5) Combes, *Compt. rend.*, **106**, 1536 (1888).

(6) Skraup and Cobenzl, *Monatsh.*, **4**, 436 (1883).

(7) There is a general tendency for 2,1-cyclization to occur in the naphthalene nucleus. In the case of the Skraup reaction, for example, this tendency is so strong that a methyl group at position-1 prevents the reaction while a bromine atom or a nitro group is displaced to give 2,1 instead of 2,3 cyclization [Lellmann and Schmidt, *Ber.*, **20**, 3154 (1887); Marckwald, *Ann.*, **274**, 331 (1893); **279**, 1 (1894)].

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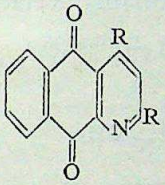
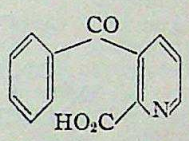
considerably milder cyclization conditions (two minutes below 60° instead of one-half hour at 100°) the sulfonation reaction could be largely eliminated and the base was produced directly from VI in yields up to 83%. The pure substance melted at 93–93.8° cor.[8] The balance of the material consisted of a small amount of the higher-melting isomer and of the sulfonic acid already mentioned. When the anil (VI) was treated with hydrogen fluoride,[9] the pure cyclized material (VIII) was produced in superior yield (96%) and to the exclusion of the angular isomer (III).[10]

It is noteworthy that hydrogen fluoride failed to cyclize the isomeric anil derived from α-naphthylamine.

In an effort to establish the structure, the 93° base was oxidized with potassium dichromate in acetic acid. A quinone (X) was produced which resembled anthraquinone in that it gave a deep colored vat with alkaline hydrosulfite and on reductive acetylation formed a crystalline hydroquinone diacetate. A number of attempts were



X (R = CH_3)
XI (R = H)



XII

made to cleave the quinone by alkali fusion,[11] but only intractable decomposition products were obtained. Acid permanganate, however, oxidized X rapidly in the cold to give a good yield of phthalic acid, the isolation of which, to be true, did not constitute a proof of structure. This facile oxidation, however, is in striking contrast to the behavior of anthraquinone, which is relatively stable. That the reactivity of the new quinone is due to the linear heterocyclic structure X was shown by an examination of the parent substance XI prepared by the unambiguous cyclization[12] of 3-benzoylpicolinic acid (XII).[13] This quinone closely resembled the one in question, responding comparably in the vat test, and in the easy oxidation to phthalic acid.

Evidence for the structures of the two benzoquinolines derived from β-naphthylamine also was supplied by a study of their absorption spectra. That of the 93° base is convincingly similar to that of anthracene (Fig. 1), while the absorption

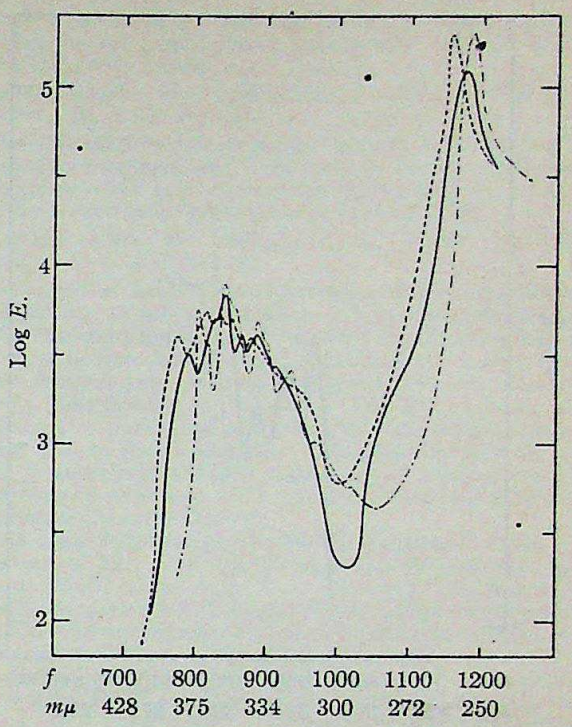


Fig. 1.— ——— 2,4-Dimethylbenzo[g]quinoline (VIII); - - - - - 2,4,10-trimethylbenzo[g]quinoline (IX); ·— · — · — anthracene.

of the 127° isomer resembles that of phenanthrene (Fig. 2). Even more striking is the comparison of the absorption of the latter base with that of

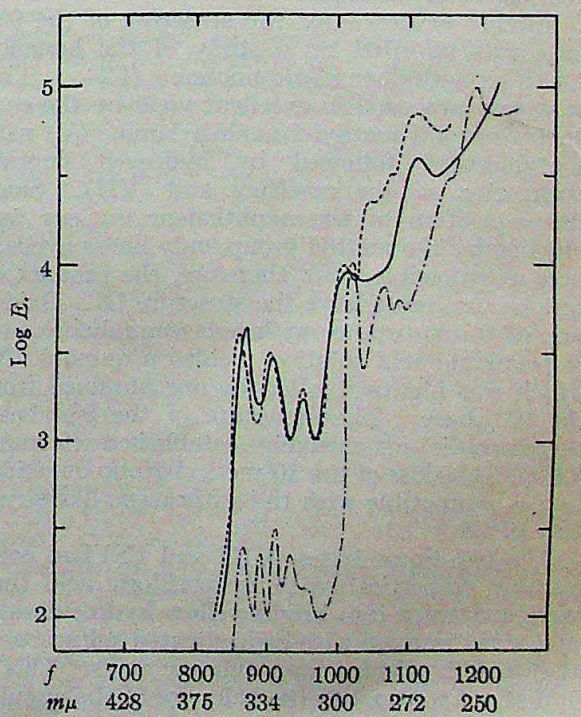


Fig. 2.— ———1,3-Dimethylbenzo[f]quinoline (III); - - - - 2,4-dimethylbenzo[h]quinoline (I); — · — · — phenanthrene.

(8) Our first preparations of Combes' base melted sharply at 74.5–75.5° cor. During the progress of the work some of this material changed into the polymorph, m. p. 93–93.8° cor., and since this occurrence only the latter has been encountered.

(9) Fieser and Hershberg, THIS JOURNAL, 61, 1272 (1939).

(10) An apparent tendency for hydrogen fluoride to favor linear cyclization of a different type has been noted previously by Fieser and Johnson, THIS JOURNAL, 61, 1647 (1939); Fieser and Daudt, *ibid.*, 63, 782 (1941), and Fieser and Heymann, *ibid.*, 63, 2333 (1941).

(11) *Cf.* Cason and Fieser, *ibid.*, 62, 2681 (1940).

(12) Philips, *Ber.*, 28, 1658 (1895).

(13) Kirpal, *Monatsh.*, 31, 295 (1911).

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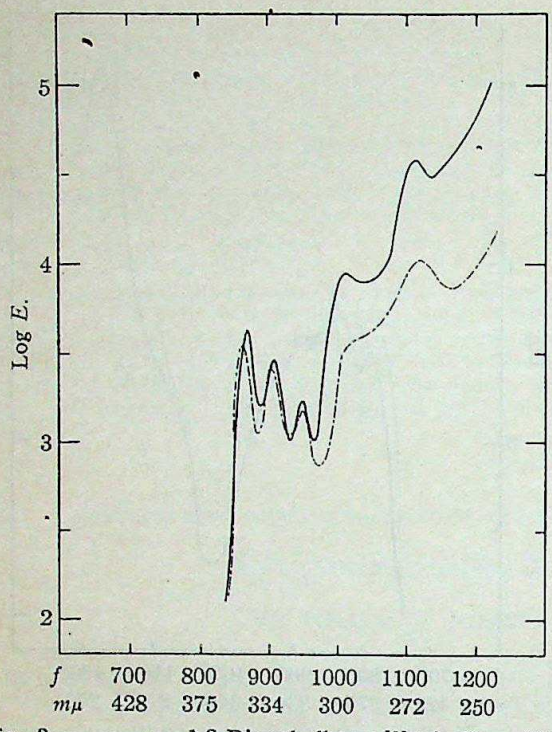
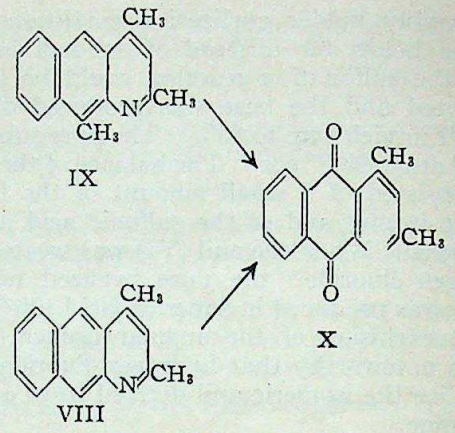


Fig. 3.— ——— 1,3-Dimethylbenzo[f]quinoline (III); — — — benzo[f]quinoline (II).

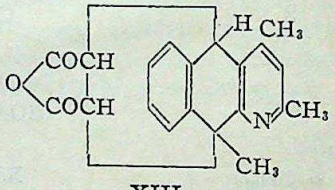
Skraup's benzo[f]quinoline (II)[14] (Fig. 3); the principal maxima appear at almost identical wave lengths. The absorption spectrum of 2,4-dimethylbenzo[h]quinoline (I) is included in Fig. 2 and bears a close relationship to those of the other angular analogs.

Further evidence for the structure of the 93° base was afforded by a study of the homolog 2,4,10-trimethylbenzo[g]quinoline (IX). This base was prepared in excellent yield by the condensation of 1-methyl-2-naphthylamine (V) with acetylacetone followed by hydrogen fluoride cyclization of the resulting anil (VII). Since the α-position of the naphthalene nucleus was blocked by the methyl group, only linear cyclization was possible, and, therefore, the product of ring closure must have the structure IX. Oxidation of this substance with potassium dichromate in propionic acid solution yielded a quinone (X) which was identical with the one obtained from the 93° base. The structure of the 93° base, therefore, is conclusively established (formula VIII). The loss of the 10-methyl group on oxidation is compatible with the anthracene-like structure of IX.[15]

The two linear bases (VIII and IX) had comparable properties: with hydrochloric acid they were converted into bright yellow hydrochlorides and when warmed with concentrated sulfuric acid they readily yielded monosulfonic acids. This is in distinct contrast to the behavior of the angular



bases which have colorless hydrochlorides and are sulfonated only under more drastic conditions.[3] This relative susceptibility of the linear and angular bases to sulfonation is reminiscent of the respective behavior of anthracene and phenanthrene. The new linear base (IX) also resembled anthracene in the reaction with maleic anhydride to form an addition product, probably XIII.[16]



XIII

The dimethyl base (VIII) also reacted readily with maleic anhydride, but the product was intractable. The angular bases, however, failed to react at all under the same conditions. The two linear bases were also closely comparable in respect to their absorption spectra (Fig. 1). A definite bathochromic shift may be noted in the maxima of the trimethyl derivative. This effect of the 10-methyl group is consistent with the observation that *meso* substituents exert such shifts in the absorption spectra of benzanthracene derivatives.[17]

Experimental Part[18]

4-(2-Naphthylimino)-pentanone-2 (VI).—The method of Combes[5] was modified by the introduction of Drierite into the reaction mixture. A mixture of 5.0 g. of β-naphthylamine, 6 cc. of acetylacetone and 10 g. of Drierite was heated on the steam-bath for three to four hours. The crude product obtained on elution with ether amounted to 7.55 g. (96% yield based on the amine), m. p. 89–96° with previous softening. One recrystallization from benzene–petroleum ether gave 6.5 g. (83% yield) of pure material, m. p. 98–99°. An additional 0.25 g., m. p. 96–98°, was obtained from the filtrate. A sample prepared for analysis formed tan flat needles and rods from ligroin, m. p. 98.5–99°.

Anal. Calcd. for $C_{15}H_{15}ON$: C, 79.97; H, 6.71. Found: C, 79.98; H, 6.66.

2,4-Dimethylbenzo[g]quinoline-x-sulfonic Acid.—A solution of 5.0 g. of the above anil (VI) in 25 cc. of concen-

(14) Structure known (see ref. 6).

(15) *Cf.* the oxidative degradation of *meso* alkylanthracenes to 9,10-anthraquinone; Barnett, "Anthracene and Anthraquinone," D. Van Nostrand Co., New York, N. Y., 1921, p. 20.

(16) *Cf.* the well-known addition of maleic anhydride to anthracene.

(17) R. N. Jones, THIS JOURNAL, 62, 148 (1940).

(18) Unless otherwise stated all melting points are corrected.

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trated sulfuric acid was heated on the steam-bath for one-half hour, cooled, and poured onto ice. The mixture was made alkaline, and a small amount (0.20 g.) of the angular 1,3-dimethylbenzo[f]quinoline (III) was obtained, m. p. 120–125°. Twice recrystallized from ligroin (90–100°) it melted at 128.5–129°, and showed no depression when mixed with an authentic specimen of the base prepared by the procedure of Reed.[3] Acidification of the alkaline solution yielded 5.8 g. (91%) of the yellow sulfonic acid of the linear base. It crystallized in small rods when a solution of the ammonium salt in dilute alcohol was boiled gently. The acid chars without melting when heated on a spatula; however, it is probably identical with the substance described by Combes[5] as shown by analysis.

Anal. Calcd. for $C_{15}H_{13}O_3NS$: C, 62.71; H, 4.56. Found: C, 62.94; H, 4.60.

2,4-Dimethylbenzo[g]quinoline (VIII): (a) By Hydrolysis of the Sulfonic Acid.—A suspension of 0.5 g. of the above sulfonic acid in 20 cc. of 10% (by volume) sulfuric acid was heated in a sealed tube at 220° for six hours. The mixture was made alkaline, and extracted with ether which gave 0.25 g. (70% yield) of the base, m. p. 63–70°. Once recrystallized from petroleum ether (60–68°) it melted at 71–72° (low-melting modification; see ref. 8). After the high-melting form was encountered in some later preparations, this material on recrystallization melted at 92–93°. Reaction temperatures above 220° caused considerable loss by charring while lower temperatures failed to effect complete hydrolysis.

(b) **Cyclization with Sulfuric Acid.**—The conditions for ring closure by this method appear to be very critical; it was not always possible to obtain yields as high as in the following experiment. To 85 cc. of chilled (2°) concentrated sulfuric acid was added with swirling 25.5 g. of 4-(2-naphthylimino)-pentanone-2 (VI). Better results were obtained when this operation did not exceed three minutes. The solution was then swirled in a flask at 60° (water-bath) for two minutes, cooled in an ice-bath and poured onto ice (300 g.). The insoluble yellow sulfate of the cyclized product was decomposed by making the mixture alkaline, and the base was taken up in ether. After treatment with Norit and drying, the ether was evaporated and the residue crystallized from ligroin (90–100°). This gave 19.6 g. (83.5% yield) of 2,4-dimethylbenzo[g]quinoline, m. p. 85–91° (high-melting form) with softening at 73°. One recrystallization gave 16.8 g. (71.5% yield) of material melting at 92–93°.

Evaporation of the filtrate from the first crystallization of VIII deposited a mixture of crystals from which could be separated mechanically about 0.5 g. (2% yield) of colorless clusters of needles, m. p. 121–125°, which consisted mainly of the angular isomer III; after two recrystallizations (90–100° ligroin) the m. p. was 128.5–129°, not depressed on mixing with authentic 1,3-dimethylbenzo-[f]quinoline. Attempts to cyclize the anil with dilute sulfuric acid resulted in hydrolysis.

(c) **Ring Closure with Hydrogen Fluoride.**—To 13.4 g. of the anil (VI) in a platinum vessel was added approximately 300 cc. of anhydrous hydrogen fluoride. After standing overnight at room temperature the residue was treated with 10% potassium carbonate solution, extracted with ether, treated with Norit, filtered, shaken with saturated salt solution and dried over anhydrous sodium sulfate. Evaporation of the ether yielded 11.75 g. (96%) of light tan crystals, m. p. 91–92.5°, not depressed on mixing with samples obtained by methods (a) and (b).

A sample of 2,4-dimethylbenzo[g]quinoline was purified for analysis by evaporative distillation at 130–140° (1 mm.). Recrystallization from acetone–ligroin gave colorless prismatic needles, m. p. 93–93.8°. Dilute solutions of the base exhibit a strong blue fluorescence. In dilute hydrochloric acid it gives an intense yellow solution of the salt.

Anal. Calcd. for $C_{15}H_{13}N$: C, 86.92; H, 6.32. Found: C, 87.05; H, 6.47.

2,4-Dimethylbenzo[g]quinoline hydrochloride was prepared by passing dry hydrogen chloride into an ether solution of the base. The salt on recrystallization from alcohol formed bright yellow microscopic crystals, m. p. 324–325° (dec.) (uncor.).

Anal. Calcd. for $C_{15}H_{14}ClN$: C, 73.91; H, 5.79 Found: C, 73.95; H, 5.76.

2,4-Dimethylbenzo[g]quinoline picrate was formed in alcohol and recrystallized from bromobenzene. It formed glistening yellow needles, m. p. about 271–273° (dec.) with previous darkening (introduced in bath at 250°).

Anal. Calcd. for $C_{21}H_{16}O_7N_4$: C, 57.80; H, 3.70. Found: C, 57.87; H, 3.46.

Reaction of 2,4-Dimethylbenzo[g]quinoline and Maleic Anhydride.—A solution of 0.4 g. of 2,4-dimethylbenzo(g)-quinoline and 1.5 g. of freshly distilled maleic anhydride in 10 cc. of benzene was allowed to stand for several hours at room temperature. The dark red precipitate amounted to 0.9 g. (air-dried), m. p. about 110–130° (dec.). All attempts to purify this material met with failure, apparently due to decomposition. This product may be the maleic anhydride addition compound by analogy to the homologous substance XIII which has been isolated in a pure state (described below).

2,4-Dimethylbenzo[g]quinoline-5,10-quinone (X).—A mixture of 16.3 g. of 2,4-dimethylbenzo[g]quinoline, 450 cc. of glacial acetic acid, 30 cc. of water and 23.5 g. of powdered potassium dichromate was boiled under reflux for one and one-quarter hours. The solution was cooled, poured into 500 cc. of saturated salt solution (to prevent emulsions) and extracted with benzene. Evaporation gave 8.9 g. (48% yield) of orange crystals of the quinone, m. p. 210.5–213.5° (dec.). A sample purified by sublimation at 180–190° (1 mm.) and recrystallization from benzene formed light orange needles, m. p. 215–216° (dec.). The quinone is photosensitive, turning bright red upon exposure to daylight for about two hours. It dissolves in alkaline sodium hydrosulfite solution to give a deep purple vat.

Anal. Calcd. for $C_{15}H_{11}O_2N$: C, 75.94; H, 4.67. Found: C, 75.80; H, 4.57.

5,10-Diacetoxy-2,4-dimethylbenzo[g]quinoline.—When the quinone (X) was treated by the customary procedure for reductive acetylation with zinc-dust, acetic anhydride and sodium acetate, only intractable oils were obtained. When sulfuric acid was used in place of the sodium acetate, the reduced diacetate was obtained.

To a solution of 0.50 g. of the quinone (X) in 15 cc. of acetic anhydride was added 0.4 cc. of concentrated sulfuric acid and 2 g. of zinc-dust. The pale orange solution presently turned bright yellow (due to the salt of the reduced diacetate; *cf.* the color of the hydrochloride of the base VIII), and was heated for one hour on the steam-bath. The filtered and cooled solution was poured onto ice, made alkaline, and extracted with benzene. The organic layer was extracted with a 3% solution of sodium hydrosulfite in 5% sodium hydroxide until all the quinone was removed as followed by the color of the vat, treated with Norit, and evaporated. The residue was sublimed at 165–180° (3 mm.) and recrystallized from benzene–ligroin (90–100°) to give yellow needles, m. p. 198–199°; yield 0.25 g. (37%). 5,10-Diacetoxy-2,4-dimethylbenzo[g]quinoline forms bright yellow solutions with dilute mineral acids, and does not give a vat test. It is relatively stable to light, but decomposes on long standing.

Anal. Calcd. for $C_{19}H_{17}O_4N$: C, 70.57; H, 5.30. Found: C, 70.68; H, 5.18.

Oxidation of 2,4-Dimethylbenzo[g]quinoline-5,10-quinone.—To a solution of 0.100 g. of the quinone (X) in 10 cc. of 20% (by volume) sulfuric acid was added dropwise a saturated solution of potassium permanganate until the latter was decolorized only slowly. The manganese dioxide was decomposed with sodium bisulfite and the solution extracted with ether. Evaporation of the dried ether layer gave 0.055 g. of almost colorless material m. p. 170–175°. Sublimation gave 0.025 g. of phthalic anhydride, m. p. 121–128°. After purification it melted at 126–128° and on mixing did not depress the m. p. of an authentic

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specimen. The free acid had the m. p. 190–192°, not depressed on mixing with authentic phthalic acid. The neutral equivalent was 84.5 (calcd. 83.1).

Oxidation of Benzo[g]quinoline-5,10-quinone.—Benzo[g]quinoline-5,10-quinone (XI) was prepared from 3-benzoylpicolinic acid (XII) by the action of sulfuric acid.[12] The picolinic acid was obtained by the Friedel and Crafts reaction of quinolinic anhydride and benzene.[13] The quinone which was obtained in 6% yield was sublimed at 170–190° (1 mm.) and recrystallized from toluene. It formed pale greenish-yellow needles, m. p. 279–280° (uncor.) (literature[12] m. p. 280°), and gave a brilliant purple vat with alkaline sodium hydrosulfite solution.

For the oxidation of the quinone (50 mg.) the procedure already described for the oxidation of the dimethyl homolog (X) was used. The reaction proceeded similarly in every respect, and phthalic acid (25 mg.) was likewise isolated.

1-Methyl-2-naphthylamine (V) has been prepared previously[19] in 50% yield by the Bucherer reaction on 1-methyl-2-naphthol. In the present work the yield was improved considerably.

A mixture of 7.8 g. of 1-methyl-2-naphthol[20] (m. p. 107–109°); 10 g. of sodium bisulfite, 40 cc. of concentrated ammonium hydroxide solution, and 10 cc. of water was heated in a sealed Pyrex tube at 200 to 205° for forty-eight hours. The mixture was then diluted with water, made strongly alkaline with sodium hydroxide and extracted with ether. If the ether layer was evaporated, the residue could not be purified satisfactorily by recrystallization since an apparently homogeneous substance, m. p. 91–93° contaminated the product. This contaminant was shown to consist of a molecular complex of amine and unchanged naphthol which could not be separated with alkali. The amine could be liberated as the hydrochloride by treating an ether solution of the complex with dry hydrogen chloride. Thus it was found expedient to apply this treatment to the original dried ether layer. The amine hydrochloride was filtered, washed with ether, dissolved in hot water and decomposed with sodium hydroxide. The liberated amine was extracted with ether and dried. Evaporation of the solvent gave a crude product m. p. 46–50°; yield 7.2 g. or 93%. Once recrystallized from petroleum ether (60–68°) it formed a colorless product, m. p. 49–50° (literature[19] m. p. 50–51°), amounting to 5.5 g. (71% yield).

4-(1-Methyl-2-naphthylimino)-pentanone-2 (VII).—The procedure already described for the homolog VI was used, except that a large excess of acetylacetone was employed since the ketone is more accessible than the amine in this case. From 14.0 g. of 1-methyl-2-naphthylamine (m. p. 49–50°) and 20 cc. of acetylacetone with 28 g. of Drierite, there was obtained 22.0 g. of crude anil (VII), m. p. 87–92°. Recrystallization from ligroin (90–100°) gave 15.2 g. of material, m. p. 92–93.5°, and a second crop amounting to 3.2 g., m. p. 90–92°; thus the yield of pure anil was 87%. A sample twice recrystallized from petroleum ether (60–68°) formed light tan prisms, m. p. 93–94.8°.

Anal. Calcd. for $C_{16}H_{17}ON$: C, 80.31; H, 7.16. Found: C, 80.37; H, 7.21.

2,4,10-Trimethylbenzo[g]quinoline (IX).—The cyclization of the above anil (VII) was carried out according to both procedures (b) and (c) for the preparation of 2,4-dimethylbenzo[g]quinoline already described. The sulfuric acid method (b) gave good yields (up to 93%) of the cyclized base, but suffered from the same type of uncertainty already mentioned in the case of the lower homolog. Consistently excellent yields of the new quinoline derivative were realized when the hydrogen fluoride method (c) was employed. Thus from 5.0 g. of 4-(1-methyl-2-naphthylimino)-pentanone-2 (m. p. 91–93°) was obtained 4.42 g. (96% yield) of 2,4,10-trimethylbenzo[g]-quinoline, m. p. 122–125°. Material purified by evaporative distillation at 130–140° (1 mm.) and recrystallization from acetone–petroleum ether formed colorless prisms, m. p. 126.2–127°. Like the lower homolog its solutions exhibit a strong fluorescence, and with dilute hydrochloric acid it gives a bright yellow salt.

Anal. Calcd. for $C_{16}H_{15}N$: C, 86.84; H, 6.83. Found: C, 86.75; H, 6.71.

2,4,10-Trimethylbenzo[g]quinoline hydrochloride was prepared as described above for the homologous substance. The orange-yellow salt crystallized from alcohol in microscopic crystals, m. p. 295–296° (dec.) (uncor.).

Anal. Calcd. for $C_{16}H_{16}ClN$: C, 74.55; H, 6.26. Found: C, 74.75; H, 6.02.

2,4,10-Trimethylbenzo[g]quinoline picrate crystallized in yellow rods from the solvent pair nitromethane–tetrachloroethane. The m. p. was 253–255° (dec.) with previous darkening (introduced in bath at 240°).

Anal. Calcd. for $C_{22}H_{18}O_7N_4$: C, 58.66; H, 4.03. Found: C, 58.72; H, 4.16.

2,4,10-Trimethylbenzo[g]quinoline-x-sulfonic acid was prepared according to the procedure already described for the homolog. From 15.0 g. of the anil (VII) was obtained 17.4 g. (92% yield) of the acid. On slow hydrolysis of the ammonium salt the pure acid crystallized in small orange-yellow rods. It is hygroscopic, and more soluble than the lower homolog.

Anal. Calcd. for $C_{16}H_{15}O_3NS$: C, 63.77; H, 5.02. Found: C, 63.41; H, 4.98.

Reaction of 2,4,10-Trimethylbenzo[g]quinoline with Maleic Anhydride.—A solution of 0.30 g. of the base and 0.75 g. of freshly distilled maleic anhydride in 6 cc. of benzene was boiled under reflux for six hours. After cooling the solution was diluted with 15 cc. of benzene, dry hydrogen chloride passed in, and the precipitated hydrochloride filtered. This product was colorless, indicating that the addition was complete (*cf.* the intense yellow color of the salt of the starting base). The adduct was regenerated by boiling for ten minutes with acetone and powdered sodium acetate, filtering and evaporating the solvent; yield 0.33 g. The residue was purified by recrystallization from ether (poor recovery). It formed colorless microscopic crystals, m. p. 203.5–204.5°. Attempts to prepare the dibasic acid in a pure state were discouraged by difficulties attributable to the amphoteric nature of the substance.

Anal. Calcd. for $C_{20}H_{17}O_3N$: C, 75.22; H, 5.37. Found: C, 74.90; H, 5.26.

When the angular bases (I and III) were submitted to the reaction conditions above they were recovered unchanged.

Potassium Dichromate Oxidation of 2,4,10-Trimethylbenzo[g]quinoline.—A solution of 2.0 g. of the benzoquinoline and 5.4 g. of potassium dichromate in 40 cc. of propionic acid and 5 cc. of water was boiled under reflux for two hours. The cooled, green solution was poured into 300 cc. of water and extracted with benzene. The quinone was extracted from the benzene solution with a 1 to 1 mixture of 5% sodium hydrosulfite and 10% sodium hydroxide solution. The quinone was regenerated from the purple vat by passing air through the aqueous solution for several hours. Thus was obtained 0.1 g. (about 5% of the theoretical) of crude quinone, m. p. 180–195°. The reduced diacetate was prepared by the procedure already described. Sublimation and recrystallization gave material, m. p. 196–198°, identical in appearance with the reduced diacetate obtained from 2,4-dimethylbenzo[g]quinoline quinone. A mixture of the two samples showed no m. p. depression.

2,4-Dimethylbenzo[h]quinoline (I) was prepared from α-naphthylamine and acetylacetone according to previous procedures.[5,21] The use of Drierite (see above) was found to increase the yield (99%) of the anil which we were not able to obtain homogeneous. Fusion of the material occurred over a wide range below 100° even after several recrystallizations (*cf.* v. Braun, *et al.*,[21] who give the m. p.

(19) Scholl and Neuberger, *Monatsh.*, **33**, 507 (1912); Shimomura and Cohen, *J. Chem. Soc.*, 740 (1921).

(20) Robinson and Weygand, *J. Chem. Soc.*, 386 (1941).

(21) v. Braun, Gmelin and Petzold, *Ber.*, **57**, 382 (1924).

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165°). The crude anil, however, could be cyclized with sulfuric acid in good yields (80–90%). The benzoquinoline twice recrystallized from petroleum ether (40–60°) formed colorless needles, m. p. 51.5–53°. Material of the same m. p. was obtained laboriously in about 2% yield using the procedure of Reed.[3] The mixed m. p. showed no depression. It was surprising to find that hydrogen fluoride failed to cyclize noticeably 4-(1-naphthylimino)-pentanone-2; hydrolysis to α-naphthylamine took place instead.

Absorption Spectra.—A Hilger quartz spectrograph equipped with a Hilger photometer was used in conjunction with a hydrogen discharge tube as the light source. Ethanol, specially dried over magnesium ethoxide[22] and distilled in an all-glass apparatus, was used as the solvent.

The analytical samples of the benzoquinolines were used. Benzo[f]quinoline (Eastman Kodak Company) was recrystallized from 60–68° petroleum ether, m. p. 90.5–91.5°. Anthracene was sublimed and recrystallized from chloroform and ethanol, m. p. 214.5–215.5°. A pure sample of phenanthrene was prepared by dehydrogenation of pure 9,10-dihydrophenanthrene[23] over 30% palladium-charcoal,[24] followed by recrystallization from ethanol, m. p. 98–99°.

The linear compounds were determined at four concentrations: *M*/4000, *M*/10,000, *M*/40,000 and *M*/200,000. For anthracene a determination was made also at *M*/400,000. The angular substances were determined at *M*/2000, *M*/10,000, *M*/50,000 and *M*/200,000. In the figures the abscissas are plotted in fresnel (*f*) units in accordance with the suggestion of Brode.[25] The log *E* values observed for anthracene and phenanthrene do not check those of Capper and Marsh,[26] but in the case of anthracene are in agreement with those of Heertjes and Waterman.[27]

The principal maxima are given below. The wave lengths are in ångström units, the intensity in log *E* (in parentheses), and * indicates inflections.

Anthracene.—3740 (3.75), 3700* (3.55), 3560 (3.9), 3505* (3.75), 3375 (3.70), 3340* (3.58), 3200 (3.43), 3090 (3.05), 2940 (2.75), 2530 (5.30).

2,4-Dimethylbenzo[g]quinoline.—3800 (3.45), 3640 (3.70), 3575 (3.85), 3470 (3.62), 3380 (3.62), 3290 (3.45), 2565 (5.10).

2,4,10-Trimethylbenzo[g]quinoline.—3870 (3.6), 3695 (3.75), 3600 (3.7), 3530 (3.7), 3420 (3.6), 2590 (5.3).

Phenanthrene.—3460 (2.4), 3375 (2.24), 3290 (2.5), 3220 (2.34), 3150 (2.18), 3080 (2.00), 2935 (4.00), 2815 (3.88), 2760 (3.80), 2600 (4.48), 2525 (5.00).

2,4-Dimethylbenzo[h]quinoline.—3480 (3.6), 3310 (3.50), 3160 (3.30), 2980 (4.00), 2870 (4.35), 2790 (4.50), 2700 (4.85).

1,3-Dimethylbenzo[f]quinoline.—3450 (3.65), 3300 (3.48), 3160 (3.24), 2970 (3.95), 2700 (4.60).

Benzo[f]quinoline.—3470 (3.54), 3310 (3.41), 3160 (3.18), 2900* (3.57), 2665 (4.06).

Summary

The preparation and proof of structure of some benzoquinoline derivatives is considered. Particular attention is given to the cyclization of the anil from β-naphthylamine and acetylacetone, which, surprisingly, takes place so as to give a linear benzoquinoline. The latter represents a class of compounds about which little has been known. Some of the properties of this type of substance are considered.

(22) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Company, 2nd ed. Part II, 1941, p. 359.

(23) Fieser and Johnson, THIS JOURNAL, **61**, 168 (1939).

(24) Zelinsky and Turowa-Pollak, *Ber.*, **58**, 1295 (1925).

(25) W. Brode, "Chemical Spectroscopy," John Wiley and Sons, New York, N. Y., 1939, p. 191.

(26) Capper and Marsh, *J. Chem. Soc.*, 724 (1926).

(27) Heertjes and Waterman, *Bull. soc. chim.*, [5] **7**, 187 (1940).

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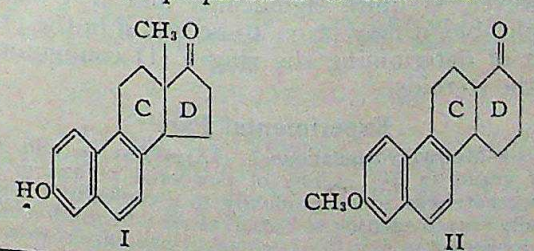
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Introduction of the Angular Methyl Group. II.[1] *cis*- and *trans*-8-Methylhydrindanone-1[2]

BY WILLIAM S. JOHNSON

The purpose of this communication is to describe a method for converting decalone-1 (III) into the angularly methylated hydrindanones (IX and X). This process affords a means of arriving at the structure defined by rings C and D (compare formula I) of a number of the steroid hormones, and obviously serves as a model synthesis for the preparation of hormones of the equilenin (I) type from chrysene derivatives like II.[3]



Considerable attention already has been devoted to 8-methylhydrindanone-1[4–11] but with one exception[11] all of the syntheses have led to one and the same isomer of this compound which, however, can exist in two racemic forms described by *cis* (IX) and *trans* (X) fusion of the rings. The present synthesis affords a means of obtaining each of these diastereoisomers, which is fortunate particularly in view of the fact that the ring C/D

(1) For the first paper of this series see Johnson, THIS JOURNAL, **65**, 1317 (1943).

(2) This work was assisted in part by a grant from the Wisconsin Alumni Research Foundation.

(3) The unsaturated progenitor (double bond in ring D) of compound II is available by the Robinson–Schlittler synthesis; Robinson and Thompson, *J. Chem. Soc.*, 1739 (1939).

(4) Chuang, Tien and Ma, *Ber.*, **69**, 1494 (1936).

(5) Kon, Linstead and Simons, *J. Chem. Soc.*, 814 (1937).

(6) Linstead, Millidge and Walpole, *ibid.*, 1140 (1937).

(7) Robinson and Walker, *ibid.*, 1160 (1937).

(8) Elliott and Linstead, *ibid.*, 660 (1938).

(9) Burnop and Linstead, *ibid.*, 720 (1940).

(10) Nenitzescu and Przemetzky, *Ber.*, **74B**, 676 (1941).

(11) Bachmann and Kushner, THIS JOURNAL, **65**, 1963 (1943).

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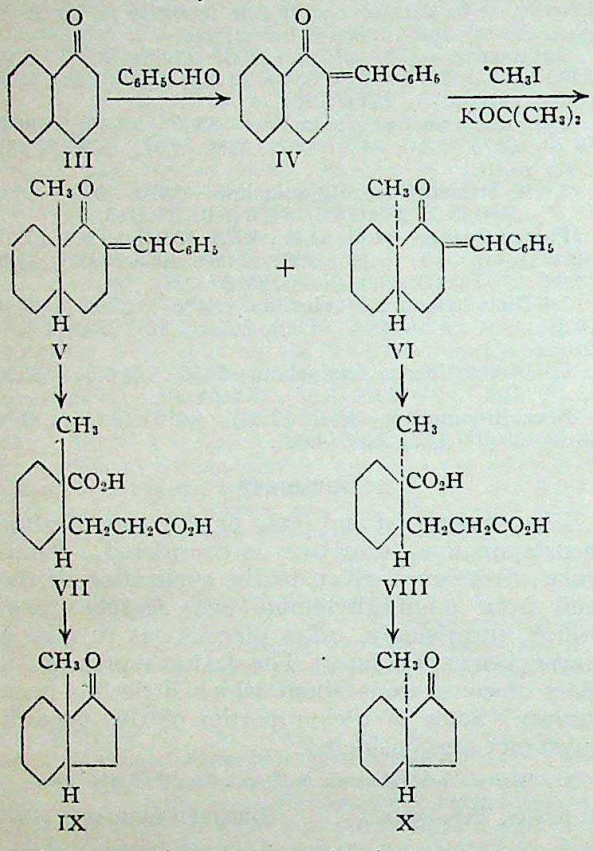
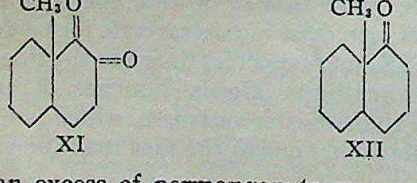
configuration of the steroids has not yet been established unequivocably.



In a previous communication[1] was described a practicable preparation of the two stereoisomeric forms of 2-benzal-9-methyldecalone-1 from decalone-1 (III → VI). In the present work these benzal derivatives were found to be very susceptible to oxidative degradation by potassium permanganate in acetone solution. With the amount of oxidizing agent calculated to produce the α-diketone XI a mixture of starting material and acidic substances was obtained. None of XI was found even when the reaction was conducted at 0°. This suggests that under the conditions employed, the diketone, if formed, is more sensitive to oxidation than the benzalketone.



When an excess of permanganate was employed the benzal derivatives V and VI were converted into the dibasic acids VII and VIII, respectively, and benzoic acid. For the purpose of preparing the hydrindones it was found unnecessary to isolate these acids. Thus by distillation from a small amount of barium oxide[12] the crude acidic fractions from the oxidation gave the 8-methylhydrindanones IX and X isolated as the semicarbazones in over-all yields of 35 and 55%, respectively. The pure ketones were obtained by steam distillation of these derivatives in the presence of oxalic acid.

From the benzal derivative, m. p. 104°, which formerly[1] was converted to the 9-methyldecalone-1 (XII) of *cis* (probable[8]) configuration, was obtained the well-known[4-11] *cis*-8-methylhydrindanone-1. This relationship between the two homologous ketones is consistent with the previous demonstration[8] that they belong to the same stereochemical series. From the isomeric benzal derivative, m. p. 94°, was produced the stereoisomeric 8-methylhydrindanone-1 (configuration provisionally *trans*) which has been obtained through a different synthesis by Bachmann and Kushner.[11] Their description of the new ketone (which was published since the completion of the present work), is in good agreement with the current findings. A comparison of the two stereoisomeric ketones and derivatives is found in Table I.

TABLE I[a]

8-METHYLHYDRINDANONE-1[b]

		cis[c]	*trans*[c]
B. p.	°C.	106	109
	Mm.	20	20
M. p., °C.		34.5–36	...
Semicarbazone, m. p., °C.		224.5–225.5	242–243
Oxime, m. p., °C.		87–88	115–115.5
2,4-Dinitrophenylhydrazone, m. p., °C.		140.5–141	146.5–147 153.5–154[d]

[a] All melting points are corrected. [b] The comparison of melting and boiling points with those which have been reported previously may be found in the experimental part of this paper. [c] Probable configuration. [d] Double melting point.

The difference which has been observed between members of the *cis* and *trans* series with respect to reactivity of the carbonyl group[1] is consistently carried over to the hydrindanones as shown by the fact that the so-called *trans* substance forms the semicarbazone with marked rapidity relative to its stereoisomer. As with the 9-methyldecalones ordinary molecular models fail to show any pronounced difference in degree of hindrance of the carbonyl group. The chemical distinction, however, is quite significant, and if generally applicable, it may prove to be useful in the problem of determining the ring C/D configuration of the steroids.

Experimental Part[13]

cis-8-Methylhydrindanone-1 (IX).—Twelve and one-half grams (a 5% excess) of powdered potassium permanganate was added gradually to a cooled and mechanically stirred solution of 7.20 g. of *cis*-2-benzal-9-methyl-

(12) The pyrolytic cyclization of the acids VII and VIII was used rather than the Dieckmann method principally because of the simplicity of manipulation. The latter method should be useful, however, particularly when applied to larger molecules. *Cf.* Bachmann, Cole and Wilds, THIS JOURNAL, **62**, 824 (1940).

(13) (a) All melting points are corrected. (b) The configurations of the substances described herein are provisional.

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decalone-1[1] (m. p. 99–102°) in 250 cc. of acetone. The rate of addition was controlled so that the temperature was maintained between 2 and 4°. After the addition was complete, stirring was continued for about one hour at 0°; then the solvent was evaporated in a stream of air and replaced by water. This mixture was chilled (ice–salt bath) and stirred mechanically while dilute sulfuric acid (20 cc. of concentrated acid in 20 cc. of water) was added followed by 20 cc. of a saturated solution of sodium bisulfite. The colorless mixture was extracted thoroughly with several portions of ether, and the latter solution was in turn extracted with portions of saturated sodium bicarbonate solution. Evaporation of the ether yielded 0.88 g. of a semicrystalline neutral fraction which consisted mainly of starting material. Acidification of the combined aqueous extracts yielded an oily mixture of the dicarboxylic acid VII and benzoic acid. In one experiment the benzoic acid was removed by steam distillation, leaving *cis*-β-(2-carboxy-2-methylcyclohexyl)-propionic acid (VII) as an oil which solidified on standing, m. p. 93–97°. As reported by Burnop and Linstead, reference 9 (footnote p. 721), recrystallization was difficult. The m. p. of once recrystallized material was 99.5–103°. The pure substance is reported to melt at 108–109°.[9] The mixture of organic acids was extracted with ether, washed with water, saturated salt solution and dried over anhydrous sodium sulfate. Evaporation of the ether left 7 to 8 g. of crude acid fraction which was mixed with 0.35 g. of barium oxide and pyrolyzed according to previous procedures[5,7] in a two-bulb flask at 300–320° for one to two hours. The colorless distillate which had partially solidified (benzoic acid) was dissolved in ether and extracted with a saturated solution of sodium bicarbonate which on acidification yielded benzoic acid. The ether solution was washed with saturated salt solution, dried over anhydrous potassium carbonate and the solvent was removed through a short Vigreux column. The residue which had a strong camphor-like odor was dissolved in 15 to 20 cc. of methanol, 3.0 g. of semicarbazide hydrochloride and 3.0 cc. of pyridine were added, and the mixture refluxed for one hour during which the semicarbazone gradually precipitated. After the addition of a little water and cooling 1.97 g. of material m. p. 221–222.5° (dec.) was obtained. An additional 0.10 g., m. p. 208–215°, was obtained from the mother liquors, making the total yield 35%. A sample of the semicarbazone recrystallized to constant m. p. from methanol formed small colorless blades, m. p. 224.5–225.5° (dec.) (reported m. ps. range from 213°[4,11] to 224–225°[11]).

The free ketone was obtained easily in practically quantitative yield by distillation of an aqueous solution of oxalic acid containing a suspension of the semicarbazone, m. p. 221–222.5° (dec.). The distillate contained the oily colorless ketone which solidified on standing in ice. Ether extraction followed by distillation gave *cis*-8-methylhydrindanone-1 of constant boiling point, 106° (20 mm.); m. p. 34.5–36° (reported m. ps. range from 33–34°[5] to 39.5°[10]). In agreement with the observation of Elliott and Linstead[8] the semicarbazone formed readily only on heating.

The **oxime** of *cis*-8-methylhydrindanone-1 was prepared in methanol with hydroxylamine hydrochloride and pyridine. The crude product was sublimed at 65–70° (0.1 mm.) and recrystallized twice from aqueous methanol. The colorless crystals melted at 87–88°. Bachmann and Kushner[11] give m. p. 85.5–87°.

Anal. Calcd. for $C_{10}H_{17}ON$: C, 71.81; H, 10.25. Found: C, 71.60; H, 9.92.

The **2,4-dinitrophenylhydrazone** of IX formed short orange needles from methanol, m. p. 140.5–141°.

Anal. Calcd. for $C_{16}H_{20}O_4N_4$: C, 57.82; H, 6.07. Found: C, 57.87; H, 6.19.

trans-**8-Methylhydrindanone-1** (X) was prepared by essentially the same procedure which is described above for the *cis* isomer. For the oxidation of 16.56 g. of *trans*-2-benzal-9-methyldecalone-1 (m. p. 92–93.5°) 250 cc. of acetone and 31.6 g. (a 15% excess) of potassium permanganate were used. The larger excess of oxidizing agent seemed to improve the reaction; only a negligible amount of neutral material remained. After the addition of the sulfuric acid (50 cc. concentrated acid and 50 cc. water) and the sodium bisulfite solution (50 cc.) the dibasic acid VIII and benzoic acid remained as a colorless precipitate which was filtered, dissolved in sodium bicarbonate solution, filtered, and reprecipitated with hydrochloric acid. The filtrate from this operation was combined with the original filtrate from the oxidation step and worked up by extraction as in the previously described procedure. (This method of working up the organic acids in two fractions seemed desirable because of the low solubility of the dibasic acid VIII in non-polar solvents.) The additional oily acidic material thus obtained was combined with the above solid fraction, and 0.8 g. of barium oxide was added for the pyrolysis. In this preparation the crude distillate from the pyrolysis was treated directly, without removal of the benzoic acid, with 50 cc. of ethanol, 7 g. of semicarbazide hydrochloride and 15 cc. of pyridine. The insoluble semicarbazone began to precipitate after two minutes' heating on the steam-bath. After one hour the mixture was cooled, filtered and washed thoroughly with water; yield 7.39 g. of colorless crystals, m. p. 243–244° (dec.). From the mother liquors was obtained an additional 0.16 g. of good material, m. p. 239–242° (dec.), making the total yield 55%. Hydrolysis of the semicarbazone as described above gave *trans*-8-methylhydrindanone-1 of constant b. p. 109° (20 mm.), $n^{26}D$ 1.4800, d^{26}_4 0.9793, M_D (found) 44.16, M_D (calcd.) 43.99. Bachmann and Kushner[11] report, b. p. 108–109° (20 mm.), $n^{25.8}D$ 1.4807. The ketone had the characteristic camphor-like odor and reformed the semicarbazone readily at room temperature.

Anal. Calcd. for $C_{10}H_{16}O$: C, 78.89; H, 10.60. Found: C, 78.78; H, 10.66.

The **semicarbazone** of *trans*-8-methylhydrindanone-1 on recrystallization from ethanol formed colorless plates, m. p. 242–243° (dec.) (reported, 234°[11]).

Anal. Calcd. for $C_{11}H_{19}ON_3$: C, 63.13; H, 9.15. Found: C, 62.87, H, 9.01.

The **oxime** was purified by sublimation at 70–80° (0.1 mm.) and recrystallization from aqueous methanol. It formed small colorless plates, m. p. 115–115.5° (reported, 113–115.5°[11]).

Anal. Calcd. for $C_{10}H_{17}ON$: C, 71.81; H, 10.25. Found: C, 72.30; H, 10.21.

The **2,4-dinitrophenylhydrazone** formed orange blades from methanol–ethyl acetate. It melted sharply at 146.5–147° and resolidified as the temperature was raised, remelting at 153.5–154°.

Anal. Calcd. for $C_{16}H_{20}O_4N_4$: C, 57.82; H, 6.07. Found: C, 58.16; H, 6.00.

trans-β-**(2-Carboxy-2-methylcyclohexyl)-propionic Acid (VIII).**—A sample of the solid reprecipitated acid mixture obtained in the above oxidation was triturated with benzene in which the dicarboxylic acid VIII is relatively insoluble. The latter was filtered, washed with benzene and recrystallized to constant m. p. from aqueous methanol and then once from ethyl acetate. It formed colorless pointed blades, m. p. 179–180°.

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.80; H, 8.41.

Summary

A method is described for obtaining *cis*- and *trans*-8-methylhydrindanone-1 from decalone-1.

MADISON, WISCONSIN RECEIVED OCTOBER 1, 1943

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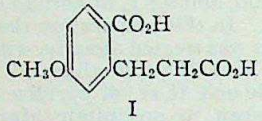
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

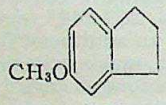
Derivatives of 5-Methoxyhydrindene and 6-Methoxytetralin. Synthesis of β-(2-Carboxy-5-methoxyphenyl)-propionic Acid[1]

BY WILLIAM S. JOHNSON, JOHN M. ANDERSON AND WESLEY E. SHELBERG

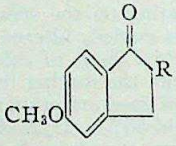
For the synthesis of β-(2-carboxy-5-methoxyphenyl)-propionic acid (I) which was desired as an intermediate in some projected syntheses of steroid types, the readily available[2] 5-methoxyhydrindene (II) and the similarly accessible[3] 6-methoxytetralin (VI) were chosen as promising starting materials.



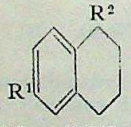
I



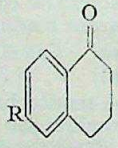
II



III (R = H)
IV (R = Br)
V (R = CN)



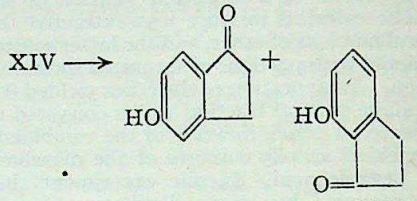
VI (R^1 = OCH_3, R^2 = H)
VII (R^1 = H, R^2 = $OCOCH_3$)
VIII (R^1 = OCH_3, R^2 = $OCOCH_3$)
IX (R^1 = OCH_3, R^2 = OH)



X (R = OCH_3)
XI (R = H)

Since it has been shown[4] that 6-methoxytetralin (VI) is converted by oxidation with chromic oxide into 6-methoxytetralone-1 (X) in yields up to 70%,[3b] it was hoped that a similar selective oxidation would take place in the case of the five-membered ring homolog II to produce 5-methoxyhydrindone-1 (III). This indeed was realized, and conditions were found whereby the pure ketone (III) was obtained in 75–80% yields. The identity of the substance was confirmed by comparison with material prepared by a conventional synthesis involving no new compounds, but describing a new series of reactions[5]

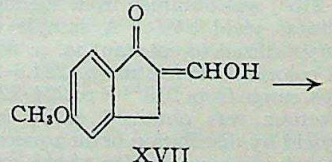
m-HOC_6H_4CHO (XII) ⟶
m-$HOC_6H_4CH{=}CHCO_2H$ (XIII) ⟶
m-$HOC_6H_4CH_2CH_2CO_2H$ (XIV)



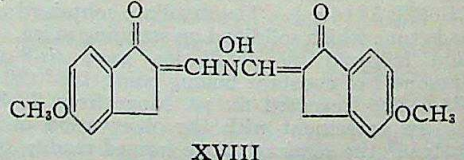
XV (85%) XVI (13%)

The cyclization of *m*-hydroxyhydrocinnamic acid (XIV) with hydrogen fluoride[6] gave a 98% yield of a mixture of isomeric ketones easily and quantitatively separated by steam distillation. The non-volatile 5-hydroxyhydrindone-1 (XV) was formed in preponderance (yield 85%), and methylation afforded the ether III, identical with the oxidation product of II described above.

It was planned to degrade 5-methoxyhydrindone-1 to the desired acid (I) by a series of reactions employed by Lapworth[7] to open the ketonic ring of camphor to obtain homocamphoric acid. This method has been used also by Bardhan[8] to open ring D of estrone, and by Robinson and Rydon[9] to cleave the analogous ring of a synthetic product related to equilenin. The Claisen condensation of III with ethyl formate gave 2-hydroxymethylene - 5 - methoxyhydrindone - 1 (XVII) in 98% yield. This in glacial acetic acid



XVII



XVIII

condensed with hydroxylamine to give—instead of the expected[7,8,9] nitrile (V)—a 90% yield of an insoluble orange compound, $C_{22}H_{19}O_5N$, probably bis - (5 - methoxy - 1 - keto - 2 - hydrindylidenemethyl)-hydroxylamine (XVIII).[10] The condensation product has an acidic hydrogen, and on

(1) This work was assisted in part by a grant from the Wisconsin Alumni Research Foundation.

(2) A. H. Cook and Linstead, *J. Chem. Soc.*, 946 (1934).

(3) (a) Schroeter, *Ann.*, **426**, 83 (1922); (b) Burnop, Elliott and Linstead, *J. Chem. Soc.*, 727 (1940).

(4) Goertz, Dissertation, Berlin, p. 17 (1924); German Patent 397,150 [*Chem. Zentr.*, **95**, II, 1404 (1924)].

(5) *Cf.* the syntheses of (a) Ingold and Piggott, *J. Chem. Soc.*, 1469 (1923), and (b) Brand and Horn, *J. prakt. Chem.*, [2] **115**, 351 (1927).

(6) Fieser and Hershberg, THIS JOURNAL, **61**, 1272 (1939).

(7) Lapworth, *J. Chem. Soc.*, 1053 (1900).

(8) Bardhan, *ibid.*, 1848 (1936).

(9) Robinson and Rydon, *ibid.*, 1394 (1939).

(10) During a study of the condensation of hydroxylamine with a number of hydroxymethylene ketones under various conditions we have come to the conclusion that the product obtained by Robinson and Rydon (reference 9) and presumed by them to be a nitrile, probably was a dimolecular condensation product like XVIII. The formation and alkaline cleavage of compounds of this type will be considered in a subsequent communication.

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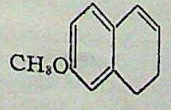
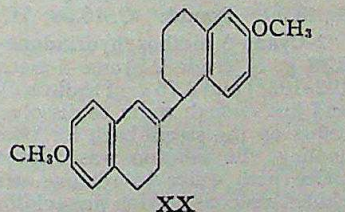
dissolving in alkali gives an intense purple color which is gradually dispelled on warming. Prolonged heating of XVIII with one equivalent of hydroxylamine in alkaline solution was accompanied by the evolution of ammonia and the formation of β-(2-carboxy-5-methoxyphenyl)-propionic acid (I) in 61% yield. Lower yields were obtained in the absence of hydroxylamine. The structure of the acid was confirmed by distillation with barium oxide to regenerate 5-methoxyhydrindone-1. The mechanism of the degradation of XVIII to the dicarboxylic acid (I) may involve the nitrile (V) as an intermediate,[10] although we have not yet been able to prepare V from either XVIII or the hydroxymethylene derivative XVII. The nitrile could be obtained, however, in 73% yield from 2-bromo-5-methoxyhydrindone-1 (IV), and on alkaline hydrolysis afforded an 88% yield of the acid (I).

Preliminary attempts to prepare β-(2-carboxy-5-methoxyphenyl)-propionic acid by direct oxidation of 6-methoxytetralin (VI) or of the tetralone derivative X using acid permanganate[11] or chromic acid were so unpromising that this method of attack was abandoned. A more favorable approach was found in the oxidation of VI with lead tetraacetate. Since it has been shown[12] that this reagent reacts with tetralin to give 1-acetoxytetralin (VII), it was expected that the 6-methoxy derivative (VI) also would be acetoxylated. This indeed was realized, the reaction proceeding at room temperature, and a monoacetoxy derivative was obtained in 62% yield. Since the methoxyl group of VI activates the hydrogen atoms on the carbon atom in the *para* position toward chromic acid oxidation,[4] it was presumed that lead tetraacetate had attacked the same position to produce 1-acetoxy-6-methoxytetralin (VIII). This substance exhibited a remarkable tendency to lose acetic acid, also probably due to the activating effect of the *p*-methoxyl substituent. The decomposition was catalyzed by mineral acid, and 7-methoxy-1,2-dihydronaphthalene (XIX) was thus obtained in 87% yield as a liquid, b. p. 95° (2–3 mm.). A



XIX



XX

solid, m. p. 73–74°, presumed to have the structure XIX has been described by Long and Burger.[13]

Their substance was prepared by the action of hydrobromic acid on 1-hydroxy-6-methoxytetralin (IX).[14] The structural similarity between XIX and anethole, which is known to dimerize in the presence of mineral acids,[15] suggested that XIX would not be stable in such a medium. Indeed when our liquid compound was treated with hydrobromic acid it was converted into a solid dimer, m. p. 75.5–76.5°, apparently identical with the previously reported substance. By analogy to the anethole dimer of known structure, the present substance may be formulated tentatively as XX.

Oxidation of XIX with cold permanganate in acetone solution gave β-(2-carboxy-5-methoxyphenyl)-propionic acid (I) in 40% yield. The identity of this product established the structure of XIX and, in turn, that of the acetoxylation product VII.

Experimental Part[15a]

5-Methoxyhydrindone-1 (III). (a) **By the Oxidation of 5-Methoxyhydrindene (II).**—A solution of chromic anhydride (28 g.) in 14 cc. of water and 80 cc. of glacial acetic acid was added slowly with mechanical stirring to a chilled solution of 26.2 g. of 5-methoxyhydrindene (prepared[16] from hydrindene according to A. H. Cook and Linstead[2]) in 160 cc. of glacial acetic acid. The temperature was maintained between 5 and 10° during the addition (one hour). The mixture was kept cool for five hours and then allowed to come to room temperature. After standing overnight most of the acetic acid was removed at 40° under diminished pressure, water was added, and the oil extracted with ether. The combined extracts were washed cautiously with 10% potassium carbonate solution until all of the acid was removed, then with concentrated sodium chloride solution, and finally dried over anhydrous potassium carbonate. The product on evaporation of the ether distilled at 130–132° (2–3 mm.), giving a yellowish oil which presently solidified, m. p. 95–108°; yield 22.3 g. (78%). A single crystallization from dilute methanol gave 20.0 g. of long colorless prismatic rods, m. p. 108–110°. A sample was recrystallized from benzene to a constant m. p. 109.8–110.5° (literature m. p. 110°[5a] and 108°[5b]). This material as well as the semicarbazone, m. p. 240–241° (dec.) (literature m. p. 239°[5a]) showed no depression of m. p. on mixing with the specimens prepared as described below.

(b) **By the Cyclization of *m*-Hydroxyhydrocinnamic Acid (XIV).**—*m*-Hydroxycinnamic acid (XIII) was prepared in 91% yield from *m*-hydroxybenzaldehyde by heating the latter (20.9 g.) with malonic acid (31.2 g.) in pyridine (32 cc.) and piperidine (8 drops) for four and one-half hours on the steam-bath. Acidification with dilute hydrochloric acid yielded 25.5 g. of XIII, m. p. 192–194°. Material once recrystallized from dilute methanol solution had the m. p. 194–195° (literature m. p. 191°[5a,17] and 193°[18]). This was reduced in methanol solution with platinum oxide to give a quantitative yield of *m*-hydroxy-

(11) The permanganate oxidation of tetralin to *o*-carboxyhydrocinnamic acid was reported by Bamberger and Kitschelt, *Ber.*, **23**, 1561 (1890). Later, however, v. Braun and Deutsch, *ibid.*, **45**, 1267 (1912), produced evidence indicating that the previous work had been carried out on impure tetralin containing some dihydronaphthalene which was actually the principal source of the dicarboxylic acid.

(12) Criegee, *Ann.*, **481**, 263 (1930).

(13) Long and Burger, *J. Org. Chem.*, **6**, 852 (1941).

(14) Salzer, *Z. physiol. Chem.*, **274**, 39 (1942), reported material b. p. 103° (1 mm.) from the dehydration of IX. The reactions of this material indicated that it was, at least in part, 7-methoxy-1,2-dihydronaphthalene, but no analytical data were given. Compare German Patent 708,114 [*Chem. Abs.*, **37**, 2748 (1943)] and U. S. Patent 2,223,664 [*Chem. Abs.*, **35**, 1808 (1941).]

(15) Goodall and Haworth, *J. Chem. Soc.*, 2482 (1930).

(15a) All melting points are corrected.

(16) The preparation of 5-methoxyhydrindene was carried out by Mr. E. Goldstein who also performed some of the preliminary oxidation experiments.

(17) Tiemann and Ludwig, *Ber.*, **15**, 2043 (1882).

(18) Posner, *J. prakt. Chem.*, [2] **82**, 425 (1910).

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hydrocinnamic acid (XIV), m. p. about 99°. The pure acid, m. p. 111.8–112.5° (literature m. p. 111°[17]) was obtained by distillation under diminished pressure and crystallization from benzene.

For the cyclization 3.31 g. of pure XIV was treated in a platinum vessel with approximately 100 g. of anhydrous hydrogen fluoride.[6] On standing overnight the yellow solution evaporated, leaving a colorless crystalline mass which was submitted to steam distillation. 7-Hydroxyhydrindone-1 (XVI) crystallized from the distillate which was saturated with sodium chloride and extracted with ether. This extract after drying over anhydrous sodium sulfate and evaporation yielded 0.40 g. (13%) of almost colorless material, m. p. 109–111°. Recrystallized from methanol–petroleum ether, it formed colorless prisms, m. p. 110.5–111.5° (literature m. p. 111°[19,5]) and gave an intense violet color with ferric chloride.[19,5] Practically pure crystalline 5-hydroxyhydrindone-1 (XV) remained in the distilling flask from the steam distillation, and amounted to 2.50 g. (85% yield), m. p. 184–185°. Recrystallized from dilute alcohol (Norit) it formed almost colorless prisms, m. p. 184–185.5° (literature m. p. 182°[5a] and 183°[19]); semicarbazone, m. p. 222–222.5° (dec.) (introduced in bath at 215°) (literature m. p. 223°[19]). The **acetate** of XV crystallized from ether–petroleum ether in colorless plates, m. p. 92.8–93.2°.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.66; H, 5.55.

When the cyclization was performed on distilled but unrecrystallized *m*-hydroxyhydrocinnamic acid (yield 90–95%) the total yield of ketones was 94% instead of 98%.

Crude 5-hydroxyhydrindone-1 (11 g.) prepared as above was converted into the methyl ether III by the action of dimethyl sulfate in alkaline solution. The yield of crude III was 11.6 g. (97%), m. p. about 110° with previous softening. Recrystallized from benzene it melted at 110–110.5°; semicarbazone m. p. 240–241° (dec.) (*cf.* the product prepared in (a) above). The **2,4-dinitrophenylhydrazone** formed red needles from chloroform, m. p. 282–284° (dec.) (uncor.).

Anal. Calcd. for $C_{16}H_{14}O_5N_4$: N, 16.37. Found: N, 16.45.

The ***p*-nitrophenylhydrazone** crystallized from dilute alcohol in small orange needles, m. p. 209–211.5° (dec.) (introduced in bath at 200°).

Anal. Calcd. for $C_{16}H_{15}O_3N_3$: N, 14.14. Found: N, 14.25, 14.31.

2-Hydroxymethylene-5-methoxyhydrindone-1 (XVII).[20]—A solution of sodium methoxide prepared from 0.74 g. (0.032 mole) of sodium and 10 cc. of methanol was evaporated to dryness at 200° under reduced pressure. The colorless cake was broken up, and a solution of 2.38 g. (0.032 mole) of ethyl formate in 16 cc. of dry benzene was added, and the system evacuated and filled with nitrogen. To the cooled mixture was added with swirling, a solution of 2.60 g. (0.016 mole) of 5-methoxyhydrindone-1 in 20 cc. of dry benzene. A precipitate having a pink tinge gradually formed, and after four to five hours slightly below room temperature it was hydrolyzed with cold water, and a few cc. of ether was added to minimize emulsion formation. The organic layer was washed once with water and with dilute sodium hydroxide. The aqueous portions were combined, washed with ether, and acidified with ice and hydrochloric acid. Almost pure 2-hydroxymethylene-5-methoxyhydrindone-1 precipitated; yield 2.98 g. (98%), m. p. 136.5–138°. Recrystallized from benzene it formed almost colorless plates, m. p. 138–138.5° (dec.), which gave an intense purple color with ferric chloride.

Anal. Calcd. for $C_{11}H_{10}O_3$: C, 69.46; H, 5.30. Found: C, 69.65; H, 5.53.

The **bis-(2,4-dinitrophenylhydrazone)** of XVII crystallized from bromobenzene in short, orange needles, m. p. 223–226° (dec.) (introduced in bath at 220°).

Anal. Calcd. for $C_{23}H_{18}O_9N_8$: N, 20.36. Found: N, 20.40.

2-Hydroxymethylene-5-methoxyhydrindone-1, on melting, turns dark red and slowly gives off a gas. This decomposition represents the elimination of formic acid between two molecules of XVII to form a condensation product of the type described by Ruhemann and Levy.[21] The product, probably **2-(5-methoxy-1-keto-2-hydrindylidenemethyl)-5-methoxyhydrindone-1**, was obtained after heating for one hour at 140–150°. It crystallized from benzene–petroleum ether or from glacial acetic acid in orange prisms, m. p. 213–215° (dec.) (introduced in bath at 205°).

Anal. Calcd. for $C_{21}H_{18}O_4$: C, 75.43; H, 5.43. Found: C, 75.82; H, 5.51.

Bis-(5-methoxy-1-keto-2-hydrindylidenemethyl)-hydroxylamine (XVIII).—A solution of 1.42 g. (0.0075 mole) of 2-hydroxymethylene-5-methoxyhydrindone-1 in 20 cc. of glacial acetic acid was treated with 0.59 g. (0.0085 mole) of powdered hydroxylamine hydrochloride. Although the latter is sparingly soluble, the reaction started presently as indicated by coloring of the solution followed by the formation of a red precipitate. The mixture was stirred or shaken mechanically for twenty-four hours, and the product filtered and triturated with water which caused the color to change from red to orange. The yield of dry material amounted to 1.27 g. (90%), m. p. 190–204° (dec.) (introduced in bath at 180°). It crystallized from pyridine in the form of orange needles, m. p. 216–218° (dec.) (introduced in bath at 214°). The same m. p. was observed in an evacuated tube.

Anal. Calcd. for $C_{22}H_{19}O_5N$: C, 70.01; H, 5.07; N, 3.71. Found: C, 69.93; H, 5.14; N, 3.62.

The condensation product XVIII is sparingly soluble in the common organic solvents. It dissolves in dilute alkali to give an intense violet color like that of permanganate solution.

2-Bromo-5-methoxyhydrindone-1 (IV).—A solution of 5-methoxyhydrindone-1 (1.68 g.) in 200 cc. of anhydrous ether was treated with 0.60 cc. of bromine according to the procedure of Wilds[22] for the bromination of 1-keto-1,2,3,4-tetrahydrophenanthrene. A purer product was obtained when the reaction mixture was allowed to stand overnight after the addition of the bromine. The crude material amounted to 2.38 g. (95% yield), m. p. 102–105°. A sample recrystallized for analysis from benzene formed colorless prisms, m. p. 107.8–108.5°.

Anal. Calcd. for $C_{10}H_9O_2Br$: C, 49.81; H, 3.77. Found: C, 49.93; H, 3.77.

2-Bromo-5-methoxyhydrindone-1 2,4-dinitrophenylhydrazone formed red needles from chloroform, m. p. 202.5–204.5° (dec.) (introduced in bath at 195°).

Anal. Calcd. for $C_{16}H_{13}O_5N_4Br$: C, 45.62; H, 3.12; N, 13.30. Found: C, 45.58; H, 3.11; N, 13.48.

2-Cyano-5-methoxyhydrindone-1 (V).—A solution of 2.38 g. of crude 2-bromo-5-methoxyhydrindone-1 (m. p. 102–105°) and 4.76 g. of sodium cyanide in 70 cc. of alcohol and just enough water to dissolve the salt, was allowed to reflux on the steam-bath for twenty-five minutes. After cooling, the solution was diluted with water, extracted twice with ether to remove neutral material, and the chilled aqueous portion was acidified with cold hydrochloric acid. The oily cyano ketone which separated was extracted with chloroform, and this solution was clarified with Norit, then extracted with small portions of 5% potassium hydroxide solution until a test portion no longer gave a precipitate on acidification. Acidification of the combined cold aqueous layers gave 1.34 g. (73%) of 2-cyano-5-methoxyhydrindone-1 which soon solidified, m. p. 90–92.5°. The pure material crystallized from alcohol in tan plates, m. p. 96–96.5°; ferric chloride test negative.

(19) v. Auwers and Hilliger, *Ber.*, **49**, 2410 (1916).

(20) An adaptation of the procedure of Bachmann and Thomas, THIS JOURNAL, **63**, 598 (1941), for the condensation of tetralone-1 with dimethyl oxalate.

(21) Ruhemann and Levy, *J. Chem. Soc.*, 2542 (1912).

(22) Wilds, THIS JOURNAL, **64**, 1421 (1942).

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Anal. Calcd. for $C_{11}H_9O_2N$: C, 70.57; H, 4.86; N, 7.48. Found: C, 70.70; H, 4.78; N, 7.50.

The 2,4-dinitrophenylhydrazone of V formed small red crystals from glacial acetic acid, m. p. 217.5–219.5° (dec.) (introduced in bath at 214°).

Anal. Calcd. for $C_{17}H_{13}O_5N_5$: N, 19.07. Found: N, 19.02.

The semicarbazone of V formed buff-colored microscopic prisms from dilute alcohol, m. p. 219.5–220° (dec.) (introduced in bath at 215°).

Anal. Calcd. for $C_{12}H_{12}O_2N_4$: N, 22.94. Found: N, 22.99, 23.01.

1-Acetoxy-6-methoxytetralin (VIII).—A suspension of 100 g. of lead tetraacetate[23] in 150 cc. of glacial acetic acid (previously distilled from permanganate) containing 33 g. of 6-methoxytetralin[3] was stirred at room temperature for sixteen hours. The reaction, at first slightly exothermic, was controlled by external cooling. The excess oxidizing agent was decomposed with a small amount of glycerol[24] (using the starch-iodide test) and most of the solvent removed under reduced pressure. The oil obtained on dilution with water was extracted with ether, washed with water followed by successive portions of 10% sodium carbonate solution to remove the acetic acid. Two washings with 2% sodium hydroxide solution removed a small amount of dark material (phenolic ?). The ether solution was then washed with water, saturated sodium chloride solution, and dried over anhydrous potassium carbonate. The oil obtained on evaporation was roughly fractionated through a short Vigreux column, and the pale yellow portion, b. p. 132–139° (1–2 mm.), was 1-acetoxy-6-methoxytetralin; yield 27.9 g. (62%). The analytical sample boiled at 118.5° (0.5 mm.); $n^{25}D$ 1.5348.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32. Found: C, 71.21; H, 7.19.

This ester is quite unstable, having a pronounced tendency to lose acetic acid to form 7-methoxy-1,2-dihydronaphthalene (XIX). Even on standing, the substance gradually darkens and develops the odor of acetic acid. Since the decomposition is catalyzed by mineral acid, all glassware to come in contact with the ester must be freed of traces of acid by washing with alkali.

7-Methoxy-1,2-dihydronaphthalene (XIX).—When 1-acetoxy-6-methoxytetralin (9.4 g.) was heated at 120° (22 mm.) with a crystal of potassium acid sulfate the elimination of acetic acid was complete in a few minutes. The remaining product distilled at 85–86° (about 1 mm.); yield 5.9 g. (87%). Redistilled material had the b. p. 94–95° (2–3 mm.); 75–76° (0.3–0.4 mm.), $n^{26.5}D$ 1.5837, $d_4^{26.5}$ 1.0561, M_D (found) 50.75, M_D (calcd.) 48.37.

Anal. Calcd. for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 82.48; H, 7.48.

The exaltation of the molecular refractivity of XIX is in close agreement with that predicted from data on similar compounds.[25] The exaltation for 1,2-dihydronaphthalene is 1.47. The additional influence of the methoxyl group *para* to the olefinic bond may be estimated from the increase (0.60) in the exaltation produced in the case of styrene by introduction of a *p*-methoxyl group. The expected exaltation for 7-methoxy-1,2-dihydronaphthalene therefore would be 2.07. The observed value is 2.38.

Dimeric 7-Methoxy-1,2-dihydronaphthalene (possibly formula XX).—Four g. of XIX was treated with 40 cc. of 48% hydrobromic acid as described by Long and Burger[12] for 1-hydroxy-6-methoxytetralin. The fraction b. p. about 230° (0.5–1 mm.) amounted to 3.3 g. Recrystallization from 40–60° petroleum ether gave 2.8 g. (70% yield) of material, m. p. 73–76°. A sample purified by recrystallization from methanol formed colorless needles, m. p. 75.5–76.5°. Long and Burger give the m. p. 73–74°.

Anal. Calcd. for $C_{22}H_{24}O_2$: C, 82.46; H, 7.55; mol. wt., 320. Found: C, 82.30; H, 7.53; mol. wt., 333 (Rast).

β-(2-Carboxy-5-methoxyphenyl)-propionic Acid (I). (a) From bis-(5-Methoxy-1-keto-2-hydrindylidenemethyl)-hydroxylamine (XVIII).—A solution of 0.500 g. (0.0013 mole) of uncrystallized XVIII and 0.092 g. (0.0013 mole) of hydroxylamine hydrochloride in 85 cc. of 2% aqueous sodium hydroxide was boiled under reflux. The deep purple color gradually faded, and usually within forty minutes the solution was light-red. Ammonia was slowly evolved as the heating was continued for four days. The filtered solution was acidified and the precipitated acid extracted with ether from which it was recovered by extraction with 5% sodium bicarbonate solution. Acidification of the combined aqueous extracts yielded 0.360 g. (61%) of yellowish β-(2-carboxy-5-methoxyphenyl)-propionic acid, m. p. 194–199° with previous softening. A pure sample of the acid was obtained by sublimation under reduced pressure and crystallization from alcohol. It formed colorless needles, m. p. 203.5–204°.

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.40. Found: C, 58.94; H, 5.44.

(b) By Hydrolysis of 2-Cyano-5-methoxyhydrindone-1 (V).—A solution of 1.07 g. (0.006 mole) of the crude nitrile in 170 cc. of 5% aqueous potassium hydroxide was boiled under reflux until ammonia was no longer evolved (forty-eight hours). The dibasic acid was isolated from the alkaline solution just as described in (a). The yield of colorless material was 1.13 g. (88%), m. p. 201–202.5°; after sublimation under reduced pressure and recrystallization from water it formed colorless needles, m. p. 201.5–203.7°.

(c) By Oxidation of 7-Methoxy-1,2-dihydronaphthalene (XIX).—Powdered potassium permanganate (3.62 g.) was added in portions with stirring to a solution of 1.38 g. of XIX in 30 cc. of acetone. During the addition (twenty minutes) the temperature was maintained between 0 and 3°, then the mixture was stirred at room temperature for about forty minutes. The acetone was removed, dilute sulfuric acid added followed by sodium sulfite to dissolve the manganese dioxide, and the residue extracted with ether. This solution was extracted with 5% sodium bicarbonate solution which on acidification yielded 0.78 g. (40%) of the dibasic acid (I), m. p. 195–199° with previous softening. A sample purified by clarification of a solution of the sodium salt with Norit, followed by recrystallization from alcohol had the m. p. 201–203.5°.

The samples of β-(2-carboxy-5-methoxyphenyl)-propionic acid prepared by the three methods above showed no melting point depressions on mixing.

Cyclization of β-(2-Carboxy-5-methoxyphenyl)-propionic Acid.—Each of the products obtained by the three methods described above was submitted to the following treatment: about 0.2 g. of the acid mixed with a few mg. of barium oxide was distilled slowly in a two-bulb flask. The distillate was dissolved in warm dilute alcohol containing about 2% of sodium bicarbonate. On cooling, crystals of 5-methoxyhydrindone-1 separated, m. p. 108–110°, no depression on mixing with an authentic sample.

Summary

During a search for methods of obtaining β-(2-carboxy-5-methoxyphenyl)-propionic acid several transformations in the 6-methoxytetralin and 5-methoxyhydrindene series have been correlated.

5-Methoxyhydrindone-1 is obtained in good yield by oxidation of 5-methoxyhydrindene. The structure of the ketone was confirmed by com-

(23) A slight modification in the procedure (Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 2nd ed., 1941, p. 436) for the preparation of lead tetraacetate seemed to be advantageous. When the reaction temperature was kept lower (between 40 and 50°) very little darkening occurred, and the crude product was pale yellow. A single recrystallization without the use of Norit gave an excellent yield of colorless material.

(24) Fieser, "Experiments in Organic Chemistry," 1941, p. 438.

(25) v. Auwers, *Ann.*, **413**, 284 (1917); *Ber.*, **46**, 2088 (1913).

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parison with material prepared by a conventional synthesis involving the cyclization of *m*-hydroxyhydrocinnamic acid. Condensation of 2-hydroxymethylene-5-methoxyhydrindone-1 with hydroxylamine hydrochloride in acetic acid yields, instead of the expected nitrile, a dimolecular condensation product which is probably bis-(5-methoxy - 1 - keto - 2 - hydrindylidenemethyl) - hydroxylamine. Alkaline hydrolysis of the latter in the presence of hydroxylamine gives β-(2-carboxy-5-methoxyphenyl)-propionic acid. This acid is also obtained on alkaline cleavage of 2-cyano-5-methoxyhydrindone-1 which can be prepared from 5-methoxyhydrindone-1 through the 2-bromo derivative.

Oxidation of 6-methoxytetralin with lead tetraacetate gives the 1-acetoxy derivative in 62% yield. The latter readily loses the elements of acetic acid to form 7-methoxy-1,2-dihydronaphthalene which forms a crystalline dimer in the presence of hydrobromic acid. Oxidation of the monomeric substance gives β-(2-carboxy-5-methoxyphenyl)-propionic acid.

MADISON, WISCONSIN RECEIVED NOVEMBER 1, 1943

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Morpholinomethyl Derivatives of Urea and Substituted Ureas[1]

BY WELCOME I. WEAVER,[2] J. K. SIMONS[2] AND WILMER E. BALDWIN

The aminomethylation of active hydrogen compounds by primary or secondary amines and formaldehyde has received considerable attention. The work with active methylene compounds, the Mannich reaction, has been reviewed recently,[3] while that with nitrogen compounds has been reported in a number of investigations of amines,[4] imides,[5] amides[6] and thiourea.[7] Einhorn and Spröngerts[8] described the reaction products of diethylaminomethanol and piperidinomethanol with urea. Later Einhorn[9] patented the reaction products of these alcohols with isovalerylurea. More recently there has appeared a patent[10] on the use of several bis-(dialkylaminomethyl)-ureas including bis-(morpholinomethyl)-urea.

The object of the present work was to prepare morpholinomethyl derivatives of urea and a number of substituted ureas and to investigate their behavior under conditions which would bring about cleavage, *e. g.*, reduction, treatment with acid anhydrides, picric acid or alkali.

Monomorpholinomethyl- and bis-(morpholinomethyl)-urea were prepared in yields of 85–95% by the reaction of urea with one or two equivalents of morpholinomethanol in aqueous solution or with paraformaldehyde and morpholine in dioxane. The reaction of dimethylol urea and morpholine gave the bis derivative in a yield of 60%. Methylene-bis-morpholine and urea produced monomorpholinomethylurea in a yield of 33%.

Hydrolysis of these compounds in hot alkaline solution yielded morpholine quantitatively. Zinc and hydrochloric acid reduction of either compound produced N-methylmorpholine. Catalytic reduction of monomorpholinomethylurea under non-hydrolyzing conditions described in the experimental part yielded urea and the calculated anount of N-methylmorpholine.

Monomorpholinomethylurea treated with an excess of acetic anhydride yielded N-acetylmorpholine and a white solid which was provisionally identified by analysis as polymeric dimethylene urea $(—CH_2NCONCH_2—)_x$. Butyric anhydride and monomorpholinomethylurea produced a similar product.

The reaction of picric acid and the morpholinomethylureas in ethanol or water solution formed impure products. Recrystallization progressively changed the melting points until they were near that of morpholine picrate. The hydrolysis indicated by this result is similar to the reported behavior of the morpholinomethyl derivatives of ketones and phenylacetonitrile.[11] It was found that the picrates of both mono- and bis-(morpholino-methyl)-urea could be prepared in glacial acetic acid.

Monomorpholinomethyl derivatives of 18 different substituted ureas were prepared. The N-morpholinomethyl-N′-acetylurea was more stable to hydrolysis than any other urea derivative studied. It formed a picrate stable in water, ethanol and glacial acetic acid, which could be recrystallized without decomposition. Acetic or butyric anhydrides reacted to form N-acetoxymethyl-N′-acetylurea and N-butyroxymethyl-N′-acetylurea, respectively. The acylmorpholine was formed simultaneously.

(1) From a thesis submitted by Welcome I. Weaver in partial fulfillment of requirements for the degree of Doctor of Philosophy, University of Pittsburgh, 1943.

(2) Present address: Plaskon Division, Libbey–Owens–Ford Glass Company, Toledo, Ohio.

(3) Adams, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1942, pp. 303–341.

(4) Henry, *Bull. soc. chim.*, **13**, 157 (1895).

(5) (a) Sach, *Ber.*, **31**, 1230 (1898); (b) Cherbuliez and Sulzer, *Helv. Chim. Acta*, **8**, 567 (1925); (c) Feldman and Wagner, *J. Org. Chem.*, **7**, 31 (1942).

(6) Einhorn, *Ann.*, **342**, 269 (1905).

(7) Morgan and Wells, German Patent 575,114; *C. A.*, **27**, 3483 (1933).

(8) Einhorn and Spröngerts, *Ann.*, **361**, 113 (1908).

(9) Einhorn, German Patent 248,440; *Frdl.*, **12**, 702 (1915).

(10) Burke and Peters, U. S. Patent 2,281,460.

(11) Zief and Mason, *J. Org. Chem.*, **8**, 1 (1943).

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Monomorpholinomethylthiourea was prepared from thiourea and one equivalent of the aminomethanol. Succinimide and phthalimide yielded N-(morpholinomethyl)-succinimide and N-(morpholinomethyl)-phthalimide. The N-morpholinomethyl derivatives of benzenesulfonamide and *p*-toluenesulfonamide were prepared.

The symmetrical structure suggested by Einhorn[9] for the piperidinomethyl derivative of isovalerylurea has been assigned to bis-(morpholinomethyl)-urea and to the monomorpholinomethyl derivatives of the substituted ureas. Morpholinomethanol reacts only with an amido group ($—NH_2$) of a urea where that group is not substituted. Thus symmetrical diphenyl- and dibutylurea failed to react with morpholinomethanol under the same experimental conditions as phenyl- and butylurea. Normal butylurea yielded only a monomorpholinomethyl derivative even though it reacted with an excess of the aminomethanol. Urea formed only bis-(morpholinomethyl)-urea where two, three or four equivalents of morpholinomethanol were allowed to react with urea.

Dimethylol urea, which is the symmetrical derivative, reacted with morpholine to form a bis-(morpholinomethyl)-urea which was identical with the product formed from two (or more) moles of morpholinomethanol.

N-Carbamylmorpholine is an example of a urea in which both hydrogens of one amido group are substituted. It readily formed a monomorpholinomethyl derivative which must have the symmetrical structure.

Experimental Part

General and Preparations of Materials.—Morpholinomethanol was prepared according to the general procedure of Henry.[4] The unpurified product was used directly. Some of the substituted ureas were commercially available, others were prepared by reported methods.[12] β-Benzoyloxyethylurea, a new substituted urea, was prepared as follows: β-benzoyloxyethylamine hydrochloride[13] from benzoyl chloride and ethanolamine hydrochloride was heated with an equivalent of urea at 130–140°; the product was isolated by washing with water and purified by recrystallizing from ethanol. The melting point was 122–124°; yield, 36%.

Anal. Calcd. for $C_{10}H_{12}N_2O_3$: N, 13.5. Found: N, 13.6.

All melting points were determined with an Anschütz thermometer and were not corrected for stem immersion.

Monomorpholinomethylurea.—A mixture of urea (0.5 mole) and an aqueous solution of morpholinomethanol (0.5 mole) was heated to 80–90°. After the vigorous exothermic reaction took place, the mass was cooled to precipitate a white crystalline solid; yield of crude product was 92%. It was obtained in needle crystals, m. p. 162–163°, by recrystallization from a mixture of ethanol and acetone.

Combination of equivalent quantities of urea, morpholine and paraformaldehyde in boiling dioxane gave the same product in 84% yield. Interaction of methylene-bis-morpholine[5e] and urea in boiling dioxane yielded only 33% of the theoretical monomorpholinomethylurea.

(12) (a) Davis and Blanchard, THIS JOURNAL, 51, 1790 (1929); (b) "Organic Syntheses," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1923, pp. 95–97; (c) Rudqvist, *Arch. Pharm.*, 236, 452 (1898); (d) Harvey and Caplan, U. S. Patent 2,247,495.

(13) Mannich, *Arch. Pharm.*, 272. 341 (1934).

Bis-(morpholinomethyl)-urea.—Urea (0.25 mole) and two equivalents of aqueous morpholinomethanol were heated until the mixture boiled. On cooling there was obtained a 95% yield of crude product which was purified by crystallization from a mixture of ethanol and acetone. It was obtained in platelets melting at 163–164°. The mixed melting point with monomorpholinomethylurea was slightly lower, 157–159°.

Interaction of urea with two equivalents each of paraformaldehyde and morpholine in boiling dioxane gave the bis derivative in 90% yield. By evaporation of a mildly refluxed solution of dimethylol urea (0.063 mole) and morpholine (0.2 mole) in 50 cc. of water a crude product was obtained, which yielded 60% of the theoretical quantity of bis-(morpholinomethyl)-urea.

Morpholinomethyl Derivatives of Substituted Ureas.—These compounds were prepared from the substituted urea by interaction with one equivalent of morpholinomethanol in aqueous solution (see Table I for several exceptions). In a few cases sufficient ethanol was added so that a homogeneous solution was obtained as the mixture was brought to a boil. The morpholinomethyl derivatives usually crystallized on cooling; a few were obtained by concentrating the solution *in vacuo* and then cooling, while others crystallized after standing for several days in a cold room (0°).

The morpholinomethyl derivatives of *s*-hexylurea and *as*-dimethylurea crystallized at 0° but melted below room temperature and were not purified. The derivative of *as*-diethylurea failed to crystallize after six months.

The preparative and analytical data for the morpholinomethyl derivatives of urea and substituted ureas are listed in Table I.

Symmetrical Disubstituted Ureas and Morpholinomethanol.—*sym*-Diphenylurea (0.1 mole) was refluxed for five minutes with one equivalent of morpholinomethanol in 50 cc. of ethanol. Ninety-five per cent. of the original weight of diphenylurea was recovered unchanged and no evidence of reaction was observed.

sym-Di-*n*-butylurea was heated with one and with two equivalents of morpholinomethanol in dilute ethanol solution. Only unreacted dibutylurea was recovered from the mixture.

Experiments with urea and 2, 3 and 4 equivalents of morpholinomethanol yielded only bis-(morpholinomethyl)-urea in yields of 95, 78 and 63%, respectively. Formation of no other product was indicated.

n-Butylurea and different excess amounts of morpholinomethanol yielded only the mono derivative.

Morpholinomethanol with Thiourea, Imides and Sulfonamides.—These compounds combined readily with morpholinomethanol in dioxane, water or aqueous alcohol by refluxing for thirty minutes. The data are summarized in Table II.

Hydrolysis of Monomorpholinomethylurea.—Monomorpholinomethylurea (0.05 mole) in 100 cc. of 10% sodium hydroxide was steam distilled. The distillate was acidified and concentrated. The concentrated solution by treatment with benzenesulfonyl chloride and 20% alkali yielded 11.7 g. of N-benzenesulfonylmorpholine (m. p. 118–119°). This accounted for 97% of the calculated amount of morpholine present.

Reductions of Monomorpholinomethylurea.—Zinc dust (4 equivalents) was added in small portions to a mildly refluxing hydrochloric acid solution (10%) of the urea derivative. After complete solution of the zinc, the reaction was made alkaline and steam distilled. Organic base in the distillate was determined by titration and identified as methylmorpholine by conversion to picrate, m. p. 224–226°. Morpholine was proved to be absent by testing with benzenesulfonyl chloride; yield of methylmorpholine, 79%. By the same procedure bis-(morpholinomethyl)-urea and morpholinomethanol gave, respectively, 70 and 57% yields of methylmorpholine.

In order to eliminate the probability that morpholinomethanol was first formed by hydrolysis and then reduced, the hydrogenation of monomorpholinomethylurea was

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TABLE I

MORPHOLINOMETHYL DERIVATIVES OF UREA AND SUBSTITUTED UREAS RNHCONHCH$_2$N(CH$_2$CH$_2$)$_2$O(CH$_2$CH$_2$)

R	Yield, %[a,b]	M. p., °C.[c]	Empirical formula	Analyses: Nitrogen, % Found	Nitrogen, % Calcd.	Neut. equiv. Found	Neut. equiv. Calcd.
Hydrogen-	92	162.0–163.0[e]	$C_6H_{13}N_3O_2$	26.44	26.41	160.2	159.1
Methyl-	44	124.4–125.4[h]	$C_7H_{15}N_3O_2$	24.25	24.27	175.0	173.1
Ethyl-	77	109.6–110.8[f]	$C_8H_{17}N_3O_2$	22.28	22.45	188.8	187.2
n-Propyl-	57	89.2– 90.0[i]	$C_9H_{19}N_3O_2$	20.81	20.89	202.7	201.2
Isopropyl-	80	126.8–128.0[j]	$C_9H_{19}N_3O_2$	20.70	20.89	202.8	201.2
Allyl-	85	104.0–105.0[h]	$C_9H_{17}N_3O_2$	21.08	21.10	198.7	199.2
n-Butyl-	70	109.0–109.6[j]	$C_{10}H_{21}N_3O_2$	19.37	19.53	215.5	215.2
Isobutyl-	74	112.0–112.6[j]	$C_{10}H_{21}N_3O_2$	19.46	19.53	214.4	215.2
s-Butyl-	75	111.0–112.0[j]	$C_{10}H_{21}N_3O_2$	19.50	19.53	214.0	215.2
t-Butyl	54[d]	137.8–138.8[i]	$C_{10}H_{21}N_3O_2$	19.33	19.53	213.4	215.2
s-Amyl	83	107.0–108.4[h]	$C_{11}H_{23}N_3O_2$	18.34	18.33	229.7	229.3
t-Amyl	68	107.4–109.0[f]	$C_{11}H_{23}N_3O_2$	18.39	18.33	231.5	229.3
Cyclohexyl-	64	138.0–139.0[f]	$C_{12}H_{23}N_3O_2$	17.38	17.42	241.3	241.1
Phenyl-	97	149.4–150.0[k]	$C_{12}H_{17}N_3O_2$	17.80	17.87	234.3	235.2
Benzyl-	67	149.3–149.8[l]	$C_{13}H_{19}N_3O_2$	16.88	16.87	248.4	249.1
Acetyl-	87[d]	161.0–161.8[g]	$C_8H_{15}N_3O_3$	20.91	20.89	201.8	201.1
β-Hydroxyethyl-	82[d]	118.0–119.8[f]	$C_8H_{17}N_3O_3$	20.61	20.69	203.1	203.2
β-Benzoyloxyethyl-	52	125.4–127.6[k]	$C_{16}H_{21}N_3O_4$	13.60	13.68	310.9	307.2
N-Carbamyl morpholine[m]	63	131.6–133.0[f]	$C_{10}H_{19}N_3O_3$	18.37	18.34	225.8	229.2
Morpholinomethyl-	95	163.0–164.0[l]	$C_{11}H_{22}N_4O_3$	21.48	21.70	131.2	129.1

[a] Yield based on crude products. [b] Yield of compound prepared in aqueous solution unless otherwise designated. [c] Melting points on purified products. [d] Yield of compound prepared in dioxane. [e] Crystallized from ethanol–acetone. [f] Crystallized from acetone. [g] Crystallized from acetone–dioxane. [h] Crystallized from methyl isobutyl ketone. [i] Crystallized from benzene–ligroin. [j] Crystallized from methyl ethyl ketone. [k] Crystallized from ethanol–water. [l] Crystallized from ethanol. [m] This is the complete name for this compound.

TABLE II

MONOMORPHOLINOMETHYL DERIVATIVES OF THIOUREA, IMIDES AND SULFONAMIDES

Compound	Yield, %[a,b]	M. p., °C.[c]	Empirical formula	Analyses: Nitrogen, % Found	Nitrogen, % Calcd.	Neut. equiv. Found	Neut. equiv. Calcd.
Thiourea	71	141.4–142.0[d]	$C_6H_{13}N_3OS$	23.98	23.99	175.8	174.2
Succinimide	67	109.6–110.4[e]	$C_9H_{14}N_2O_3$	14.12	14.14	197.9	198.1
Phthalimide	81	117.8–118.8[e]	$C_{13}H_{14}N_2O_3$	11.37	11.38	246.8	246.1
Benzenesulfonamide	81	81.6– 82.6[f]	$C_{10}H_{16}N_2O_3S$	10.86	11.01	254.5	256.2
p-Toluenesulfonamide	90	109.6–111.2[g]	$C_{11}H_{18}N_2O_3S$	10.26	10.37	272.6	270.2

[a] Yield based on crude product. [b] Yield of compound prepared in aqueous solution. [c] Melting points on purified products. [d] Crystallized from ethanol. [e] Crystallized from acetone. [f] Crystallized from benzene. [g] Crystallized from ethanol–water.

attempted under conditions where hydrolysis was unlikely.

Catalytic Reduction of Monomorpholinomethylurea.—Monomorpholinomethylurea (0.0094 mole) in absolute ethanol was hydrogenated at room temperature and atmospheric pressure using a platinum catalyst (0.1056 g.).[14] One molecular equivalent of hydrogen was absorbed. A quantitative yield of methylmorpholine was isolated as its picrate (m. p. 224–226°). Urea was identified as the other hydrogenolysis product by formation of characteristic crystals of urea nitrate.

Exactly similar results were obtained by hydrogenation in glacial acetic acid.

Acid Anhydride and Monomorpholinomethylurea.—Monomorpholinomethylurea did not react with cold (0–5°) acetic anhydride. At steam-bath temperature reaction took place and an insoluble solid was formed. This product was washed in turn with alkali, alcohol and ether to obtain material, m. p. 235–236°, with fairly reproducible nitrogen values. Found: N, 33.29, 33.21, 33.94. Acetylmorpholine was obtained in 62% yield from the acetic anhydride mother liquors.

Monomorpholinomethylurea and butyric anhydride at steam-bath temperatures yielded the same white insoluble solid, m. p. 233–236°. The mixture of this compound with the preceding product melted at 235–236°. Found: N, 33.69, 33.94. The identity of this solid product is not known, but it may be some urea-formaldehyde condensation product, *e. g.*, $(-CH_2NCONCH_2-)_x$; calcd.: N, 33.3.

N-Acetoxymethyl-N′-acetylurea.—Morpholinomethylacetylurea (0.05 mole) and acetic anhydride (0.39 mole) were heated on the steam-bath for three hours. Solution occurred slowly and cooling yielded a white crystalline product. Crystallization from ethyl acetate yielded 5.5 g. (64%) of material with m. p. 144.6–145.2°. Its saponification equivalent indicated that under the conditions used[15] the acetylurea part of the molecule was saponified also. This conclusion was substantiated by a blank with acetylurea.

Anal. Calcd. for $C_6H_{10}N_2O_4$: N, 16.09; saponification equivalent, 87. Found: N, 16.07; saponification equivalent, 87.

(14) Thanks are owed R. P. Mariella, Carnegie Institute of Technology, who prepared the catalyst and carried out the hydrogenation.

(15) Huntress and Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1941, pp. 21–22.

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Distillation of the acetic anhydride mother liquors yielded 4.6 g. (72%) of acetylmorpholine, b. p. 230–240°.

N-Butyroxymethyl-N′-acetylurea.—Morpholinomethylurea (0.05 mole) and butyric anhydride (0.31 mole) were heated on the steam-bath for two and one-half hours. A clear solution formed within five minutes and on cooling yielded 8.5 g. (84%) of plate-like crystals which, crystallized from ethyl acetate, melted at 116.8–117°.

Anal. Calcd. for $C_8H_{14}N_2O_4$: N, 13.85; saponification equivalent, 101. Found: N, 13.80; saponification equivalent, 100.

Picrates of Morpholinomethyl Derivatives.—Mono- and bis-(morpholinomethyl)-urea formed unstable picrates (m. p. 140–160°) from alcohol and water solutions. In contrast to these results stable picrates were prepared from glacial acetic acid solutions in a yield expected for a one to one molecular combination from mono- and bis-(morpholinomethyl)-urea. They melted at 162.0–163.3° and 163–164°.

Morpholinomethyl derivatives of alkylureas did not form picrates in glacial acetic acid solutions. In alcohol and water solutions unstable picrates were obtained which on purifying yielded morpholine picrate (m. p. 148.8–149.2°).

Stable picrates of morpholinomethyl derivatives of acetylurea (m. p. 195°), phenylurea (156–158°), phthalimide (205°), and succiuimide (188–189°) were prepared in either water, alcohol or glacial acetic acid solutions.

Summary

Mono- and bis-(morpholinomethyl)-urea were prepared and described. These compounds were cleaved by hydrolysis, reduction, and acetic anhydride to yield morpholine, methylmorpholine and acetylmorpholine.

Morpholinomethyl derivatives of 18 substituted ureas were prepared and characterized; N-morpholinomethyl-N′-acetylurea underwent reaction with acetic anhydride, yielding N-acetoxymethyl-N′-acetylurea and acetylmorpholine. Butyric anhydride gave the analogous butyroxymethyl derivative.

The morpholinomethyl derivatives of thiourea, succinimide, phthalimide, benzene- and *p*-toluenesulfonamide were prepared and characterized.

TOLEDO, OHIO RECEIVED OCTOBER 16, 1943

[CONTRIBUTION FROM THE INSTITUTE OF EXPERIMENTAL BIOLOGY, UNIVERSITY OF CALIFORNIA]

Kinetics of Reactions between Iodine and Histidine

BY CHOH HAO LI

Imidazole compounds react readily with iodine.[1] The imidazole containing amino acid, histidine, however, has not hitherto been iodinated. Bauer and Strauss[2] were not able to halogenate the histidine with ICl, but their results[3] with globin indicate the possibility of iodohistidine formation. On the other hand, Pauly[1b] succeeded in preparing benzoyldiiodo-histidine and tetraiodo-histidine anhydride. The fact that histidine cannot be iodinated in the free state but both its anhydride and its benzoyl derivative smoothly take up one mole of iodine (on the two C atoms of the imidazole ring) in a slightly alkaline solution has recently been confirmed by Bauer, Strauss and Maschmann.[4]

When histidine and iodine are allowed to react in a nearly neutral solution, the disappearance of iodine follows the rate law

$$dx/dt = (a - x)(b - 2x) \qquad (1)$$

where a and b are the initial concentrations of histidine and titatable iodine, respectively; k_2 is the specific rate constant and x is the concentration of diiodo-histidine which is formed according to the reaction: histidine + 2 I_2 → di-iodohistidine + 2HI. The rate law (1) is identical with that found in the formation of diiodotyrosine.[5] Table I gives the values of k_2 in a typical run for successive time intervals by means of the integrated form of equation (1). The concentrations are in moles per liter and time in minutes. The bimolecular rate law is further verified when one varies the initial concentrations of iodine and histidine. The specific rate is not changed by the addition of neutral salts.

TABLE I

A TYPICAL KINETIC EXPERIMENT AT 25°

$b = 2a = 5.26 \times 10^{-3}m$, $(I^-) = 3.15 \times 10^{-2}m$, *p*H 7.21 citrate–phosphate buffer $(HPO_4^-) = 3.50 \times 10^{-2}m$.

t, min.	$(b)\ 10^3$	$(x)\ 10^3$	k_2
0	(5.26)		
5.0	4.50	(0.38)	(6.4)
12.5	3.72	.77	6.2
18.0	3.30	.98	6.2
30.0	2.65	1.30	6.1
50.0	2.00	1.63	6.3
			Av. 6.2

The Rate as a Function of *p*H.—The dependence of specific rate on *p*H of the environment is similar to that found for the iodine-phenol reaction,[5] *i. e.*, the reaction becomes slower as the acidity of the solution increases. Data, summarized in Table II, give a relationship

$$k_2 = 0.10 + (5 \times 10^{-8}/(H^+)) \qquad (2)$$

in citrate buffers containing $(I^-) = 3.15 \times 10^{-2}$.

(1) (a) H. Pauly and K. Gundermann, *Ber.*, **41**, 3999 (1909); (b) H. Pauly, *ibid.*, **43**, 2243 (1910); (c) H. Pauly and E. Arauner, *J. prakt. Chem.*, **118**, 33 (1928).

(2) H. Bauer and E. Strauss, *Ber.*, **69B**, 245 (1936).

(3) H. Bauer and E. Strauss, *Biochem. Z.*, **284**, 197, 231 (1936).

(4) H. Bauer, E. Strauss and E. Maschmann, *Ber.*, **68B**, 1108 (1935).

(5) C. H. Li, THIS JOURNAL, **64**, 1147 (1942).

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TABLE II

EFFECT OF *p*H ON THE RATE AT 25°

Citrate buffer $(I^-) = 3.15 \times 10^{-2} m$

*p*H	k_2	k_2 calcd.
6.00	0.05	0.06
6.56	.25	.28
6.94	.50	.54
7.07	.72	.70
7.21	1.00	.90

The Rate as a Function of (I^-).—In a constant *p*H solution, the rate decreases as the (I^-) increases. This is evident from the results shown in Table III. The last column of Table III is calculated by the equation

$$k_2 = \frac{4.0 \times 10^{-3}}{(I^-)} + \frac{6.0 \times 10^{-4}}{(I^-)^2} \qquad (3)$$

The agreement between the observed and calculated k_2 appears satisfactory.

TABLE III

EFFECT OF (I^-) ON THE RATE AT 25°

Citrate buffer, *p*H 7.07

$(I^-)\ 10^2$	k_2	k_2 calcd.
3.15	0.72	0.73
3.80	.52	.52
5.00	.33	.32
7.10	.19	.17
10.00	.10	.10

From the preceding studies of diiodo-tyrosine formation,[5] it may be assumed that free iodine and hypoiodous acid react with the histidine. The rate law becomes

$$\frac{-\mathrm{d(histidine)}}{dt} = k_2'\,(\text{histidine})(I_2) + k_2''\,(\text{histidine})(\mathrm{HOI}) \qquad (4)$$

Since the concentrations of iodine and hypoiodous acid are determined by the equilibria (5) and (6)

$$I_2 + I^- \rightleftarrows I_3^- \qquad (5)$$

$$I_2 + H_2O \rightleftarrows HOI + H^+ + I^- \qquad (6)$$

it follows that

$$-\frac{\mathrm{d(histidine)}}{dt} = \left[\frac{k_2'}{K_5(I^-)} + \frac{k_2''K_6}{K_5}\frac{1}{(H^+)(I^-)^2}\right](\text{histidine})(I_3^-) \qquad (7)$$

therefore

$$k_2 = \frac{k_2'}{K_5(I^-)} + \frac{k_2''K_6}{K_5}\frac{1}{(H^+)(I^-)^2} \qquad (8)$$

Thus, in a constant *p*H with variations of (I^-) the specific rate may be represented by the expression

$$k_2 = \frac{A}{(I^-)} + \frac{B}{(I^-)^2} \qquad (9)$$

where $A = k_2'/K_5$ and $B = k_2''K_6/K_5(H^+)$. This expression is in accordance with the empirical equation (3). By comparison of equations (3) and (9) together with the equilibrium constants,[6,7] $K_5 = 715$, $K_6 = 3 \times 10^{-13}$ at 25°, we have obtained $k_2' = 2.9$ and $k_2'' = 1.2 \times 10^5$.

When the reaction occurs in a constant (I^-) with variations of (H^+), equation (8) may be written as

$$k_2 = C + (D/(H^+)) \qquad (10)$$

where $C = k_2'/K_5\,(I^-)$ and $D = k_2''\,K_6/K_5\,(I^-)^2$. This is identical with the empirical equation (2). From equations (2), (10), and equilibrium constants K_5, K_6, the specific rate k_2' and k_2'' are computed to be 2.3 and 1.18×10^5, respectively. These values agree very well with those obtained with a different set of data as described.

Therefore, the reaction of iodine and histidine in citrate buffer follows the course expressed by

$$-\mathrm{d(histidine)}/dt = 2.5(\text{histidine})(I_2) + 1.2 \times 10^5(\text{histidine})(\mathrm{HOI}) \qquad (11)$$

It is evident that hypoiodous acid is far more reactive as an iodinating agent than free iodine. This conclusion is consistent with that obtained in the study of the iodination of phenols.[5]

Catalytic Effect of $(HPO_4^=)$ on the Rate.—When a phosphate buffer instead of the citrate buffer of the same *p*H was used, the specific rate was greatly increased. Since the rate is not accelerated by the addition of neutral salt, the effect of phosphate buffer must be specific.

When a phosphate buffer of the same *p*H was added gradually to the citrate buffer, the rate appeared to increase according to the concentration of $(HPO_4^=)$. The data in Table IV bear out these conclusions. A similar catalytic effect of phosphate buffer was observed in the kinetic studies of diiodo-tyrosine formation.[8]

TABLE IV

EFFECT OF $(HPO_4^=)$ ON THE RATE AT 25°, $(I^-) = 3.15 \times 10^2$

*p*H of buffer	$(HPO_4^=)\ 10^2$	k_2
7.21	0.00	1.0
	1.75	3.2
	3.50	6.2
	5.25	8.4
	7.00	11.1
6.56	0.00	0.25
	1.10	.55
	2.20	1.0
	3.30	1.2
	4.40	1.6

Discussion

The fact that the kinetic data herein reported are analogous to those secured in the iodination of tyrosine indicates that iodine reacts with the imidazole ring of the histidine molecule to form diiodo-histidine

(6) W. C. Bray and Mackay, THIS JOURNAL, 32, 914 (1910).
(7) W. C. Bray, *ibid.*, 32, 932 (1910).
(8) See footnote 8a on ref. 5 and the following paper.

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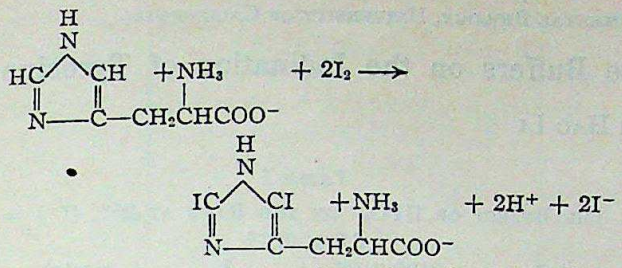
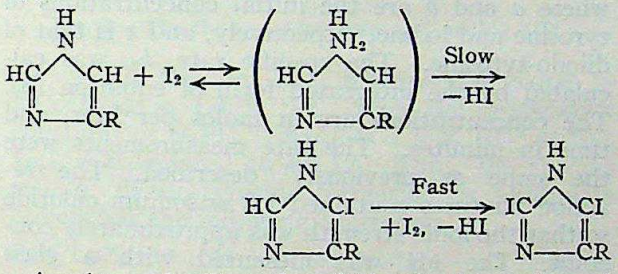
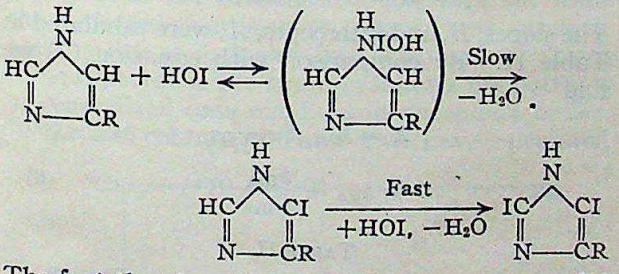


Preliminary experiments in which diiodo-histidine was isolated, indicated that this is indeed the case. Bauer and Strauss[3] have postulated that one iodine atom is attached to the amino group of the imidazole ring. Our experiments do not support this assumption.

The kinetic data here reported show that the rate-determining step requires a reaction of the first order with respect to both histidine and iodine although the net reactions use up two moles of iodine. Since most aromatic substitution reactions are usually explained by the rearrangement mechanism,[5,9] a similar scheme may be applied to the present case

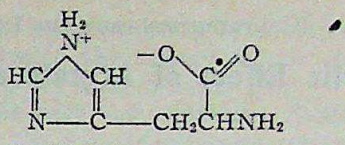


As shown in Equation (11), the formation of diiodo-histidine is also achieved through another path in which the hypoiodous acid is the iodinating agent



The fact that hypoiodous acid is a more powerful iodinating agent than iodine may be partly attributed to the greater tendency to form *undissociated* water molecule as compared with the formation of ionizing hydrogen iodide when free iodine acts as an iodinating agent.

In acid solution the occurrence of $>NH_2^+$ ion prevents the formation of the $>NHI_2$ or $>NHIOH$ complex and in turn the rate becomes slower. A similar explanation may be offered of the ease of isolation of the tetraiodo-histidine anhydride as observed by Pauly and others. In free histidine, it is probable that there exists a dipolar ion



which is absent in histidine anhydride.

The iodination of tyrosine is much faster than that of histidine and this may be partly due to the occurrence of such a dipolar ion in the histidine molecule. Table V summarizes the specific rates of diiodo-histidine and diiodo-tyrosine formation under comparative conditions. At *p*H 6.0, for instance, k_2 for histidine is about one hundredth of that for tyrosine. It is of interest to note that in the iodination of certain proteins, such as insulin[10] and pituitary lactogenic hormone,[11] the I_2 reacts only with the tyrosine residue although the protein contains both tyrosine and histidine. If the iodine is in excess and the solution is allowed to react longer, the histidine residue in the protein may take up iodine as well as the phenolic groups of the molecule.

TABLE V

COMPARISON OF THE RATE OF DIIODO-HISTIDINE AND DIIODO-TYROSINE FORMATION AT 25°

*p*H	Buffers	$(I^-)\ 10^2$	k_2 Tyrosine	k_2 Histidine
7.21	Citrate	3.15	27.0	1.0
7.21	Phosphate[a]	3.15	(310)	16.0
7.00	Phosphate[b]	10.00	7.4	0.34
6.00	Citrate	3.15	3.9	.05

[a] $(HPO_4^-) = 0.125\ m$. [b] $(HPO_4^-) = 3.06 \times 10^{-2}\ m$ containing 0.90 m $NaNO_3$.

Experimental

The crystalline l-histidine monohydrochloride (Eastman Kodak Co.) was used without further purification. Citrate and phosphate buffers were made according to Clark.[12] A weighed amount of histidine in 20 cc. of buffer was mixed with 20 cc. of iodine buffer solution containing the known concentration of potassium iodide in a glass-stoppered flask at 25.0 ± 0.02° thermostat, after both histidine and iodine solutions had attained the temperature of the thermostat. The time of mixing was taken as 0 time. The disappearance of iodine during the reaction was followed at known time intervals by pipetting 5 cc. of solution into 10 cc. of 1.0 m hydrochloric acid, which stopped the reaction. The excess of iodine was titrated with 0.010 N thiosulfate solution using starch solution as indicator.

Summary

The reaction between iodine and histidine to form diiodo-histidine is evident from the kinetic data; the kinetics of its formation is similar to that found in diiodo-tyrosine formation. At 25° in citrate buffer the rate of diiodo-histidine formation follows the expression: rate = 2.5 (histidine) $(I_2) + 1.2 \times 10^5$ (histidine) (HOI).

BERKELEY, CALIF. RECEIVED OCTOBER 27, 1943

(9) L. F. Fieser, in H. Gilman, "Organic Chemistry," II, 2nd Edition, 1943, pp. 174–202.

(10) C. R. Harrington and A. Neuberger, *Biochem. J.*, **30**, 810 (1936).

(11) C. H. Li, W. R. Lyons and H. M. Evans, *J. Biol. Chem.*, **43**, 139 (1941).

(12) W. M. Clark, "The Determination of Hydrogen Ions," Williams and Wilkins Co., Baltimore, Maryland, 1922.

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[CONTRIBUTION FROM THE INSTITUTE OF EXPERIMENTAL BIOLOGY, UNIVERSITY OF CALIFORNIA]

Catalytic Effect of Acetate and Phosphate Buffers on the Iodination of Tyrosine

BY CHOH HAO LI

In the reactions between iodine and tyrosine[1] it was observed that the rate is accelerated by the phosphate buffer. It was further noted that such an effect is not due to the increase of ionic strength. It is now possible to show that the specific rate, k_2, in phosphate buffer corresponds to the sum of a series of catalytic effects represented by the equation

$$k_2 = k_{OH}(OH^-) + k_{HA}(HPO_4^-) + k_{H_2A}(H_2PO_4^-) \quad (1)$$

where k_{OH}, k_{HA} and k_{H_2A} are the catalytic coefficients of hydroxide, dibasic and monobasic phosphate ions, respectively. In view of the equilibria

$$H_2PO_4^- \rightleftharpoons H^+ + HPO_4^-$$
$$H_2O \rightleftharpoons H^+ + OH^-$$

equation (1) may be written

$$k_2 = k_{OH} K_W \frac{1}{(H^+)} + (HPO_4^-)\left[k_{HA} + \frac{k_{H_2A}}{K_{H_2A}}(H^+)\right] \quad (2)$$

where K_{H_2A} is the dissociation constant of $H_2PO_4^-$.

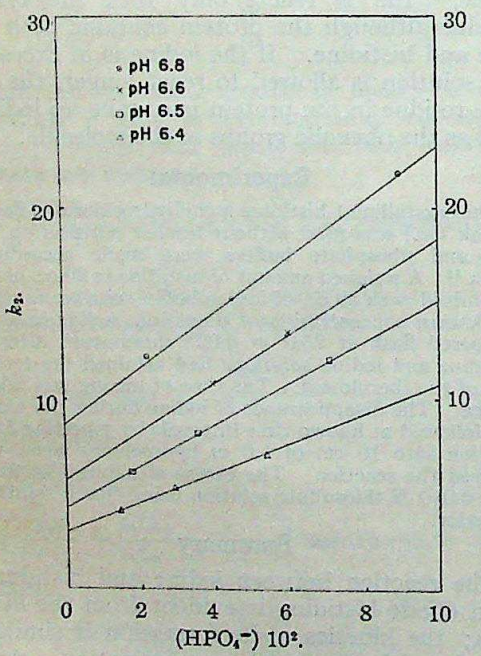

Fig. 1.—Specific rate, k_2, as the function of (HPO_4^-) at 25°.

Catalytic Activity of Phosphate Buffer.—Table I presents a summary of the specific rates obtained in different pH of different concentrations of phosphate at 25°. It may be recalled that the iodination of tyrosine[1] follows a bimolecular reaction rate

$$dx/dt = k_2(a - x)(b - 2x) \quad (3)$$

TABLE I

THE EFFECT OF HPO_4^- ON THE RATE AT 25°, $(I^-) = 6.3 \times 10^{-2}$

pH	$(HPO_4^-)\ 10^2$	k_2	k_2 calcd.
6.80	2.23	12.2	11.5
6.80	4.47	15.4	16.9
6.80	8.95	22.0	21.1
6.60	4.02	10.8	10.7
6.60	6.03	13.6	14.0
6.60	8.06	16.0	17.4
6.50	1.79	6.2	6.4
6.50	3.58	8.2	9.5
6.50	7.16	12.31	15.6
6.40	1.50	4.2	5.1
6.40	3.00	5.4	7.8
6.40	5.40	7.2	11.8

where a and b are the initial concentrations of tyrosine and iodine, respectively, and x is that of diiodo-tyrosine. The specific rate, k_2, was calculated by the integrated form of equation (3). The concentrations are in moles per liter, and time in minutes. The rate measurements were the same as previously[1] described. The reaction mixtures contained 1.0 m sodium chloride so that the ionic strength was approximately constant. The pH was measured with a glass electrode.

As shown in Fig. 1, a plot of (HPO_4^-) against the specific rate reveals a linear function

$$k_2 = A + B(HPO_4^-) \quad (4)$$

The slopes, B, and intercepts, A, were tabulated in Table II. By comparison with equation (2) we find

$$A = k_{OH} K_W \frac{1}{(H^+)} \quad (5)$$

$$B = k_{HA} + \frac{k_{H_2A}}{K_{H_2A}}(H^+) \quad (6)$$

TABLE II

THE VALUES OF A AND B IN PHOSPHATE BUFFER

pH	A	B
6.80	8.8	130
6.60	5.8	110
6.50	4.3	105
6.40	3.0	85

In Fig. 2 we have drawn the relation[2] between A and $1/(H^+)$ from the slope of this curve and $K_W = 1.2 \times 10^{-14}$ we have computed the catalytic coefficient of hydroxide ion, k_{OH}, to be 1.0×10^8.

Similarly Fig. 3 presents the plot of B *versus* (H^+); it appears that equation (6) holds very well. From the intercept of the curve in Fig. 3

(1) C. H. Li, THIS JOURNAL, 64, 1147 (1942).

(2) We have assumed that $a_{H^+} = (H^+)$ throughout in this paper.

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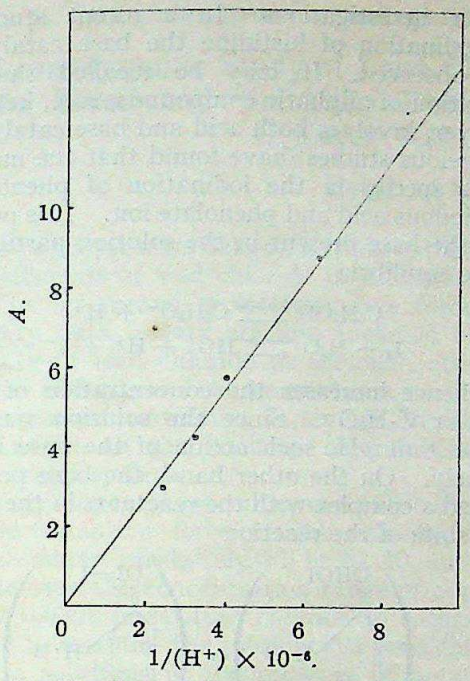

Fig. 2.—The change of intercepts, A, with $1/(H^+)$.

we obtain $k_{HA} = 150$, whereas the slope $= k_{H_2A}/K_{H_2A} = 1.6 \times 10^8$. Since the dissociation constant[3] of $H_2PO_4^-$, $K_{H_2A} = 7.5 \times 10^{-8}$ at 25°, k_{H_2A} is calculated to be 12. Thus, the specific rate of diiodo-tyrosine formation in phosphate buffers has the following expression

$$k_2 = 1.0 \times 10^8 (OH^-) + 150 (HPO_4^-) + 12 (H_2PO_4^-) \quad (7)$$

Hence it may be said that the catalytic effect of dibasic phosphate ion is about 10 times more active than the monobasic phosphate ion while the hydroxide ion is most potent in its catalytic activity due to its highly basic character. This is to be expected if the reaction follows the patterns of generalized base catalysis in phosphate buffer. In the last column of Table I we have calculated the specific rate using equation 7; there is a closer agreement between the observed and calculated values in higher pH than at lower pH.

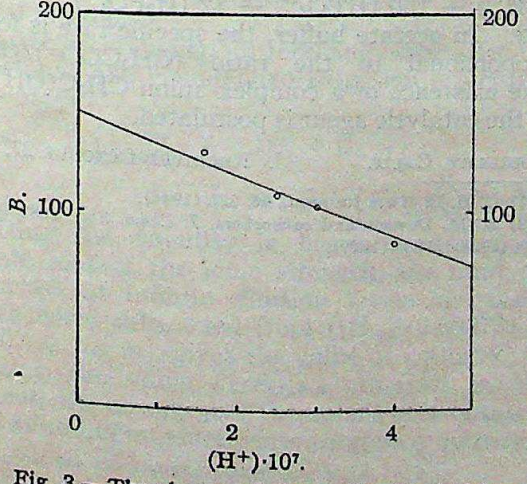

Fig. 3.—The change of slopes, B, with (H^+).

Catalytic Activity of Acetate Buffers.—In acetate buffer, the acetate ion itself does not seem to involve the catalytic mechanism. This is surprising because one would expect that the catalytic coefficient of acetate ion should be of the same magnitude as that for monobasic phosphate. Table III summarizes the kinetic data studied in acetate buffers with different concentrations. The relations between the concentration of acetate ion and specific rate do not conform to similar equations given for the phosphate buffer.

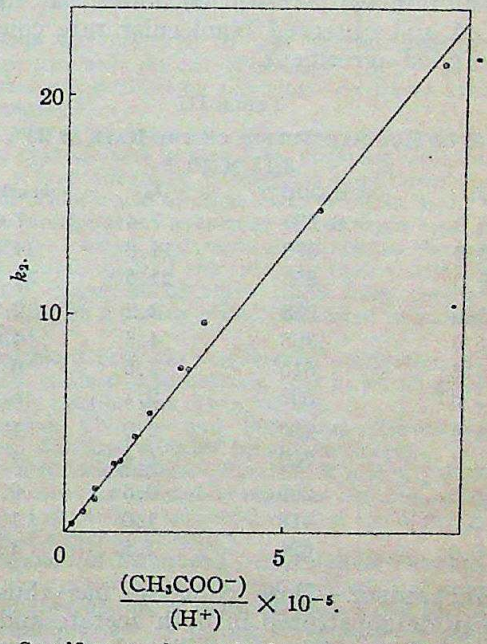

Fig. 4.—Specific rate, k_2, as the function of $(CH_3COO^-)/(H^+)$ at 25°.

As given in Fig. 4 it is possible to show that the specific rate is a function of $(CH_3COO^-)/(H^+)$

$$k = C(CH_3COO^-)/(H^+) \quad (8)$$

where C is a constant. This result may be explained if the acetate buffers are assumed to contain the complex acetate ion $CH_3C(OH)O_2^-$ formed by combination[4] of the simple ion with the hydroxide ion. The relation between the concentrations of these entities is given by $K_c = (CH_3C(OH)O_2^-)/(CH_3COO^-)(OH^-)$, where K_c is the complex constant. The catalytic coefficient for the complex anion being denoted by k_c, equation (8) becomes

$$K_2 = K_w K_c k_c \frac{(CH_3COO^-)}{(H^+)} \quad (9)$$

(3) A. Kossiakoff and D. Harker, THIS JOURNAL, 60, 2047 (1938).

(4) In dilute acetic acid solution we may have some acetic acid hydrate

$$CH_3COOH + H_2O \rightleftharpoons CH_3C(OH)_3 \rightleftharpoons CH_3C(OH)O_2^- + 2H^+$$

The formation of the complex acetate ion may not be unreasonable.

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From Fig. 4 the slope of the curve gives $K_wK_ck_c = 2.5 \times 10^{-5}$. Since the magnitude of the complex anion constant K_c is unknown, it is not possible to assign a value to the catalytic coefficient[5] k_c. However, it may be expected that the complex anion, $CH_3C(OH)O_2^=$, is more basic than the simple hydroxide ion; this in turn suggests that the catalytic coefficient of the complex anion would be greater than that of hydroxide ion. It is of interest to note that Dawson and Spivey[6] have suggested the formation of the complex ion ($CH_3COOH \cdot CH_3COO^-$) as an active catalytic species in the reaction of iodine and acetone in acetate buffer.

Table III includes the specific rate calculated by equation (9). It will be noted that the calculated and observed binolecular rate constants are in good agreement.

TABLE III

EFFECT OF ACETATE BUFFER ON THE RATE AT 25°, $(I^-) = 3.15 \times 10^{-2}$

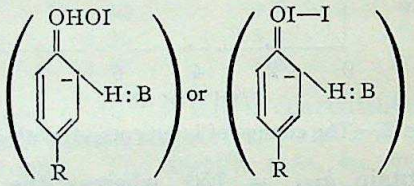
pH	(CH_3COO^-)	k_2	k_2 calcd.
6.0	0.280	7.4	7.0
6.0	.570	14.8	14.3
6.0	.850	21.5	21.2
5.6	.268	3.2	2.7
5.6	.398	4.5	4.0
5.6	.645	7.5	6.5
5.6	.805	9.7	8.1
5.4	.250	2.0	1.6
5.4	.760	5.4	4.8
5.0	.209	0.6	0.5
5.0	.418	1.0	1.1
5.0	.626	1.5	1.6

Mechanism.—Base catalysis has thus been clearly demonstrated in both acetate and phosphate buffers. The possibility that the catalysis may belong to the generalized base type needs further investigations. In a recent study[7] of the iodination of histidine the base catalysis is also observed. It may be recalled that the iodination of aliphatic compounds, *e. g.*, ketones,[8] however, involves both acid and base catalysis.

Previous studies[1] have found that the most reactive species in the iodination of phenols are hypoiodous acid and phenolate ion. It is possible that the base present in the solution participates in the equilibria

$$C_6H_5OH \rightleftharpoons C_6H_5O^- + H^+$$
$$I_2 + H_2O \rightleftharpoons HOI + H^+ + I^-$$

and hence increases the concentration of either HOI or $C_6H_5O^-$. Since the solution was kept at constant pH, such action of the base is very unlikely. On the other hand, the base probably formed a complex with the reactants in the transition state of the reaction



where :B denotes the base. Thus the removal of hydrogen atom from the ring is assisted by :B and in turn enhances the rate of the iodine atom entering into the ortho position. It is obvious that the catalytic coefficients of :B depend on its basicity. In the present investigation we have obtained an order of the catalytic effect: $CH_3C(OH)O_2^= > OH^- > HPO_4^= > H_2PO_4^-$, which approximately follows the order of their basicity.

Summary

1. The catalytic effect of phosphate and acetate buffers in the reactions between iodine and tyrosine has been investigated at 25°. In phosphate buffer, the specific rate is $k_2 = 1.0 \times 10^8 (OH^-) + 150 (HPO_4^=) + 12 (H_2PO_4^-)$.

2. In acetate buffer, the specific rate is found proportional to the ratio $(CH_3COO^-)/(H^+)$. The existence of a complex anion $CH_3C(OH)O_2^=$ as the catalytic agent is postulated.

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(5) We may assume that K_c is very small and has a magnitude of 10^{-10}. This is not unreasonable if we compare the following equilibria

$$OP(OH)_2O^- \rightleftharpoons OP(OH)O_2^= + H^+$$
$$OC(OH)_2 \rightleftharpoons OC(OH)O_2^- + H^+$$
$$H_3CC(OH)_2O^- \rightleftharpoons H_3CC(OH)O_2^= + H^+$$

Since we know the dissociation constants of monobasic phosphate and carbonic acid of about 10^{-3}, the assumption of taking 10^{-10} as K_c for the complex anion $CH_3C(OH)_2O^-$ may be justified. Thus, if $K_c = 10^{-10}$, k_c is computed to be 2.5×10^{10}; it is far greater than the catalytic coefficient for hydroxide ion as obtained in phosphate buffer.

(6) H. M. Dawson and E. Spivey, *J. Chem. Soc.*, 2180 (1930).

(7) C. H. Li, THIS JOURNAL, 66, 225 (1944).

(8) H. M. Dawson and co-workers, *J. Chem. Soc.*, 2282 (1926); 2844 (1928); 1884 (1929).

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[A CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

A Thermodynamic Study of Lead Chloride in Dioxane–Water by Means of Electromotive Force and Solubility Data at 25°; The Acetone-, Ethanol-, Dioxane-, Glycerol–Water–Lead Chloride Systems[1a]

BY M. V. NOBLE AND A. B. GARRETT

This paper presents data on a study of the activity coefficients of lead chloride in dioxane–water solutions by means of electromotive force and solubility data. Data are also included on the solubility of lead chloride in acetone-, ethanol-, dioxane- and glycerol–water mixtures.

The general procedure is similar to that of other work[1] on the thallous chloride–ethylene glycol–water system.

The experimental procedure was (1) to measure the electromotive force of the cell Ag/AgCl/dioxane–water/$PbCl_2$/(Hg)Pb in 20, 40, and 60% dioxane over the concentration range of approximately 0.0004 molal lead chloride to saturation, and (2) to measure the solubility of lead chloride in these solutions in the presence of potassium chloride.

The cell data are used to evaluate the activity coefficients of lead chloride below the saturation point, and the solubility data are used for this evaluation above saturation. Solubility measurements in alcohol–water, acetone–water, and glycerol–water mixtures supplement the dioxane–water data and give an interesting picture of the effect of dielectric constant *versus* the solvent character upon the solubility of lead chloride.

The activity coefficients are evaluated by the method of Carmody.[2]

In a cell without liquid junction

$$E = E_0 - \frac{RT}{NF} \ln a_{AB_2} \text{ or} \qquad (1)$$

$$E_0 - E_{obs.} = \frac{3RT}{Nf} \ln (4a_{\pm}) = \frac{3RT}{Nf} \ln 4(\gamma_{\pm} m_{\pm}) \qquad (2)$$

where $E_{obs.}$ is the measured e. m. f., E_0 is the standard potential and the other quantities have their usual meaning.[1]

After rearranging, introducing values for the constants, and changing to Briggsian logarithms, we obtain

$$-\log \gamma_{\pm} = \left[\frac{E_{obs.}}{0.08873} + 0.2007 + \log m\right] - \frac{E_0}{0.08873} \qquad (3)$$

Plotting the quantity in brackets against the square root of the ionic strength, the limit approached at infinite dilution gives $E_0/0.08873$ which when subtracted from $[(E_{obs.}/0.08873) + 0.2007 + \log m]$, gives the value of $(-\log \gamma_{\pm})$.

Using the value $(1/m)_{\mu=0}$ obtained in this manner, the accuracy of the values of γ obtained from solubility measurements are greatly increased.

(1a) Original manuscript received August 14, 1941.

(1) Black and Garrett, THIS JOURNAL, 65, 862 (1943); *cf.* also Garrett, Bryant and Kiefer, *ibid.*, 65, 1905 (1943).

(2) Carmody, *ibid.*, 51, 2905 (1929).

III. Experimental Procedure

Conductivity water was used to prepare the solvent mixtures. Dioxane was purified[3,4] by refluxing it for two days with concentrated hydrochloric acid and then for two days over metallic sodium. The purified dioxane was stored over sodium until time to be used, at which time it was redistilled from the sodium and stored under nitrogen.

Glycerol was prepared by distilling at reduced pressure Merck C. P. grade glycerol; only the middle portion was used.

Acetone was prepared for use by fractionating C. P. grade acetone as in the case of glycerol.

Alcohol was purified by refluxing over silver oxide and fractionating.[5]

The solvent mixtures were all prepared on weight basis.

Lead chloride was prepared by dropping Coleman and Bell C. P. lead nitrate (1 *N* solution) simultaneously with 1 *N* hydrochloric acid solution into a two-liter flask. During the precipitation a current of nitrogen was passed through the solution to exclude air and to stir the mixture. The precipitate of lead chloride was then washed by decantation, recrystallized three times from conductivity water, dried on a porous plate, and stored in a desiccator until used.

Hydrochloric acid was prepared by distillation of Grasselli C. P. grade of hydrochloric acid in an all-glass still; the middle fraction was taken for use.

Potassium Chloride and Potassium Nitrate.—Baker Analyzed was used without futher purification.

Diphenylthiocarbazone.—Eastman Kodak Co. diphenylthiocarbazone was purified by repeated extraction between water and chloroform as recommended by Wilkins, Willoughby, Kramer and Smith.[6]

Preparation of Electrodes.—Silver–silver chloride electrodes were prepared by different methods,[7-12] several of which involve plating of platinum with silver and subsequent chloridization, or baking silver oxide on platinum followed by chloridization. Due to several chemical and mechanical difficulties involved, it was decided to investigate the possibility of simply chloridizing pure silver wire as described in previous work.[12] This gave a firm white coating of silver chloride in a solution free from impurities such as are present in a silver plating bath (particularly the cyanide ion). These electrodes gave the required potential reproducible to 0.1 mv. against a calomel half-cell. Electrodes were prepared in this manner only a short time in advance of making up the cell and were stored in distilled water until ready for use.

Preparation of Amalgam.—The amalgam was prepared thermally[13] by dissolving enough freshly cleaned Baker Reagent stick lead in carefully purified mercury to make a 6% amalgam. The amalgam was run through a capillary tube and stored in a sealed Pyrex tube under nitrogen pressure until used.

(3) Scatchard and Benedict, *ibid.*, 58, 837 (1936).

(4) Eigenberger, *J. prakt. Chem.*, 130, 73 (1931).

(5) Gross, Kuzmany and Wald, THIS JOURNAL, 59, 2692 (1937).

(6) Wilkins, Willoughby, Kramer and Smith, *Ind. Eng. Chem., Anal. Ed.*, 7, 33 (1935).

(7) Smith and Taylor, *J. Research Natl. Bur. Standards*, 20, 837 (1938), and 22, 307 (1939).

(8) Harned, THIS JOURNAL, 51, 416 (1929).

(9) MacInnes and Parker, *ibid.*, 37, 1445 (1915).

(10) Noyes and Ellis, *ibid.*, 39, 2532 (1917).

(11) Carmody, *ibid.*, 51, 2901 (1929).

(12) Black and Garrett, *ibid.*, 65, 862 (1943).

(13) Cowperthwaite and Thomas, *ibid.*, 55, 568 (1933).

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Preparation of Cells.—The cell was a modification of the one used by Carmody.[1,2]

Purification of Nitrogen.—Tank nitrogen was purified by successively passing it through soda lime, calcium chloride, reduced copper at 700°, calcium sulfate, alkaline pyrogallol, and a solution of the same composition as that in the cell. All work was done in an atmosphere of nitrogen.

Measurement of e. m. f.—The e. m. f. of the cells was measured with a Leeds and Northrup type K-2 potentiometer. The standard cell used was checked at regular intervals against another cell certified by the National Bureau of Standards which was kept for that purpose only. The galvanometer used was a Type R (Leeds and Northrup) with a sensitivity of 3×10^{-9} ampere per millimeter with scale at one meter. All leads were shielded.

Preparation of Solubility Samples.—These were prepared by the method described in earlier work.[1,14]

Sampling and Analysis.—After equilibration, the samples were sedimented for a day in the 25° bath, and were then filtered by means of nitrogen pressure through a Jena glass filter into a dry flask. The sample was weighed, density determinations were then made and the weighed sample analyzed by the chromate method given by Scott[15] (test analyses by this method gave results reproducible to two parts in one thousand) or by the colorimetric method of Craig and Vinal.[16]

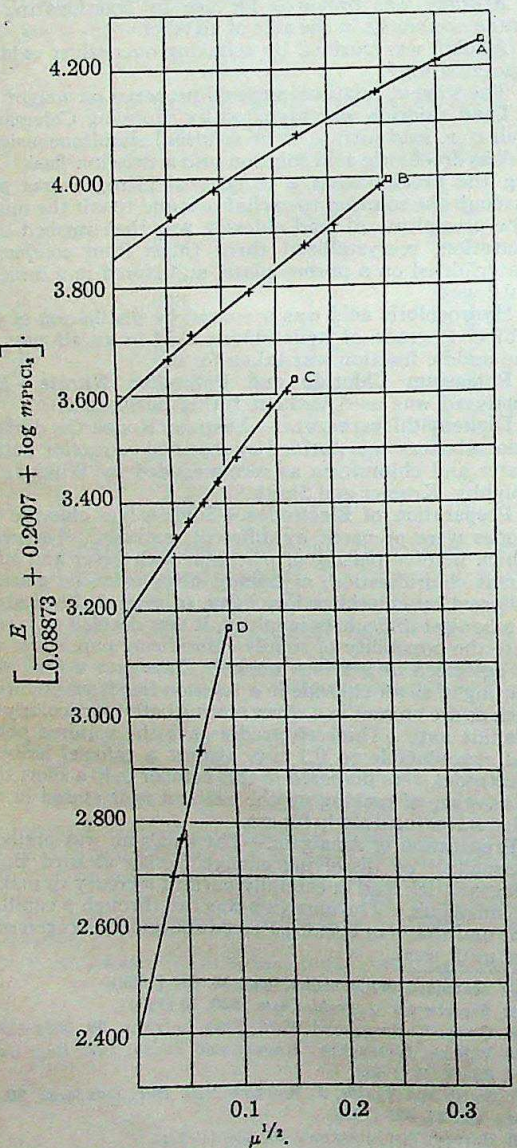

Fig. 1.—A, Water; B, 20% dioxane; C, 40% dioxane; D, 60% dioxane.

The Data

A. Electromotive Force Data; Activity Coefficients to Saturation (at 25 ± 0.02°).—The apparatus and techniques of the cell measurements were first studied in the lead chloride–water system previously reported by other investigators;[2,17] the values of E and γ obtained were in agreement with their data. The mixed solvent system was then investigated.

The activity coefficients of lead chloride were calculated from cell data in 20, 40 and 60% dioxane–water mixtures which are given in Table I.

TABLE I

ACTIVITY COEFFICIENTS OF LEAD CHLORIDE FROM E. M. F. DATA

Moles of $PbCl_2$ per 1000 g. solvent	20% dioxane–80% water		40% dioxane–60% water		60% dioxane–40% water	
	$E_{obs.}$	γ	$E_{obs.}$	γ	$E_{obs.}$	γ
0.02173 (s)[a]	0.4842[a]	0.387				
.02013	.4857	.397				
.01399	.4938	.470				
.01049	.5017	.511				
.00932 (s)			0.4842[a]	0.358		
.00856			.4855	.374		
.00699			.4909	.401		
.00525	.5209	.619				
.00428			.5016	.496		
.00323 (s)					0.4842[a]	0.173
.00293			.5120	.546		
.00214			.5201	.604		
.00175	.5561	.745				
.00153					.4929	.295
.00142			.5334	.656		
.000951			.5462	.702		
.000874	.5788	.828				
.000694					.5081	.434
.000424					.5207	.511
	$\left(\frac{1}{m_\pm}\right)_{\mu \text{ at s}} = 29.0$		$\left(\frac{1}{m_\pm}\right)_{\mu \text{ at s}} = 67.6$		$\left(\frac{1}{m_\pm}\right)_{\mu \text{ at s}} = 195$	
	$\left(\frac{1}{m_\pm}\right)_{\mu = 0} = 75.0$		$\left(\frac{1}{m_\pm}\right)_{\mu = 0} = 187$		$\left(\frac{1}{m_\pm}\right)_{\mu = 0} = 1127$	

[a] s = saturation.

The extrapolations used to obtain values of E_0 are reproduced in Fig. 1. The values of γ were obtained by means of equation (3) described above and referred to the standard state of infinite dilution in the particular solvent mixture used.

The reproducibility of the cells was within ±0.1 mv. except in solutions less than 0.0004 molal where the deviations became greater (0.5 mv.) as is expected for cell measurements at such solutions.[18]

(14) Garrett, Noble, Kiefer and Bryant, THIS JOURNAL, 65, 293 (1943).

(15) Scott "Standard Methods of Chemical Analysis," D. Van Nostrand Company, New York, N. Y., 1927, p. 275.

(16) Craig and Vinal, *J. Research Natl. Bureau of Standards*, 22, 55 (1939).

(17) Allmand and Hunter, *Trans. Faraday Soc.*, 24, 300 (1928).

(18) Early work on these cells was discouraging due to the difficulty experienced in reproducing the data. However, this was almost entirely eliminated as a result of the observation that even small traces of oxygen will apparently cause rapid oxidation of the organic solvent in the presence of the solute. Consequently, standard solutions prepared and stored under nitrogen were discarded and the general policy adopted was to prepare the lead chloride–dioxane–water solutions just before it was to be used.

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TABLE II

SOLUBILITY OF $PbCl_2$ IN KCl SOLUTIONS OF DIOXANE–WATER AT 25 ± 0.02°[a]

20% dioxane–80% water		40% dioxane–60% water		60% dioxane–40% water	
Moles KCl	Moles $PbCl_2$	Moles KCl	Moles $PbCl_2$	Moles KCl	Moles $PbCl_2$
0.000	2.173×10^{-2}	0.000	0.932×10^{-2}	0.000	0.323×10^{-2}
.01005	1.84	.0098	.660	.010	.208
.03016	1.33	.0294	.442	.030	.204
.0695	.874	.0688	.348	.050	.210
.0995	.725	.099	.336	.070	.207
.199	.537	.199	.335	.085	.198
.299	.509	.295	.312	.100	.154
.401	.437	.399	.252	.300	.135
.553	.353	.693	.225		
.711	.325	.859	.211		
.868	.314	1.008	.254		
.970	.312	1.224	.283		
1.180	.323				
1.455	.371				
1.674	.418				

[a] All concentrations are expressed as moles of solute for 1000 g. of solvent.

Considering the error in extrapolation to $\mu = 0$ and the reproducibility of the data, the maximum probable error is in the order of ±0.005.

From the value of $\gamma_{\pm}$ at saturation and $(1/m_{\pm})_{\mu \text{ at sat.}}$, the value of $(1/m_{\pm})_{\mu=0}$ could be evaluated for use in evaluating γ from the solubility data.

B. Solubility Data in Potassium Chloride and in Potassium Nitrate Solutions.—The data in potassium chloride solutions are summarized in Table II. All solubility values are expressed in moles per 1000 g. of solvent. A plot of the solubility of lead chloride as a function of added chloride ion is shown in Fig. 2. The common ion effect, complex formation and relative degree of dissociation may be noted in this graph.

An indication of the degree of dissociation of lead chloride in these solvents is given by extrapolating the solubility curve to $m_{Cl^-} = 0$ to obtain the amount of undissociated lead chloride.[19] This value divided by the total amount of lead chloride in solution (solubility in the pure solvent) gives the per cent. of dissociated lead chloride; these values range for 5% in water through 6, 9 and 20% in the three mixtures studied. The data in water solubility are those obtained by Deacon in solutions of sodium chloride.[20] Fromherz[21] claims that absorption spectra data indicate the following relative ion concentrations in a saturated aqueous solution of lead chloride: 48%$PbCl^+$, 48%Pb^{++} and 4%$PbCl_2$. His conclusions are compatible with the above calculations.

TABLE III

ACTIVITY COEFFICIENTS OF LEAD CHLORIDE AT ROUNDED VALUES OF IONIC STRENGTH

Dioxane	20%	40%	60%
μ	γ	γ	γ
0.0005	0.919	0.870	0.662
.001	.887	.818	.562
.004	.782	.661	.318
.008	.705	.561	.202
.01	.678	.527	.173
.04	.471	.301	.060
.08	.356	.198	.039
.1	.323	.171	.035
.3	.176	.084	.020
.5	.117	.064	
.7	.080	.055	
.9	.053	.046	
1.0	.045		

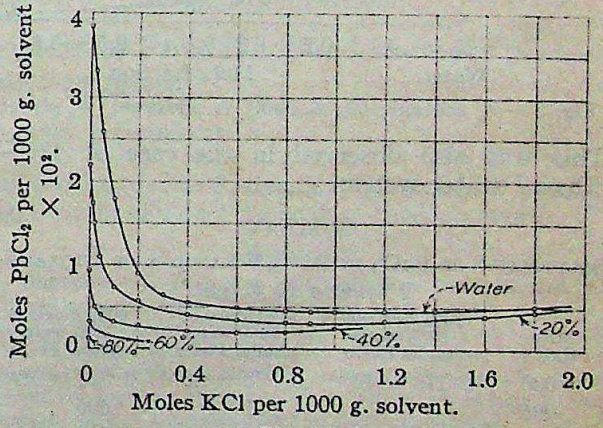

Fig. 2.

Values of γ at rounded values of m_{PbCl_2} are given in Table III.

The solubility of lead chloride as a function of added potassium nitrate (at 25°) is summarized in Table IV. The increased ionic strength due to the presence of potassium nitrate has the obvious and expected effect of increasing the solubility of lead chloride.

The limiting slopes of $-\log \gamma_{\pm}$ *vs.* $\sqrt{\mu}$ are 1.69, 2.73 and 8.00 for the three mixtures studied; they are all larger than the theoretical slopes calculated from the limiting law, $-\log \gamma = C\sqrt{\mu}$.

(19) See Johnston, Cuta and Garrett, THIS JOURNAL, 55, 2320 (1933), who used this method for $AgCO_3^-$.

(20) Deacon, *J. Chem. Soc.*, 2063–2065 (1927).

(21) Fromherz, *Z. physik. Chem.*, 153, 382 (1931).

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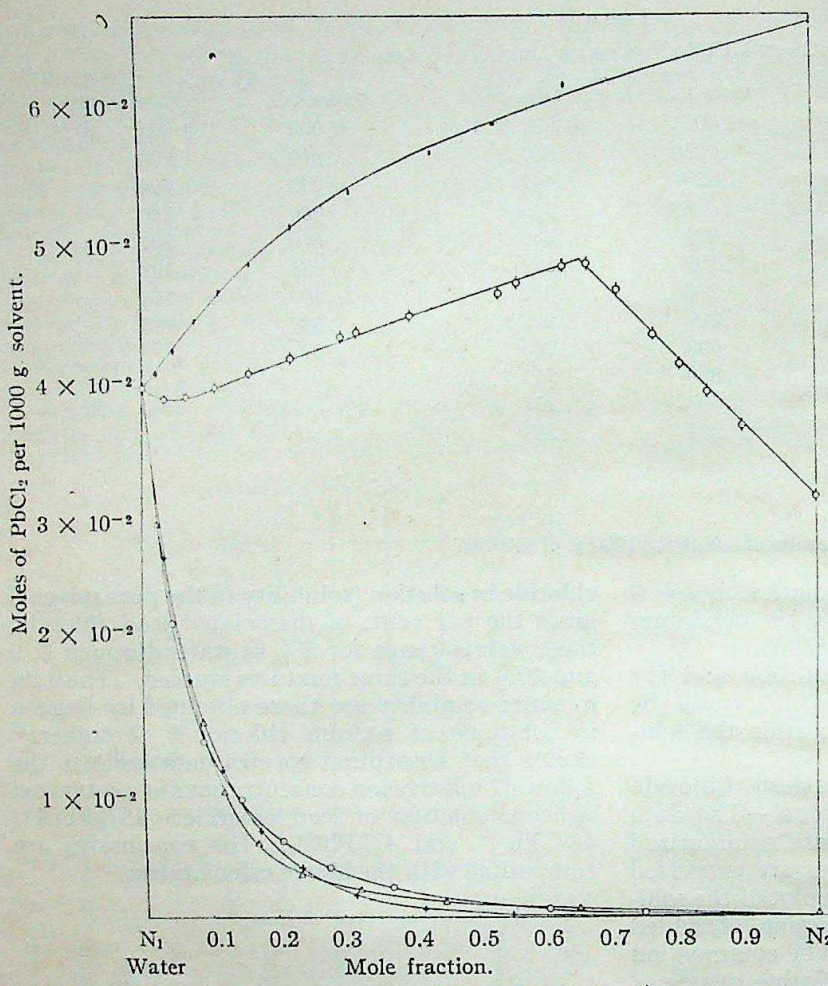

Fig. 3.—+, acetone; ⊙, alcohol; △, dioxane; ∓, glycerol; ○, ethylene glycol.

This was also observed in the case of TlCl–ethanol–water system.

TABLE IV

SOLUBILITY[a] OF $PbCl_2$ IN KNO_3 SOLUTIONS OF DIOXANE–WATER AT 25 ± 0.01°

Moles KNO_3	20% dioxane–80% water Moles $PbCl_2$	40% dioxane–60% water Moles $PbCl_2$	60% dioxane–40% water Moles $PbCl_2$
0.000	2.173×10^{-2}	0.932×10^{-2}	0.323×10^{-2}
.005		1.011	.505
.010		1.052	.756
.030	2.323	1.222	
.050	2.445	1.352	
.070	2.584	1.486	
.085	2.772	1.539	
.100	2.869	1.605	
.300	3.145	2.382	

[a] All concentrations are expressed as moles of solute per 1000 g. of solvent.

Other situations where the experimental slopes are greater than the theoretical slopes have been observed in the $CdBr_2$–water system,[22] in which it is well known the cadmium bromide is a weak electrolyte; furthermore, it is observed in mixed solvent systems,[23] and in liquid ammonia system.[24] It may safely be concluded that the deviation from the limiting law can be accounted for primarily by the increased association at these low values of the dielectric constant. The changing a values should be considered but are probably of secondary importance.

Solubility Products.—The thermodynamic solubility products of lead chloride have been calculated in water, 20, 40 and 60% dioxane from the relationship $K_{s.p.} = 4(m\gamma)^3$, and are given in Table V.

WITH MICHAEL ERCHACK, STANLEY MILLER AND HENRY FLOYD

C. The Solubility of Lead Chloride in Dioxane–Water, Ethanol–Water, Acetone–Water, Glycerol–Water and Ethylene Glycol–Water Solutions.—Preliminary treatment of the lead chloride–dioxane–water data indicated that a plot of the log of the solubility of lead chloride *vs.* log D along with the data of Dunning and Shutt[25] taken in solutions of glycine and water of high dielectric constant, gave a break at the water point. This behavior led us to become interested in the behavior of other solvent pairs to obtain at least qualitative information about the specific solvent effect *versus* the dielectric constant effect. Consequently, solubility data were obtained in several

TABLE V

SOLUBILITY PRODUCTS OF $PbCl_2$ IN DIOXANE–WATER MIXTURE

$K_{s.p.} = 4(m\gamma)^3$

% Dioxane	D	m	γ	$K_{s.p.}$	ΔF, cal.
0	78	0.03905	0.409[a]	1.63×10^{-5}	6530
20	61	.0217	.387	2.37×10^{-6}	7680
40	43	.00932	.358	1.49×10^{-7}	9320
60	26	.00323	.173	7.0×10^{-10}	12500

[a] Carmody, ref. 2.

(22) Bates THIS JOURNAL, 61, 308 (1939).

(23) For HCl in water–dioxane see Harned and others, THIS JOURNAL, 61, 49 (1939); for TlCl in water–ethanol see Hogge and Garrett; for alkali halides in water–methanol see Akerlof, *ibid.*, 51, 2359 (1929). It is also of interest to note a recent paper by H. S. Frank, *ibid.*, 63, 1789 (1941), in which he discusses the necessity to assume an association–solvation equilibrium at low values of the dielectric constant in order to correlate experimental data with deductions from his derivation for the Debye–Pauling equation, *cf. ibid.*, 47, 2129 (1925).

(24) Hunt, *J. Phys. Chem.*, 45, 351 (1941).

(25) Dunning and Shutt, *Trans. Faraday Soc.*, 34, 1192 (1938).

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pairs of mixed solvents; they are tabulated in Table VI and shown graphically in Fig. 3.[26]

TABLE VI

SOLUBILITY OF LEAD CHLORIDE IN MIXED SOLVENTS

Weight % water in solvent	Moles $PbCl_2 \times 10^{-3}$ per 1000 g. of solvent: Dioxane–water	Alcohol–water	Acetone–water	Glycerol–water
100	3.905[a]	3.905	3.905	3.905
90	2.90	2.380	2.65	4.04
80	2.173	1.410	1.74	4.20
70	1.44	0.885	1.08	4.38
60	0.932	.568	0.640	4.57
50	.550	.360	.350	4.79
40	.323	.215	.164	5.04
30	.210	.111	.064	5.33
20	.120	.050	.016	5.66
10	.060	.021	.0091	6.07
0	.0013	.0077	.0038	6.55

[a] Carmody, ref. 2.

The plot of solubility *vs.* mole fraction (Fig. 3) gives an interesting comparison of relative solvation effects in mole for mole of solvent.

It appears that the number and the character of polar groups on the solvent which is used with water is a factor that determines the direction of the solubility effect. Within the particular solvent pair the dielectric constant of the mixture plays an important role, but a minor one compared with the "solvent character" effect. This is in accord with the conclusions of Kraus.[27]

(26) The data on the lead chloride–ethylene glycol–water system were published in THIS JOURNAL, **65**, 293 (1943). The data are tabulated here in weight per cent. rather than mole per cent. for the sake of condensing the tables. The data are shown in Fig. 3 as mole fraction which serves as a better basis of comparison of solvation effects.

Summary

1. The electromotive force of the cell $Pb(Hg)/PbCl_2/AgCl/Ag$ has been measured at several concentrations in 20, 40, and 60% dioxane–water mixtures.

2. The solubility of lead chloride has been determined in dioxane–water mixtures with added potassium chloride and potassium nitrate. The solubility has also been determined in alcohol–water, glycerol–water and acetone–water mixtures with no added salt present.

3. From these data the activity coefficients of lead chloride are calculated over a wide range of concentrations. The divergence in the slope of $-\log \gamma$ *vs.* $\sqrt{\mu}$ is attributed to association.

4. The solubility product constants are calculated for the 20, 40, and 60% mixtures of dioxane and water and for pure water.

5. The data in the various mixed solvent pairs are discussed.

(27) Kraus, *Science*, **90**, 381 (1939).

COLUMBUS, OHIO RECEIVED NOVEMBER 12, 1943

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF MARYLAND]

The Dipole Moments of Friedelin, Cerin, Isomers of Friedelinol and Isomers of 3-α-Naphthyl-1-chloro-1-propene[1,2]

BY JOHN J. LANDER AND W. J. SVIRBELY

The presence of specific functional groups in friedelin, cerin and high and low melting friedelinol have been decided upon on the basis of chemical evidence.[3] While dipole moment determinations would not be able to locate the positions of the functional groups in these cases, nevertheless such measurements could be regarded as a check on the accepted structures since their magnitudes should be of about the same order as those usually attributed to those same functional groups. This investigation was undertaken to check the structures of the above compounds. Dipole moments were also determined for two compounds which were suspected of being *cis–trans* isomers of 3-α-naphthyl-1-chloro-1-propene to decide whether such isomerism was possible on the basis of their moments.

(1) Presented in part at the Washington Section meeting of the A. C. S. held at the University of Maryland, May, 1942. Original version received March 15, 1943.

(2) A portion of this paper is abstracted from the Master's thesis presented by John J. Lander to the Graduate School of the University of Maryland, December, 1942.

(3) Drake and Jacobsen, THIS JOURNAL, **57**, 1570 (1935); Drake and Shrader, *ibid.*, **57**, 1854 (1935); Drake and Campbell, *ibid.*, **58**, 1681 (1936); Drake and Haskins, *ibid.*, **58**, 1684 (1936); Drake and Wolfe, *ibid.*, **62** 3018 (1940); G. K. Holmes, Thesis, University of Maryland 1940; J. Lann, Thesis, University of Maryland, 1941.

Materials

Benzene.—J. T. Baker thiophene-free benzene was refluxed over mercuric acetate, dried with calcium chloride, refluxed over sodium and fractionally distilled over sodium, collecting the middle fraction (b. p. 78.1° uncor.). Subsequent distillations of benzene solutions were made to recover the benzene for reuse. The benzene was stored over sodium wire in a glass bottle and used as required.

Friedelin.—Slightly impure friedelin was recrystallized twice from pyridine (m. p. 254–260°). This may be compared with the melting range of 256–262° for the pure material.

Low-melting Friedelinol.—Slightly impure compound was recrystallized twice from dioxane. The melting point range, 278–282°, was the same as for the pure material.

High-melting Friedelinol.—This compound was prepared by hydrogenating some of the pure friedelin in dioxane solution over a copper–chromium oxide catalyst at 200° and 2000 lb. pressure. The crude material was recrystallized once from dioxane. The melting point range, 299–301°, may be compared to the range 301–304° for the pure material.

Cerin.—Pure cerin was used,[4] m. p. 248–251°.

(4) Impure friedelin, impure low-melting friedelinol, and pure cerin were supplied us through the courtesy of Dr. N. L. Drake and his collaborators.

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TABLE I

SUMMARY OF DATA IN BENZENE

Densities in parentheses have been picked off a density–mole fraction plot. Dielectric constants of pure benzene in parentheses have been obtained by extrapolating a dielectric constant–mole fraction plot.

$N_2 \times 10^4$	d	ϵ	P_2
Friedelin at 32°, Run no. 1			
0.0000	0.86481	2.2548	$P_\infty = 298$
1.0814	.86494	2.2561	300
3.1674	.86519	2.2588	300
3.7381	(.86526)	2.2596	302
4.3511	.86532	2.2603	303
Run no. 2			
0.0000	.86450	2.2579	$P_\infty = 292$
1.0850	.86462	2.2592	293
2.1149	.86473	2.2604	290
2.1549	(.86473)	2.2605	294
3.1889	.86484	2.2622	297
3.2184	(.86480)	2.2621	305
4.2163	(.86493)	2.2634	307
4.2563	(.86494)	2.2634	302
Low-melting friedelinol at 32°, Run no. 1			
0.0000		2.2473	
.0000	.86496	(2.2478)	$P_\infty = 206$
1.0737	.86504	2.2484	211
2.2226	(.86515)	2.2491	207
3.1665	.86523	2.2496	203
4.2384	(.86532)	2.2502	205
6.4113	.86550	2.2513	203
8.4656	(.86568)	2.2526	206
Run No. 2			
0.0000		2.2432	
.0000	(.86496)	(2.2436)	$P_\infty = 201$
1.5328	(.86509)	2.2444	208
3.1805	(.86523)	2.2451	193
4.4085	(.86533)	2.2459	200
5.9086	(.86546)	2.2467	200
7.3475	(.86558)	2.2473	197
Run No. 3			
$P_\infty = 196$			
Cerin at 50°, Run no. 1			
0.0000	0.84581	2.2098	$P_\infty = 252$
1.5088	.84598	2.2111	250
2.5645	.84609	2.2121	254
Run no. 2			
0.0000	(.84581)	2.2081	$P_\infty = 243$
1.6184	(.84599)	2.2094	240
2.6152	(.84609)	2.2100	233
3.5246	(.84620)	2.2107	231
High-melting friedelinol at 50°, Run no. 1			
0.0000		2.2090	
.0000	(.84507)	(2.2085)	$P_\infty = 196$
1.3441	.84519	2.2091	193
2.6271	(.84530)	2.2095	189
3.7044	(.84539)	2.2099	180
5.4875	(.84554)	2.2109	187
Run no. 2			
0.0000	(.84507)	2.2093	$P_\infty = 203$
2.2205	(.84527)	2.2105	205
3.2496	.84535	2.2110	201
4.0342	.84542	2.2115	203
Solid $C_{13}H_{11}Cl$ at 32°			
N_2			
0.0000	0.86459	2.2427	$P_\infty = 98.8$
.001138	(.86535)	2.2465	98.4
.003842	.86680	2.2547	98.1
.006319	.86825	2.2626	98.1
.008199	(.86922)	2.2681	97.9
.009679	(.87003)	2.2719	96.8
.01481	.87276	2.2872	96.9
Liquid $C_{13}H_{11}Cl$ at 32°			
.0000	.86462	2.2502	$P_\infty = 111$
.001481	.86544	2.2560	110.6
.006758	.86833	2.2745	105.9
.01137	(.87077)	2.2933	109
.01253	(.87142)	2.2973	108.5
.02932	.88055	2.3580	107

3-α-Naphthyl-1-chloro-1-propene.—Two compounds, one a liquid and the other a solid, both having the same chemical analysis, were furnished us by Mr. T. H. Harris and Dr. Colin M. Mackall of the George Washington University. Since elaborate purification procedures had already been used[8] in their preparation, the compounds were used as received.

Experimental Procedure

The heterodyne beat apparatus and the dielectric cell used in this work have been referred to in an earlier publication.[5] The solutions were made up in the following manner. One hundred ml. of benzene was pipetted into a series of glass-stoppered flasks. Three of the flasks were weighed empty and reweighed with the benzene. The average weight of the benzene was used throughout the series. The pipet was capable of delivering 100 ml. of benzene to within ±0.01 g. Samples of the solute were weighed and transferred into the flasks containing the benzene. Since time was required for the material to go into solution, the flasks were usually allowed to stand on a warm surface (approx. 40°) overnight. The solubilities of the first four compounds were very slight (low-melting friedelinol, the most soluble one, was soluble to the extent of 0.404 g. per 100 ml. of benzene). The dielectric constants of these solutions as well as that of the benzene used in their preparation were obtained.

Densities were measured using a modified Ostwald-Sprengel pycnometer having a volume of about 24 ml. Duplicate density measurements were made on benzene and on three or four of the solutions scattered over the concentration range. Duplicate checks were obtained to ±0.005%. The densities of the solutions which were not measured were read from the linear plot of density *vs.* N_2 for the particular series of solutions being studied.

Experimental Results

Part of our experimental results are given in Table I which lists the mole fractions of the

(5) Davis, Bridge and Svirbely, THIS JOURNAL, 65, 85 (1943).

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solute, N_2, the densities of the solutions, d, the dielectric constants of the solutions, ϵ, the molar polarizations, P_2, and the extrapolated value of P_∞ obtained separately for each run from the extrapolation of the polarization data. The values of P_2 were calculated in the usual method using, however, the extrapolated value of ϵ_0 in case it appears in Table I. In all other cases the experimental value of ϵ_0 was used in all calculations.

The molar refractions MR_D were calculated in all cases from the atomic and the molar refractions given in Landolt–Börnstein. The values of $P_E + P_A$ given in the third column of Table II were taken equal to 1.05 MR_D. The value of MR_D for the last compound in Table II was also calculated from the density and the refractive index of the pure liquid and was in very good agreement with the value obtained from the atomic refractions. The fourth column of Table II gives the polarizations P_∞ obtained by averaging the results of the P_∞ values obtained for each run given in Table I. The fifth column of Table II gives the dipole moments calculated in the usual manner along with the probable errors in the values listed.

TABLE II

Compound	Formula	$P_E + P_A$	P_∞		$\mu \times 10^{18}$
Friedelin	$C_{30}H_{50}O$	136.2	295	(32°)	2.80 ± 0.03
L. M. Friedelinol	$C_{30}H_{52}O$	137.2	201	(32°)	1.78 ± .07
H. M. Friedelinol	$C_{30}H_{52}O$	137.2	200	(50°)	1.81 ± .05
Cerin	$C_{30}H_{50}O_2$	137.9	248	(50°)	2.39 ± .05
Solid	$C_{13}H_{11}Cl$	65.7	98.8	(32°)	1.27 ± .02
Liquid	$C_{13}H_{11}Cl$	65.7	111	(32°)	1.47 ± .02

Discussion of Results

The effect on the polarization of the solute (P_2) of errors in measurement of N_2, ϵ, d and P_1 has already been treated in a quantitative manner[5] and indicates that errors of 0.1% in all of these quantities except N_1 would result in the possibility of large errors in P_2 for solutions where these values are measured at concentrations below about 0.005 N_2. Since the measurements on solutions of friedelin and its related compounds reported here were made at concentrations of 0.0008 N_2 or smaller and since the change in dielectric constant in going from the pure solvent to the most concentrated solution was so small, it may well be questioned whether our results have any physical significance whatsoever.

On examining the quantities ϵ, P_1 and d in order for the effect of errors in them on the μ value in the light of the experimental data obtained, it appeared that errors in extremely dilute solutions were not as great as those assumed for calculation previously[5] and consequently these results have significance, although the precision of the moments calculated is necessarily not as good as that for moments calculated from measurements in more concentrated solutions.

The dielectric constants of the different samples of pure benzene given in Table I varied at the most ±0.009 from an average value of 2.2489. In any particular run, however, all solutions were made up from the same sample of benzene and the utmost precautions were taken to keep the circuit characteristics as constant as possible. Plots of dielectric constant against N_2 for a series of solutions indicated that the data were consistent to better than 0.1%. The question as to whether these day by day variations in the dielectric constant of the solvent affected the value of μ is easily answered. In Table III the measured

TABLE III

$N_2 \times 10^4$	ϵ (Meas.)	P_2	ϵ (Assumed)	P_2 (Based on assumed ϵ's)
0.00000	2.2502	$P_1 = 26.560$	2.2581	$P_1 = 26.679$
1.2117	2.2516	299	2.2595	299
2.1728	2.2528	302	2.2607	303
3.1011	2.2539	301	2.2617	301
4.0923	2.2553	304	2.2632	304

values of ϵ_0 and ϵ obtained from a run on friedelin are given in column two. A value of ϵ_0 is assumed in column four. The deviation between the assumed ϵ_0 and the measured ϵ_0 is about 0.4%. The difference between the measured ϵ_0 and assumed ϵ_0 is added to each in column two to obtain the ϵ values in column four. Reference to the polarization values in columns three and five of Table III shows quite definitely that the absolute values of ϵ_0 have little or no effect on the calculated polarization values provided that the slope of the resulting ϵ *vs.* N_2 curve is not affected. One concludes that in a given solvent the P_2 and ultimately the μ values of the solute depend on the change in ϵ with concentration and if the change in ϵ will be the same for the measured ϵ as it is for the true value of ϵ then the P_2 values will be the same and consequently μ will be the same. Evidently if we are dealing with the same solvent, then the day to day values of ϵ_0 will not materially affect the μ value of a solute dissolved in it, providing the ϵ values of the solutions vary correspondingly.

On plotting the values of ϵ against N_2 a linear relationship was obtained in every run for all of the compounds studied. The extrapolation of the resulting straight lines to $N_2 = 0$ gave in some cases values of ϵ_0 which agreed with the experimental values while in other cases they were either higher or lower than the experimental ϵ_0's. If it is assumed that there is a correct value for ϵ_0 relative to the best straight line which can be drawn for the ϵ *vs.* N_2 data and that this correct value is actually the extrapolated value at $N_2 = 0$, then the following conclusions may be drawn. First, if the measured value of ϵ_0 is smaller than the extrapolated value, the P_2 *vs.* N_2 curve will exhibit an upward trend as the dilution progresses. Second, if it is the same as the extrapolated value, then a positive and negative scattering of points due to experimental error will result. Third, if it is larger than the extrapolated value, then a definite downward trend will exist in the curve. This follows from the equation used for the cal-

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culation of P_2, namely, $P_2 = [P_{12} - P_1(1 - N_2)]/N_2$ where it can be seen that P_2 results from a subtraction of P_1 from P_{12} and consequently if P_1 is smaller than it should be, then P_2 will be greater and *vice versa*. As dilution progresses, however, the error in P_2 is magnified due to a division of difference which decreases rather slowly by a rapidly decreasing N_2. In Table IV we illustrate the above argument using the data of run no. 1 on low-melting friedelinol which showed an upward trend and using the data of run no. 1 on high-melting friedelinol which showed a downward trend when the experimental data were used in both cases to calculate P_1. If the extrapolated ϵ_0 value is used to calculate P_1, then the corresponding P_2 values change. These are given for the above cases in column four of Table IV. It becomes quite evident that on using[6] the extrapolated ϵ_0 value, the marked curvatures are eliminated and the spottiness of points occurs which has been shown to be due to *non-systematic experimental errors*.[5] The variations in ϵ_0 (exp.) and ϵ_0 (extrapolated) need not be very large in such dilute solutions to cause abrupt changes in curvature in the polarization curves. The values given in Table IV represent deviations of less than 0.03%.

TABLE IV

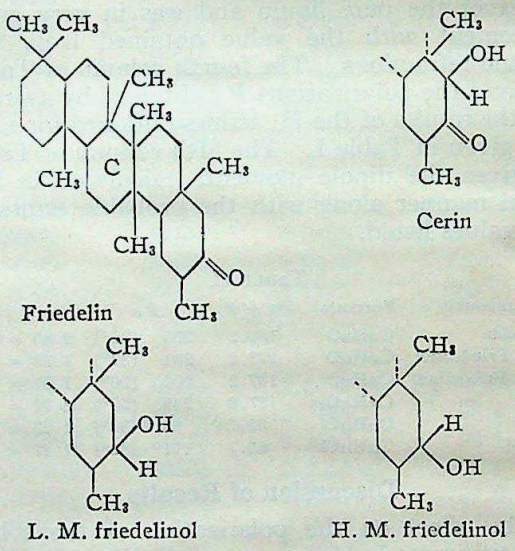
EFFECT OF CORRECTED DIELECTRIC CONSTANT OF THE PURE SOLVENT ON POLARIZATION VALUES

ϵ (meas.)	P_2	ϵ_0 (extrap.)	P_2
Low-Melting Friedelinol, Run no. 1			
$\epsilon_0 = 2.2473$	$P_1 = 26.518$	2.2478	$P_1 = 26.526$
2.2484	281		211
2.2491	241		207
2.2496	227		203
2.2502	223		205
2.2513	215		203
2.2526	215		206
High-Melting Friedelinol, Run no. 1			
$\epsilon_0 = 2.2090$	$P_1 = 26.548$	2.2085	$P_1 = 26.541$
2.2091	137		193
2.2095	142		189
2.2099	159		180
2.2109	174		187

All the polarization data given in Table I were calculated using ϵ_0 (extrapolated) if the ϵ_0 (extrapolated) and ϵ_0 (experimental) values differed.

Errors in the measurement of density because of the subtraction involved in the calculation will be relative to one another just as were those of ϵ and thus any variation of the density curve between separate runs will show up as a change in μ. Here again the absolute value obtained for the density is not important if the same assumption is made as was made previously for ϵ, *i. e.*, that the change in the density as measured would be the same as that for the absolute value. The slope in the density curve would not be expected to vary much even if widely varying values for d_0 were obtained for the same solvent.

The structures of friedelin, the friedelinols and cerin are believed[3] to be either the following



or some modification of these structures where the functional groups are, however, located near the end of the molecule, definitely not in ring C. The moment found for friedelin, $\mu = 2.8\ D$, may be compared to that of cyclohexanone which is given variously in the literature[7] as 2.75, 2.8, 2.90 and 3.00 D. The moments found for the isomers of friedelinol, $\mu = 1.8\ D$ may be compared to that of cyclohexanol which is given[7] as 1.69, 1.82 and 1.9 D. The moment found for cerin, $\mu = 2.39\ D$, could not be compared with a compound having similar functional groups since apparently none have been measured.

Thus we conclude that the moments of the compounds given above offer independent evidence for the structures which have been assigned to them. Furthermore, the residues of the structures (besides the functional groups) involved in each case affect slightly if at all the characteristic moments of the functional groups.

The solid and liquid forms of $C_{13}H_{11}Cl$ were thought to be *cis–trans* isomers.[8] While the

(6) There appeared recently a paper by Halverstadt and Kumler, THIS JOURNAL, 64, 2988 (1942), in which they discuss errors which would lead to marked rises in the polarization curves. They also develop methods of treating the data which would eliminate such rises. In this paper and in an earlier one, ref. 5, it was found necessary to explain apparent decreases as well as increases in the polarization curves at high dilutions. The method used by us in getting an extrapolated ϵ_0, while developed independently, is essentially the same as the one proposed by H. and K. However our conclusions differ inasmuch as we believe that both the apparent rise and the apparent fall in the polarization curves are due to experimental error in getting the true dielectric constant of the solvent. The value of ϵ_0 obtained by extrapolation of the ϵ *versus* N_2 curve may be either higher, lower or equal to the measured value of ϵ_0. When the experimental and extrapolated values of ϵ_0 were the same, then in the cases we investigated, the polarization curves behaved linearly; in case they differed then abnormal behavior occurred.

(7) (a) "Dipole Moments," *Trans. Faraday Soc.* (1934); (b) Halverstadt and Kumler, THIS JOURNAL, 64, 1982 (1942).

(8) T. H. Harris, M.S. Thesis, George Washington University,

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chemical evidence was inconclusive, nevertheless it appeared as though the solid form might be the *trans*-isomer and the liquid form the *cis*-isomer. The moments found for the two compounds, namely, 1.27 *D* for the solid and 1.47 *D* for the liquid, support the assumption of *cis–trans* isomerism.

Acknowledgment.—We wish to acknowledge the assistance of Dr. Peter Oesper in the experimental work on the $C_{13}H_{11}Cl$ compounds.

Summary

1. The precision of the calculated P_2 values and consequently of the dipole moment of a solute in a given solvent does not materially depend on the absolute values of the dielectric constants and densities.

2. Marked upswings and downswings in the polarization curves at high dilution are shown to be due to experimental error in measuring ϵ_0. It is suggested that an extrapolated ϵ_0 value obtained from an ϵ *vs.* N_2 plot be accepted as the dielectric constant of the pure solvent.

3. The dipole moments of friedelin, low and high-melting friedelinol, cerin and the solid and liquid forms of 3-α-naphthyl-1-chloro-1-propene have been determined.

4. The observed dipole moments of these compounds are compatible with their postulated structures.

COLLEGE PARK, MARYLAND RECEIVED OCTOBER 25, 1943

[CONTRIBUTION FROM THE BIOCHEMICAL LABORATORY, STATE UNIVERSITY OF IOWA]

The Kinetics of the Antioxygenic Synergism of Quinones with Ascorbic Acid in Fat Systems[1]

BY VINCENT P. CALKINS[2] AND H. A. MATTILL

In a study of the well-recognized capacity of ascorbic acid, under certain conditions, to act as an inhibitor of fat oxidation, Golumbic and Mattill[3] demonstrated that by itself it was a relatively ineffective antioxidant, but that in fats and oils containing tocopherols, it greatly enhanced the stabilizing action of these naturally occurring inhibitors. This reinforcing action of ascorbic acid was shown to extend to other fat stabilizers of phenolic character, including quinols and hydroxy chromans, and appeared to be accomplished by a delaying of the quinol ⇄ quinone oxidation that is fundamentally responsible for their stabilizing capacity. Isler[4] had earlier demonstrated that ascorbic acid markedly protected tocopherol from oxidation.

The oxidation potentials of the antioxygenic quinols[5] are appreciably higher than that of ascorbic acid. Since fat peroxides oxidize quinols, their oxidation potentials are still higher, but despite this considerable difference in potential between ascorbic acid and the fat peroxides, ascorbic acid added to fats is neither appreciably oxidized during their induction period nor does it sensibly prolong this period unless quinones, hydroquinones or other phenolic inhibitors are present.

This investigation is a kinetic study of the role of these intermediary agents in the antioxygenic action of ascorbic acid.

The systems used comprised the ethyl esters of lard fatty acids with and without ascorbic acid, with and without quinone; since quinone is antioxygenic because it is reduced to hydroquinone, the hydroquinone-lard ethyl esters system was also studied.

The ethyl esters of lard fatty acids were prepared according to the method of Olcott and Mattill[6] and were stored in the icebox under nitrogen. The induction period of each system was measured by the oxygen absorption method in oxygen at 75°; from time to time during its progress, determinations were made of hydroquinone, ascorbic acid, dehydroascorbic acid and glycolic acid, and these results were plotted against time.

Hydroquinone was determined by the α,α′-dipyridyl color reaction[7]; a calibration curve (Klett-Summerson photoelectric colorimeter, Filter 52) showed that the logarithmic reading was a linear function of the amount of hydroquinone present and obeyed Beer's law. Peroxides, except in a very low concentration, interfere with this determination.

Ascorbic acid and dehydroascorbic acid were determined by the method of Bessey,[8] slightly modified to fit the existing conditions. A calibration curve prepared from readings made on solutions of known concentration was linear and obeyed Beer's law. In the assay of dehydroascorbic acid, particular care was taken to remove

(1) The experimental data in this paper are taken from a dissertation submitted by Vincent P. Calkins to the Faculty of the Graduate College of the State University of Iowa in partial fulfillment of the requirements for the degree of Doctor of Philosophy, April, 1943. A preliminary report of some of the results has appeared (*Fed. Proc.*, **1**, 104 (1942)).

(2) A part-time grant to V. P. C. from Merck and Co., Inc., is gratefully acknowledged.

(3) Calvin Golumbic and H. A. Mattill, THIS JOURNAL, **63**, 1279 (1941).

(4) O. Isler, *Helv. Chim. Acta*, **21**, 1756 (1938).

(5) J. B. Conant and L. F. Fieser, THIS JOURNAL, **46**, 1868 (1924).

(6) H. S. Olcott and H. A. Mattill, *ibid.*, **58**, 2204 (1936).

(7) A. Emmerie and C. Engel, *Rec. trav. chim.*, **57**, 1351 (1938).

(8) O. A. Bessey, *J. Biol. Chem.*, **126**, 771 (1938).

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the last traces of hydrogen sulfide because of the interference of sulfhydryl compounds.[9]

To determine total ascorbic and dehydroascorbic acids, both dissolved and undissolved, in the ester mixture, the entire contents of the test flask was extracted with a mixture of benzene and 3% metaphosphoric acid in a separatory funnel. The acid layer was analyzed for ascorbic and dehydroascorbic acids. For the occasional determination of dissolved ascorbic and dehydroascorbic acids in the ester mixture, a portion of this was weighed out, made up to a definite volume with benzene and centrifuged to remove any undissolved acids. The supernatant liquid was then extracted with 3% metaphosphoric acid solution, the benzene fraction retaining any hydroquinone or quinone present, the metaphosphoric acid solution containing the ascorbic acid and its oxidation products. This solution was buffered with citrate to *p*H 3.5–3.6 and was centrifuged again to remove remaining traces of benzene. Absence of any emulsion was absolutely necessary for the successful use of the modified method for determining ascorbic acid; the second centrifugation aided the process of separation without danger of emulsification.

Glycolic acid was estimated by a new method[10] based on a color reaction with 2,7-dihydroxynaphthalene in concentrated sulfuric acid.

The average induction period of the esters was one to two hours, but since this varied with the freshness of the sample, a blank was always run simultaneously with the protected fat, thus permitting a comparison between the various runs on the basis of an antioxygenic index. Figure 1 shows the rate of disappearance of hydroquinone (0.02% in 20 cc. of esters) during the induction period, which in this case was nineteen hours as against one hour for the unstabilized fat. When plotted logarithmically, this curve suggests an order of reaction lying between 0 and 1. Half of the hydroquinone was oxidized in the first five hours; oxidation of the remainder required fourteen hours. As has appeared in other connections,[11,12] the length of the induction period is a function of the concentration of quinol; at its close, all the hydroquinone was in the form of quinone for, on reduction, all that had originally been introduced could be recovered. When very pure quinone was added to the ethyl esters, the original content of quinol, 1.2 μg per gram of quinone, was increased to 6.5 μg during fifteen minutes warming in air or under nitrogen. Quinone apparently acts as a hydrogen acceptor, and the hydrogen may come from the fat as a result of the formation of further double bonds (oxidation).[13]

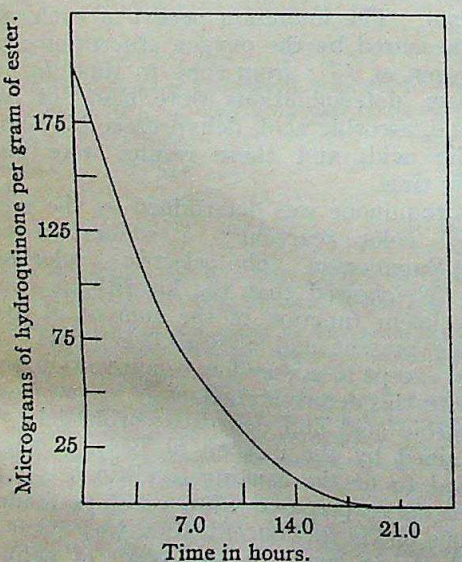

Fig. 1.—Disappearance of hydroquinone during the induction period of ethyl esters of lard fatty acids.

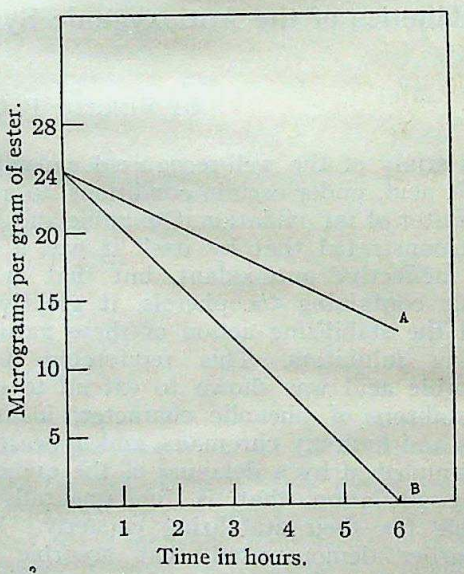

Fig. 2.—Disappearance of ascorbic acid (0.0024%) in ethyl esters: A, ascorbic acid alone; B, ascorbic acid and 0.02% quinone.

The disappearance of ascorbic acid (0.0024%), both dissolved and undissolved, during the oxidation of the ethyl esters is shown in Fig. 2. Both in the presence (Curve B) and in the absence (Curve A) of quinone, this follows a zero order reaction; the oxidation of ascorbic acid is independent of its concentration, as represented by the equation

$$-\mathrm{d}c/\mathrm{d}t = k$$

Upon integration this equation assumes the form

$$K = (C_0 - C_t)/(t_2 - t_0)$$

and from the slope of curve A, K_A is found to be 2.5×10^{-9} mole per liter per second. Similar

(9) C. G. King, personal communication.
(10) V. P. Calkins, *Ind. Eng. Chem., Anal. Ed.*, **15**, 703 (1943).
(11) Calvin Golumbic, *Oil and Soap*, **19**, 181–182 (1942).
(12) Calvin Golumbic, *ibid.*, **20**, 105 (1943).
(13) F. E. Deatherage and H. A. Mattill, *Ind. Eng. Chem.*, **31**, 1425 (1939).

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calculation for curve B gives a figure for K_B, 5.2×10^{-9} mole per liter per second. The rate of oxidation of ascorbic acid in the ethyl esters is thus approximately twice as great in the presence of quinone as in its absence. Traces of ascorbic acid were found in solution in the esters when it was present by itself (A), but never when quinone was also present (B). Apparently in the presence of quinone, ascorbic acid is oxidized as quickly as it goes into solution, but this does not necessarily imply that the interaction of quinone and ascorbic acid is solely a solution phenomenon. The significance of these two constants K_A and K_B will be discussed later.

The effect of the increased rate of oxidation of ascorbic acid in the presence of quinone is clearly demonstrated in Fig. 3. Curve E represents the peroxide formation in lard ethyl esters alone; curve D shows the slightly decreased rate of peroxide formation in esters containing 0.0024% of ascorbic acid. Curve C represents peroxide formation in the ester system containing 0.02% quinone in addition to 0.0024% ascorbic acid. Comparison of these curves shows the powerful synergistic action of ascorbic acid with quinone in the stabilization of the esters.

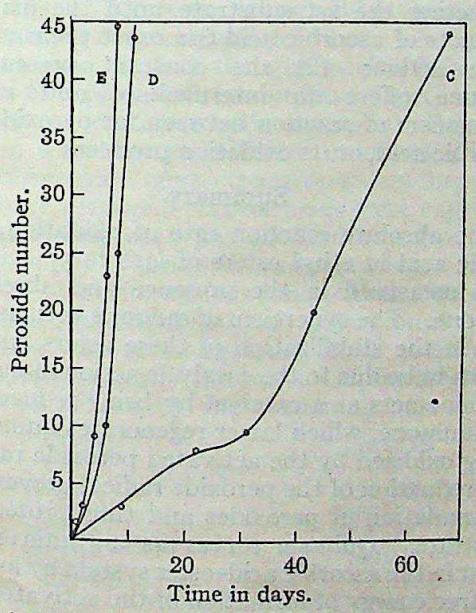

Fig. 3.—Peroxide formation in the ethyl esters containing: E, no additions; D, 0.0024% ascorbic acid; C, 0.0024% ascorbic acid and 0.02% quinone.

The actual mechanism of this synergistic action is suggested by Fig. 4, where the curves represent the course of the oxidation of ascorbic acid in the quinone–ester system as studied by the tests available. Each curve is a composite of a series of determinations and shows the mean path followed by the various substances involved.

Curve C (ascorbic acid) shows that the ascorbic acid had completely disappeared in less than six hours although the induction period lasted for nearly seventy hours. Curve A shows the gradual appearance and subsidence of dehydroascorbic acid, that is, a typical curve for the primary resultant of a consecutive reaction. Part of the oxidized dehydroascorbic acid is found in the form of glycolic acid as shown by Curve B. The glycolic acid content seems to remain relatively constant throughout the course of the induction period.

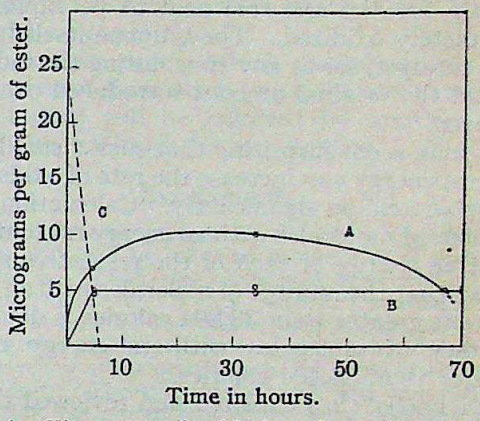

Fig. 4.—The course of oxidation of ascorbic acid in fat ethyl esters, in the presence of quinone: A, total dehydroascorbic acid; B, glycolic acid; C, total ascorbic acid.

Discussion

The significance of the two velocity constants, K_A and K_B, is best demonstrated by substituting their respective values in an equation developed by Eyring,[14] Gershinowitz[15] and others where K_1

$$K_1 = \frac{kTe^{-\frac{\Delta F^*}{RT}}}{h}$$

is the specific rate constant, ΔF^* is the free energy of formation of the activated state, T is the absolute temperature, R is the universal gas constant and k and h are the Boltzmann and Planck constants, respectively. This expression shows that the rate of a reaction is determined by a free energy change which usually is not the same as the free energy change for the total reaction. Use is made of an activated complex, and it is shown that the rate of a chemical reaction is determined by the concentration of the reacting systems in a certain fraction of the total phase space available, multiplied by the velocity with which the systems are passing through this space. ΔF^* cannot be the same as ΔF unless the energy of formation of the activated state is equal to the energy of the reaction.

By applying this equation to the velocity constants of both the ascorbic acid–lard ethyl esters and the ascorbic acid–quinone–lard ethyl esters systems, the respective ΔF^* of each system can be determined. By rearrangement of the equation and substitution of numerical values, ΔF^* values are obtained: $\Delta F_1^* = 34{,}404$ calories per mole per liter; $\Delta F_2^* = 33{,}894$ calories per mole per

(14) H. Eyring, *J. Chem. Phys.*, **3**, 107 (1935).
(15) [illegible], *Trans. Faraday Soc.*, **34**, 1323 (1938).

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liter; where ΔF_1^* and ΔF_2^* are the free energies of formation of the activated states of the ascorbic acid–lard ethyl ester system and the ascorbic acid–quinone–lard ethyl ester system, respectively.

The difference between the two ΔF^* values, 510 calories per mole per liter, indicates that the addition of quinone to the ascorbic acid–lard ethyl ester system lowers the free energy level sufficiently for the ascorbic acid to be rapidly and completely oxidized. The quinone itself behaves as a catalyst, for at any time during the induction period the original amount introduced can be recovered.

It may seem surprising that such a small difference in energy can increase the rate of oxidation of ascorbic acid so significantly. Calculation of the number of molecules with an energy content above the free energy of each of the respective systems shows that the number of molecules with an energy content greater than 33,894 calories is double the number of molecules with an energy content greater than 34,404 calories.

Michaelis[16] has explored and reviewed the role of semiquinones as intermediate steps of reversible organic oxidation–reduction. The oxidation of organic compounds is frequently sluggish, even when an oxidant of thermodynamically sufficient oxidative power is applied, because it must, as a rule, go through two univalent steps; the intermediate step generally involves climbing over an energy hill; catalysts and enzymes concerned with oxidation–reduction processes convert the substance to be oxidized into some form or compound, in which the intermediate radical has a stronger resonance and so a greater stability than the original form.

These results with ascorbic acid and quinone can be interpreted on this basis, and the following hypothetical mechanism would explain them. The oxidation of ascorbic acid must go through two univalent steps, and to go through the intermediate step means climbing over a larger energy hill when quinone is absent than when it is present. In its presence, the oxidation of ascorbic acid can readily pass through its intermediate step since the free energy of formation of the activated complex, ascorbic acid + quinone, is less than that of the formation of the activated complex, ascorbic acid + peroxide radical. The compulsory univalent oxidation of ascorbic acid is favored more by the presence of quinone than by the presence of fat peroxide radical.

Quinone may act as a catalyst by being reduced to a semiquinone which latter is oxidized back to quinone by the activated peroxide radical, thus protecting the substrate. Necessarily, the free energy of formation of the activated complex of the semiquinone with the peroxide radical must be less than the free energy of formation of the activated complex of ascorbic acid with the peroxide radical. Otherwise, quinone could not act as an intermediary agent. Since only a trace of semiquinone, tested as quinol, could be found throughout the reaction, its rate of oxidation must be very high, significantly higher than that of ascorbic acid, and its free energy value correspondingly less.

In the ascorbic acid–quinone–ester system, the early and complete disappearance of ascorbic acid relative to the long induction period of the fat suggests that the real antioxidant involved is an oxidation product of ascorbic acid. This may be dehydroascorbic, 2,3-diketogulonic, threonic, glycolic, or oxalic acid, or a combination of all of them. The oxidation of ascorbic acid proceeded beyond dehydroascorbic acid and at least to glycolic acid.

The ascorbic acid–ester system differs from the quinone–ascorbic acid–ester system in two important aspects: (1) the presence of quinone permits the rapid oxidation of ascorbic acid, thus protecting the fat substrate until the oxidation products of ascorbic acid can exert their antioxygenic action; (2) the constant presence of quinone offers an intermediate and indirect mechanism of reaction between fat peroxides and ascorbic acid, or its oxidation products.

Summary

The absolute reaction rate of oxidation of ascorbic acid in ethyl esters of lard fatty acids has been measured in the presence and absence of quinone. The synergism of quinone with ascorbic acid in the stabilization of these esters has been shown to be due to the catalytic action of quinone. Quinone acts as a catalyst by being reduced to a semiquinone, which latter regenerates quinone by being oxidized by the activated peroxide radicals; this reduction of the peroxide radical prevents the accumulation of peroxides and thus protects the substrate. Quinone serves as an intermediary agent in the ascorbic acid–ester system by lowering the free energy of formation of the activated complex to such an extent that it doubles the number of particles of ascorbic acid possessing sufficient energy of reaction. The results follow closely the views of Michaelis on compulsory univalent oxidation, and on the basis of these data a mechanism for the synergistic action of quinone with ascorbic acid is proposed.

(16) L. Michaelis, *Chem. Revs.*, 16, 243 (1935).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

The Preparation of 2-Ketopolyhydroxy Acids

BY PETER P. REGNA[1] AND B. P. CALDWELL

It was observed by one of the authors[2] that when an aqueous solution of a methyl ester of a 2-ketohydroxy acid is heated in the presence of certain metallic elements, the esters are transformed into their corresponding ascorbic acid analogs. A marked difference was noted in the speeds with which the isomeric esters methyl 2-keto-D-gluconate and methyl 2-keto-L-gulonate, enolize and lactonize during this treatment.

In view of this, the present authors decided to study the rates of rearrangements of the four theoretically possible 2-ketohydroxy acids of the six-carbon series, namely, 2-keto-gluconic, -gulonic, -galactonic and -altronic acids. The latter two acids had not previously been prepared; 2-keto-D-gluconic acid was first obtained by Ohle,[3] from diacetone fructose, and 2-keto-L-gulonic acid was later prepared by Reichstein,[4] who used it as an intermediate in the synthesis of L-ascorbic acid. While the preparation of 2-keto-D-galactonic acid is described in the present paper, that of 2-keto-D-altronic acid is the subject of an ensuing communication.

In addition, it was thought advisable and of interest to explore the rearrangement mechanisms of seven-carbon 2-ketohydroxy acids. For purposes of structure the hitherto unknown 2-keto-D-glucoheptonic and 2-keto-D-galactoheptonic acids were prepared. These acids were expressly chosen because each has the hydroxy groups of carbon atoms 3 and 4 in *trans* position. If the rates of transformations into their ascorbic analogs are functions only of those groups which enter into the rearrangement, then their rates should be practically the same. If, however, the rate is influenced by the remaining part of the

COOH	COOH
CO	CO
HCOH	HCOH
HOCH	HOCH
HCOH	HOCH
HCOH	HCOH
CH_2OH	CH_2OH
(I)	(II)

molecule, then these acids should show a marked difference in rate of rearrangement, since the hydroxy groups on carbon atoms 4 and 5 of 2-keto-D-glucoheptonic acid (I) are in the *trans* position while on 5 and 6 they are in the *cis* position. But the structure of 2-keto-D-galactoheptonic acid (II) is the opposite of this; the hydroxy groups on carbon atoms 4 and 5 are in the *cis* position while on carbon atoms 5 and 6 they are in the *trans* position.

The present paper, which describes only the preparation of these acids (with the one exception above noted) will be followed by another containing the results of the rate studies.

Experimental

Calcium 2-Keto-D-gluconate.[5]—To 178 g. of D-glucono-γ-lactone dissolved by refluxing in one liter of methanol containing 5 cc. of 85% phosphoric acid, after cooling, 37 g. of sodium chlorate and 6 g. of vanadium pentoxide were added. The mixture was shaken for four days (20°) until dehydrogenation was complete as shown by the change from the yellow of the pentoxide to the green of the vanadium trioxide. The solid catalyst was then removed, and the solution was concentrated *in vacuo* to a sirup. After standing for two days at 3° the methyl 2-keto-D-gluconate (yield 60%) contaminated with sodium chloride, was collected, washed with methanol–acetone and recrystallized from dioxane: m. p. 175–176°; $[\alpha]^{20}D$ −76.8° (*c*, 2 in water) at equilibrium.[6]

The ester was hydrolyzed by dissolving 100 g. in one liter of 2 *N* sulfuric acid and storing at 30° for four days. The SO_4^{--} precipitated with barium carbonate, was filtered, the filtrate neutralized with calcium carbonate and evaporated to 250 cc. *in vacuo* at 40°. On standing overnight (20°) the calcium 2-keto-D-gluconate·$3H_2O$ crystallized. Two recrystallizations from water gave $[\alpha]^{20}D$ −70.8° (*c*, 2 in water).

Anal. Calcd. for $Ca(C_6H_9O_7)_2 \cdot 3H_2O$: Ca, 8.34; H_2O, 11.25. Found: Ca, 8.30; H_2O, 11.2.

The physical properties and composition of the salt have apparently not been previously reported. The degree of hydration was determined by heating the salt to constant weight at 90° for sixteen hours under 0.01 mm. pressure.

2-Keto-D-galactonic Acid.—To a solution containing 43.8 g. of potassium D-galactonate in 200 cc. of water, 8.2 g. of potassium chlorate, 0.5 g. of vanadium pentoxide and 3 cc. of phosphoric acid were added. After four days the solution was filtered, treated with calcium ferrocyanide and the vanadium ferrocyanide discarded. The filtrate was neutralized with calcium hydroxide to precipitate the PO_4^{---}, filtered, treated with 15 g. of calcium acetate, evaporated *in vacuo* to 60 cc., and the unreacted calcium D-galactonate allowed to crystallize (0°) during two days. Two further crops were recovered (a total of 40% of starting material), the excess Ca^{++} precipitated with oxalic acid, and the filtrate evaporated to dryness *in vacuo*. The residue was dissolved in 25 cc. of water, methanol slowly added, and after standing several days crude crystalline potassium 2-keto-D-galactonate was obtained (yield 30%). Two recrystallizations from water gave $[\alpha]^{20}D$ −6.7° (*c*, 1.2 in water).

Anal. Calcd. for $KC_6H_9O_7$: K, 16.84. Found: K, 16.78.

The free acid was liberated from the potassium salt by treatment with the exact amount of aqueous sulfuric acid and the potassium sulfate precipitated with dioxane. From the filtrate evaporated *in vacuo* to a sirup, and al-

(1) This paper is constructed from a thesis presented in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry, June, 1942, and was presented before the Division of Organic Chemistry of the American Chemical Society, Pittsburgh meeting, September, 1943. Present address: Chas. Pfizer & Co., Inc., Brooklyn, New York, N. Y.

(2) Pasternack and Regna, U. S. Patents 2,165,151, 2,165,184, July 4, 1939.

(3) Ohle, *Ber.*, **58**, 2577 (1925).

(4) Reichstein, *Helv. Chim. Acta*, **16**, 561, 1019 (1933).

(5) *Cf.* Pasternack and Regna, U. S. Patent 2,207,991, July 16, 1940.

(6) Ohle, *Ber.*, **63**, 843 (1930).

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lowed to stand overnight (0°) the crystalline 2-keto-D-galactonic acid was recovered, washed with aqueous dioxane and recrystallized from water: m. p. 170–171°; $[\alpha]^{20}D$ −6.0° (*c*, 2 in water), and on titration with alkali showed 99.9% purity.

Anal. Calcd. for $C_6H_{10}O_7$: C, 37.12; H, 5.19. Found: C, 37.02; H, 5.30.

Methyl 2-Keto-D-galactonate.—The acid (5 g.) was dissolved in 100 cc. of freshly distilled methanol containing 0.15% hydrogen chloride. The mixture was refluxed for two hours, and evaporated by repeated concentration *in vacuo* with methanol. Crystals of methyl 2-keto-D-galactonate were washed and recrystallized from alcohol–chloroform mixtures: m. p. 138–139° and $[\alpha]^{20}D$ −11.3° (*c*, 1.2 in water). D-Ascorbic acid m. p. 192° and $[\alpha]^{20}D$ −23° was made from this ester by the method of Maurer and Schiedt,[7] and this served to establish further the constitution of 2-keto-D-galactonic acid.

Sodium 2-Keto-D-glucoheptonate Monohydrate.—A hot solution of α-D-glucohepto-γ-lactone[8] (416 g.) was neutralized with 106 g. sodium carbonate, cooled, diluted to 4.2 liters and 73 g. of sodium chlorate, 40 cc. of 85% phosphoric acid and 20 g. of vanadium pentoxide were added. After stirring for two days, the reaction was complete; it was filtered, treated with enough calcium ferrocyanide to precipitate the V^{+++}, filtered again, the PO_4^{---} precipitated with calcium hydroxide, and the excess Ca^{++} removed with oxalic acid. The colorless solution containing only sodium salts was concentrated to 2 liters and an equal volume of methanol added dropwise with stirring during thirty-six hours. The crude crystalline sodium 2-keto-D-glucoheptonate (yield 38%) was recrystallized twice from 40% aqueous methanol: $[\alpha]^{20}D$ +45.5° (*c*, 2 in water).

Anal. Calcd. for $Na(C_7H_{11}O_8)\cdot H_2O$: Na, 8.70; C, 31.82; H, 4.96. Found: Na, 8.60; C, 31.87; H, 5.10.

The constitution of the 2-keto acid was established by preparing D-glucoascorbic acid from it. The free acid liberated from the sodium salt (26.4 g.) by sulfuric acid and precipitation with methanol was repeatedly evaporated *in vacuo* with methanol. The final residue was dissolved in 100 cc. of absolute methanol, treated with a measured quantity of diazomethane and concentrated *in vacuo* to 50 cc. The ester solution was stirred with 50 cc. of sodium methylate (containing 2.42 g. of sodium) at 45° under a current of nitrogen. When the suspension thinned out, it was treated with 10 cc. of 51.5% sulfuric acid, filtered, evaporated to dryness *in vacuo*, the residue dissolved in methanol, Norite was added and filtered. The filtrate was concentrated *in vacuo* to 25 cc. and allowed to stand several days at 0°. D-Glucoascorbic acid monohydrate recrystallized twice from methanol–acetone showed m. p. 140°, $[\alpha]^{20}D$ −22.0° (*c*, 1 in water) and iodine titration 99.7% which values agree with those obtained by Haworth, Hirst and Jones[9] who prepared D-glucoascorbic acid through the addition of hydrogen cyanide to glucosone.

Potassium 2-Keto-D-galactoheptonate.—A mixture of α- and β-D-galactoheptonic acids prepared by the addition of hydrogen cyanide to galactose, was neutralized with potassium carbonate. The dehydrogenation procedure described above for the isomeric acid was followed. However, the potassium 2-keto-D-galactoheptonate crystallized very readily on the addition of methanol to the aqueous solution of the potassium salts (yield about 65%). The crude potassium salt was recrystallized from water until a constant rotation was obtained; $[\alpha]^{20}D$ +67.5° (*c*, 2 in water).

Anal. Calcd. for $KC_7H_{11}O_8$: K, 14.91; C, 32.06; H, 4.23. Found: K, 14.90; C, 32.08; H, 4.37.

The constitution of 2-keto-D-galactoheptonic acid was established by preparing *d*-galactoascorbic acid from it by employing the procedure described above for 2-keto-D-glucoheptonic acid. Recrystallization from methanol–acetone yields the monohydrate. There is an evolution of gas at its m. p. 109° and a blackening at 190°, which observations are in agreement with those of Haworth,[10] *et al.*, who prepared D-galactoascorbic acid through the addition of hydrogen cyanide to galactosone.

Summary

1. A general method is described for the catalytic dehydrogenation of α-hydroxy groups of six- and seven-carbon membered polyhydroxy acids.

2. Of the six-membered polyhydroxy acids, the previously unknown 2-keto-D-galactonic acid is described, and the properties of calcium 2-keto-gluconate trihydrate are noted.

3. In the seven-membered polyhydroxy acids, 2-keto-D-glucoheptonic and 2-keto-D-galactoheptonic acids have been prepared and described, and from these keto acids, corresponding ascorbic acid analogs were made.

(7) Maurer and Schiedt, *Ber.*, **66**, 1054 (1933).

(8) Hudson, Hartley and Purves, THIS JOURNAL, **56**, 1248 (1934).

(9) Haworth, Hirst and Jones, *J. Chem. Soc.*, 549 (1937).

(10) Baird, Haworth, Herbert, Hirst, Smith and Stacey, *ibid.*, 62, (1934).

BROOKLYN, N. Y. RECEIVED JULY 10, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

A Method for the Preparation of Calcium D-Altronate[1]

BY PETER P. REGNA[2] AND B. P. CALDWELL

In the course of work being carried out in this Laboratory in connection with the rates of transformation of 2-ketopolyhydroxy acids[3] into their ascorbic acid analogs, 2-ketoaltronic acid was needed. For this purpose we were interested in catalytically dehydrogenating either allonic or altronic acid in attempts to prepare the last remaining unknown 2-ketoaldonic acid. Accordingly we have produced D-altronic acid in large quantities by the following series of reactions: pectin → sodium calcium D-galacturonate → calcium 5-keto-L-galactonate → calcium D-altronate and calcium L-galactonate. The steps in the procedure, indicated by the acids of the foregoing salts, are represented by the configurational formulas

(1) Presented before the Division of Organic Chemistry of the American Chemical Society, Pittsburgh meeting, September, 1943.

(2) This paper is constructed from a thesis presented in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry, June, 1942. Present address: Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

(3) Regna and Caldwell, THIS JOURNAL, **65**, 246 (1943).

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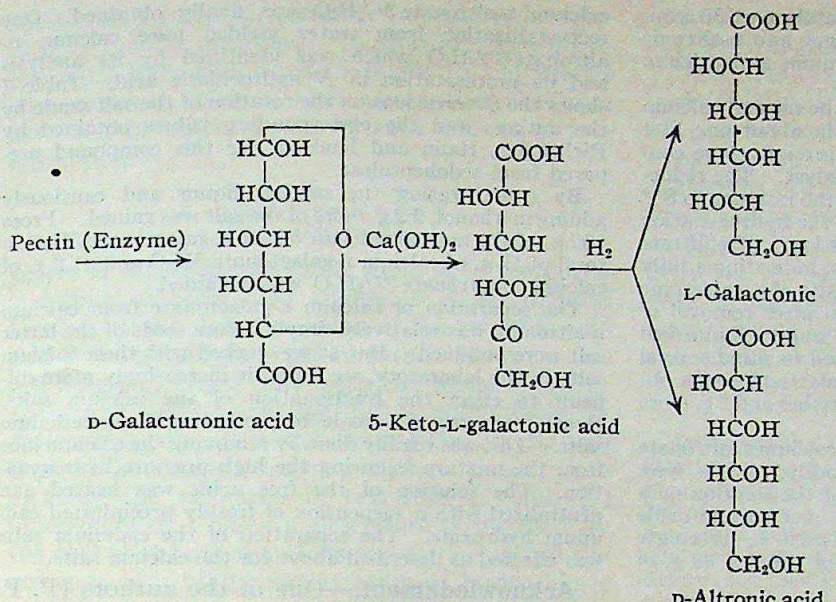

The simplicity of this method provides a convenient source of D-altronic acid for the preparation of D-ribose.[4] In addition the procedure yields about equal quantities of the isomeric L-galactonic acid as a by-product. The heretofore almost unavailable L-galactonic acid may also be prepared by direct hydrogenation of sodium calcium D-galacturonate.

The existing methods for obtaining altronic acid are of limited applicability. Levene and Jacobs[5] made use of the addition of hydrogen cyanide to the costly sugar D-ribose, while the difficultly obtainable D-talonic acid is required for a method reported by Steiger and Reichstein.[6] The recent procedure of Richtmyer, Hann and Hudson[7] starting from *Sedum spectabile* was ineffectual because of the low yields of altronic acid.

The D-altronic acid prepared by the authors was readily oxidized by the procedure previously described[8] for the catalytic dehydrogenation of α-hydroxy groups of polyhydroxy acids. Although a number of salts of D-altronic acid were oxidized to the 2-ketoaltronates, none was found to be crystalline.

Experimental

Sodium Calcium-D-Galacturonate Hexahydrate.—D-Galacturonic acid was prepared by a modification of the joint methods of Pigman[9] and Mottern and Cole.[10] To six liters of distilled water was added 35 g. of Rohm and Haas Pectinol 46 AP, standardized with diatomaceous earth 100 D. The suspension was mechanically stirred and 600 g. of commercial citrus pectin was added in small portions. The viscous solution was covered with a thin layer of toluene to prevent mold growth, stoppered and allowed to stand for fourteen days at room temperature. At the end of this time a portion of the solution was titrated with standard alkali and showed 433 g. of D-galacturonic acid. An analysis by Fehling solution and calculated on the basis of galacturonic acid, indicated 487 g.

The main solution was treated with norite and filtered. Then two-thirds of the galacturonic acid in solution was neutralized with 77 g. of calcium carbonate, and the remaining one-third with 41 g. of sodium carbonate. There was an immediate precipitation of the double salt of galacturonic acid upon stirring the solution. This crop was filtered off and washed with water. Succeeding crops were obtained as the filtrates were repeatedly evaporated *in vacuo*. The combined crops after drying at about 50° weighed 464 g. A small sample of the double salt recrystallized from water was found upon analysis to have a composition corresponding to the hexahydrate, $[\alpha]^{20}D$ +33.0 (*c*, 1 in water), corresponding to $[\alpha]^{20}D$ +38.6° for the anhydrous salt.

Anal. Calcd. for $NaCa(C_6H_9O_7)_3 \cdot 6H_2O$: Ca, 5.33; Na, 3.07, uronic acid by CO_2 determination, 77.6. Found: Ca, 5.33; Na, 2.98; uronic acid by CO_2 determination, 78.1.

Calcium 5-Keto-L-galactonate.—Ehrlich and Guttmann,[11] found that in saturated limewater D-galacturonic acid undergoes the usual Lobry de Bruyn interconversion reaction by isomerizing the end CH(OH)CHO group into $COCH_2OH$. This produces the basic calcium salt of 5-keto-L-galactonic acid which is sparingly soluble in water, and consequently, the equilibrium shifts continuously in favor of the insoluble salt. The normal calcium 5-keto-L-galactonate was prepared from the basic calcium salt which, in turn, was produced by a modification of the method of Ehrlich and Guttmann.

In a typical run, 8.2 g. of calcium chloride was added to ten liters of filtered limewater containing 16.2 g. of calcium hydroxide. Sodium calcium D-galacturonate hexahydrate (111 g.) was then dissolved in this solution with stirring until it was clear. After about six days the basic calcium salt of 5-keto-L-galactonate, $(C_6H_9O_7)\cdot Ca(OH)\cdot 2H_2O$, precipitated in pale yellow crystals. These were separated from the large volume of water by a suction filter, washed with water and dried (110 g.). The salt was not further purified, but was suspended in water, neutralized with oxalic acid to a *p*H of 6.0 and the precipitated calcium oxalate filtered off. The filtrate was treated with norite, warmed, refiltered, and the filtrate evaporated *in vacuo*.

Erhlich and Guttmann were unable to crystallize sufficient of the normal calcium 5-keto-L-galactonate to obtain its analysis and physical properties. In the present case, however, after long standing a seed was obtained which caused the ready crystallization of the main solution. Normal calcium 5-keto-L-galactonate pentahydrate is a moderately soluble white salt: $[\alpha]^{20}D$ −14.0 (*c*, 1.15 in water), corresponding to $[\alpha]^{20}D$ −17.0 for the anhydrous salt. The specific rotation on the amorphous salt was obtained by Ehrlich and Guttmann as −15.25°, perhaps due to a less hydrated salt.

Anal. Calcd. for $Ca(C_6H_9O_7)_2 \cdot 5H_2O$; Ca, 7.76. Found: Ca, 7.80.

Calcium D-Altronate.—Reichstein and Bossard[12] catalytically hydrogenated diacetone-D-tagaturonic acid (diacetone-5-keto-L-galactonic acid) for the preparation of L-galactonic acid, but they did not report the isolation of D-altronic acid. In German Patent 618,907[13] is described the hydrogenation of free 5-keto-L-galactonic acid in aque-

(4) Hudson and Richtmyer, U. S. Patent 2,162,721, June 20, 1939.
(5) Levene and Jacobs, *Ber.*, **43**, 3141 (1910).
(6) Steiger and Reichstein, *Helv. Chim. Acta*, **19**, 195 (1936).
(7) Richtmyer, Hann and Hudson, THIS JOURNAL, **61**, 343 (1939).
(8) Regna and Caldwell, *ibid.*, **65**, 243 (1943).
(9) Pigman, *J. Research Natl. Bur. Standards*, **25**, 301 (1940).
(10) Mottern and Cole, THIS JOURNAL, **61**, 2701 (1939).
(11) Ehrlich and Guttmann, *Ber.*, **67**, 573 (1934).
(12) Reichstein and Bossard, *Helv. Chim. Acta*, **17**, 760 (1934).
(13) German Patent 618,907, Sept. 19, 1935.

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ous acetic acid using platinum oxide catalyst at 50 atm. and 120–140° to a mixture of L-galactonic and D-altronic acids, which were isolated as the cadmium and calcium salts, respectively.

The authors hydrogenated 100 g. of the normal calcium 5-keto-L-galactonate by suspending it in about one liter of water in a stainless steel, high-pressure autoclave containing about 10 g. of Raney nickel catalyst. The reduction was carried out by slowly heating the mixture to 80° under 2300 lb. pressure. At the end of the hydrogenation period the nickel was removed by filtration. The filtrate showed no reduction of Fehling solution, indicating a fully hydrogenated mixture of the calcium salts of L-galactonic and D-altronic acids. The hot solution after removal of the nickel catalyst was concentrated under diminished pressure to about 200 cc. It was allowed to stand several days after which 45 g. of calcium L-galactonate was obtained. The solution was evaporated further and 2 g. more of calcium L-galactonate was gained.

The mother liquor containing chiefly calcium D-altronate could not be made to crystallize readily. Seeds were finally obtained by keeping a few cc. of the solution on a watch glass in an evacuated desiccator over barium oxide for several days. These were then used to inoculate the original solution and with the aid of stirring, 32 g. of calcium D-altronate·$3^1/_2H_2O$ was finally obtained. One recrystallization from water yielded pure calcium D-altronate·$3^1/_2H_2O$ which was identified by its analysis and its mutarotation in *N* hydrochloric acid. Table I shows the observations on the rotation of the salt made by the authors and the corresponding values obtained by Richtmyer, Hann and Hudson[7] for this compound prepared from sedoheptulose.

By concentrating the mother liquor and cautiously adding methanol, 9.2 g. more of the salt was gained. From 100 g. of the normal calcium 5-keto-L-galactonate·$5H_2O$, a total of 47 g. of calcium L-galactonate·$5H_2O$ and 41.2 g. of calcium D-altronate·$3^1/_2H_2O$ was obtained.

The separation of calcium L-galactonate from calcium D-altronate was relatively simple before seeds of the latter salt were obtained. But as we worked with these calcium salts in the laboratory, we found it increasingly more difficult to effect the fractionation of the calcium salts. Hence, recourse was made to separating their cadmium salts. This was readily done by removing the calcium ions from the mixture following the high pressure hydrogenation. The solution of the free acids was heated and neutralized with a suspension of freshly precipitated cadmium hydroxide. The separation of the cadmium salts was effected as described above for the calcium salts.

TABLE I

MUTAROTATION OF CALCIUM D-ALTRONATE·$3^1/_2H_2O$ IN *N* HCl (*c*, 3) AT 20°

Time, min.	$[\alpha]^{20}D$ from sedoheptulose	$[\alpha]^{20}D$ from 5-keto-L-galactonic acid
5	+11.5	+11.8
10	13.8	14.0
15	15.9	16.0
20	17.3	18.0
30	19.6	20.4
45	21.9	22.0
60	23.1	23.2
90	24.2	24.3
Constant	24.8	25.0

Acknowledgment.—One of the authors (P. P. R.) wishes to express his indebtedness to Dr. Richard Pasternack, with whom he collaborated in a separate investigation during which was developed the convenient method of isolating D-galacturonic acid by means of precipitation as its sodium calcium salt.

Summary

A new preparation for large quantities of D-altronic acid is reported and two intermediate products, sodium calcium D-galacturonate hexahydrate and calcium 5-keto-L-galactonate pentahydrate, are described.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

Kinetics of Transformation of 2-Ketopolyhydroxy Acids

BY PETER P. REGNA[1] AND B. P. CALDWELL

Ohle[2] and Maurer and Schiedt[3] were first to show that weak alkaline agents and alkoxides convert methyl 2-keto-D-gluconate into D-araboascorbic acid. Reichstein[4] recognized that this procedure was general for the rearrangements of 2-keto-3,4-dihydroxy acids and utilized the reaction for the enolization and lactonization of its isomer methyl 2-keto-L-gulonate into L-ascorbic acid (vitamin C). In addition he showed that hydrochloric acid can also bring about this transformation, but that the continued action of the hydrochloric acid results in decomposition of the L-ascorbic acid.

In the course of previous work, one of the authors had noted marked differences in the effect of hydrochloric acid on the rates of rearrangement of the isomers of 2-ketogluconic and 2-ketogulonic acids although similar intramolecular processes are involved. This observation led the present investigators to study the rates of the transformation of a series of 2-ketohydroxy acids into their ascorbic acid analogs and the rates at which the corresponding ascorbic acid analogs decompose.

Preliminary experiments showed the action of hydrochloric acid on L-ascorbic acid to be essentially a constant pseudo-unimolecular or first-order reaction. An analytical examination of the end product corroborated the observations of Hirst[5] and his collaborators, who showed that when ascorbic acid is heated with 12% hydro-

(1) This paper is constructed from a thesis presented in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry, June, 1942. Present address: Chas. Pfizer & Co., Inc., Brooklyn, New York.

(2) Ohle, *Angew. Chem.*, **46**, 399 (1933).

(3) Maurer and Schiedt, *Ber.*, **66**, 1054 (1933).

(4) Reichstein and Grüssner, *Helv. Chim. Acta*, **17**, 311 (1934).

(5) Herbert, Hirst, Percival, Reynolds and Smith, *J. Chem. Soc.*, 1270 (1933).

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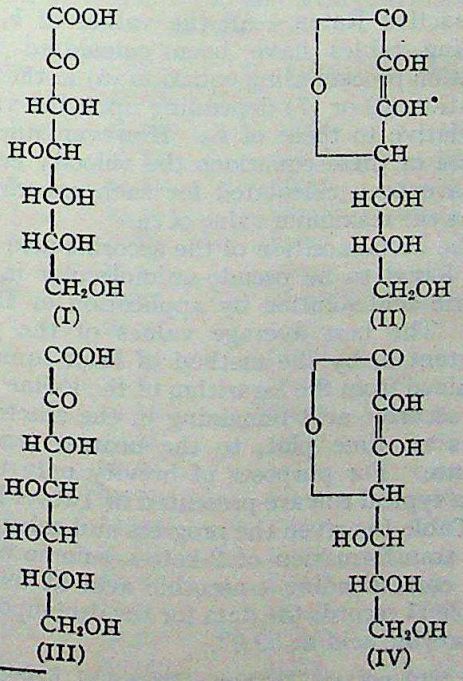
chloric acid furfural, confirmed as the phloroglucide, is readily obtained. In addition, long heating with hydrochloric acid tends to polymerize the furfural. Hence, the consecutive reactions involved in the complete process can be formulated thus

$$K \xrightarrow[(1)]{k_1} A \xrightarrow[(2)]{k_2} F \xrightarrow[(3)]{k_3} P \qquad (1)$$

where K is a 2-ketohydroxy acid, A is the corresponding ascorbic acid analog, F is the furfural formed by the decomposition of the ascorbic acid and P is the polymerized furfural. However, we are here concerned only with the first two steps. Inasmuch as a precise method is unavailable for determining the concentration of the 2-keto acid during the rearrangement, it was necessary to measure the velocities of reactions (1) and (2) independently. Such a procedure is justified by the fact that both reactions are carried out in the presence of a high concentration of hydrochloric acid.

These measurements were made by titrating portions of each reaction mixture with a standard iodine solution of approximately 0.025 *N*. This gives a quantitative indication of the ascorbic acid present in each flask at that moment, since iodine oxidizes ascorbic acid to its first oxidation product, dehydroascorbic acid.[6]

After preliminary experiments, the temperatures 59.9 and 69.9° were chosen, since the rearrangements are nearly complete within a reasonable time. Reaction rates were measured on the following pairs of acids: 2-keto-D-gluconic and D-araboascorbic acids, 2-keto-L-gulonic and L-ascorbic acids, 2-keto-D-galactonic and D-ascorbic acids, 2-keto-D-glucoheptonic (I) and D-glucoascorbic acids (II) and 2-keto-D-galactoheptonic (III) and D-galactoascorbic acids (IV).



The two particular 2-ketoheptonic acids (I) and (III) were expressly chosen in this study for their relative differences of structure. The hydroxy groups on carbon atoms 3 and 4 of both molecules are in *trans* position while the hydroxy groups on carbon atoms 5 and 6 are in *cis* position in (I) and in *trans* position in (III). Thus as a result of the identity of arrangement of substituents on the first four carbon atoms, the ascorbic acid analogs have their ring closures on the same side of the molecule.

Experimental

Apparatus and Method.—Exactly 5 *M* hydrochloric acid solutions were prepared by weighing the required amount of a previously determined stock solution in calibrated 500-ml. flasks. Stock solutions were stored in all-glass apparatus and were prepared as needed by diluting C. P. analyzed hydrochloric acid to approximately 6 *M*. Just before each kinetic run a portion of the stock solution was weighed and titrated with standard sodium hydroxide. The theoretical amount of 2-keto acid to make a 0.0500 *M* solution was weighed out and dissolved in distilled water at 20°. This solution was then quickly transferred to the flask containing the hydrochloric acid at 20°, and rapidly shaken to ensure thorough mixing. The flask was then filled exactly to the mark with distilled water, attached to its air-tight connections and the temperature rapidly raised in a steam-bath to within 0.5° of that of the thermostat. It was necessary to use thick-walled flasks to withstand the internal pressure developed during the rise in temperature. The flask was continuously shaken during its immersion in the steam-bath which usually required less than three minutes, and was then quickly submerged in the constant temperature bath. In this way thermal equilibrium between solution and thermostat was quickly reached, and it was possible to withdraw the first sample soon after the addition of the 2-keto acid. The same technique was employed in handling the ascorbic acid analogs and several portions were withdrawn from the reaction mixture as soon as equilibrium was attained, thus establishing the zero reading with considerable certainty.

Each calibrated 500-ml. flask carried a two-hole stopper, through one opening of which a fine capillary (1.5 mm.) glass tube reached 5 mm. from the bottom of the flask and led to an automatic pipet. The capillary tubes and the pipets were covered with cloth, asbestos and rubber tape to insulate the solutions against temperature drop when withdrawing samples. Through the second hole in the stopper passed a short glass tube to a source of purified nitrogen. The nitrogen was maintained at a slight positive pressure over the solution and served to force the hydrochloric acid into the capillary tube and into the two-way pipet.

Two automatic pipets were used for withdrawing samples from the reaction mixtures. These pipets were calibrated at the two temperatures of the experiments, 59.9 and 69.9° by making eight determinations of the amount of standardized 5 *M* hydrochloric acid delivered by each pipet.

The thermostat was equipped with a good mechanical stirrer mounted independent of the bath. A "mercoid-mercury" thermo-regulator, when once set, maintained the temperature inside the reaction flasks within ±0.02° during the whole series of runs at the particular temperature. The general procedure for measuring the rate was as follows: the reactions were observed by iodine titrations of the ascorbic acid present in each flask. During a run, the iodine solution was frequently standardized against a purified sample of the ascorbic acid analog. Then 1 cc. of a 0.5% solution of starch was used as an indicator and was added just before the stoichiometric point was reached. At frequent intervals the automatic pipets were flushed

(6) Hirst, *Chemistry & Industry*, 52, 221 (1933).

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with a part of the solution which then was used to locate the approximate end-point before being discarded. However, before this titration was made the pipets were filled a second time and drained, and this portion reserved for the precise titration. Samples of the reactions were arrested by draining the solutions into 75 ml. of water containing crushed ice. The time was taken as that of half drainage of the pipet.

Materials.—The crystalline, free 2-keto acids were used whenever possible. When, however, the crystalline acids were not available, the free acids were liberated from their purified salts. The absence of cations was established by ashing a portion of the acid solution, whereupon weighed portions were titrated with standard sodium hydroxide before being used for the kinetic studies. All the ascorbic acid analogs were crystalline substances and were used only after several recrystallizations. The preparations of 2-keto-D-gluconic, 2-keto-D-galactonic, 2-keto-D-glucoheptonic, 2-keto-D-galactoheptonic, D-ascorbic, D-glucoascorbic and D-galactoascorbic acids have been the subject of a preceding communication.[7]

D-Araboascorbic Acid.—This ascorbic acid was prepared, from methyl 2-keto-D-gluconate by the method of Maurer and Schiedt.[3] It showed $[\alpha]^{20}D$ −17.7° (*c*, 10 in water), m. p. 168°, and titration with standard iodine 99.7%.

2-Keto-L-gulonic Acid.—Prepared by the method of Reichstein and Grüssner[4]; m. p. 170–171°; $[\alpha]^{20}D$ −48.8° (*c*, 1.0 in water).

L-Ascorbic Acid.—This was obtained by the rearrangement of methyl 2-keto-L-gulonate as proposed by Pasternack and Regna.[8] The methyl ester[3] (41.6 g.) was dissolved in 200 ml. of water and to this solution was added 2.13 g. of magnesium powder. To the cooled solution 12 g. of oxalic acid dihydrate was added and the magnesium oxalate filtered off. The filtrate was evaporated to dryness *in vacuo* and the crystalline residue was taken up with hot methanol, treated with norite and filtered. On concentrating the filtrate *in vacuo* the L-ascorbic acid crystallized readily. After two recrystallizations from methanol, it showed $[\alpha]^{20}D$ +23°, m. p. 191–192°, and titration with iodine, 99.5%.

Rate Calculations

Inasmuch as the rates by iodine titers show the reactions to be of the first order, preliminary experiments which varied the concentration of the solvent showed the rates to be proportional to the concentration of the hydrochloric acid. However, the solvent is in such large excess (100:1) over the solute that the first-order rates are to be expected. Since the reaction of 2-ketohydroxy acid (K) to furfural (F) is a consecutive process of the first order, it can be generalized into the equation

$$\mathrm{K} \xrightarrow[(1)]{k_1} \mathrm{A} \xrightarrow[(2)]{k_2} \mathrm{F} \qquad (2)$$

where (A) is the intermediate ascorbic acid. Since the concentration of ascorbic acid c_A decreases during the course of the reaction by an amount equivalent to c_F, we will have then $c_A - c_F = c_B$ as the amount of ascorbic acid present at time t. Hence

$$c_0 = c_K + c_B + c_F \qquad (3)$$

where c_0 is the initial molecular concentration of the 2-ketohydroxy acid.

The velocity constants k_2 which evaluate the rates of decomposition of the ascorbic acid analogs were determined independently for each acid and calculated simply by the first order equation

$$k_2 = \frac{1}{t} \ln \frac{c_A}{c_A - c_F} \qquad (4)$$

where c_A is the initial concentration of the ascorbic acid, and c_F is the decrease after a lapse of time, t.

The rates of transformations, k_1, of the 2-keto-hydroxy acids into their ascorbic acid analogs were calculated from the equation[9]

$$c_A - c_F = c_B = c_0 \left(\frac{k_1}{k_2 - k_1} e^{-k_1 t} - \frac{k_1}{k_2 - k_1} e^{-k_2 t} \right) \qquad (5)$$

where c_B is equal to the amount of ascorbic acid present at any time t, and is the only constituent which was measured at progressive times, t. Equation 5, however, was rewritten and solved in the following form

$$\frac{\log \left(e^{-k_2 t} - \frac{c_B(k_1 - k_2)}{c_0 k_1} \right)}{t \log e} = -k_1 \qquad (6)$$

The value of k_1 was obtained by an iteration process. For example, on substituting an approximate value of k_1 in the left side of equation 6 when the values of c_B and t are taken from some one observation, we gained a value of k_1 usually better than the one which was assumed. This new value was again substituted in the left side of equation 6 and a second value for k_1 was obtained. This process was repeated until convergence was reached, *i. e.*, until the value satisfied the equation. Equation (6), however, converges only if $k_1 > k_2$; for the alternative case, namely, when $k_1 < k_2$, the equation was solved by writing it in the form

$$\frac{c_B k_2}{c_B + c_0(e^{-k_1 t} - e^{-k_2 t})} = k_1 \qquad (7)$$

Reaction Rates.—All the values of k_1 in the ensuing tables have been calculated by the iteration process using equation (5) in the form of equation (6) or (7) depending upon the values of k_1 relative to those of k_2. However, due to the nature of these equations the velocity constants k_1 have been calculated for each experiment as far as the maximum value of c_B.

The decomposition of the ascorbic acid analogs was found to be pseudo-unimolecular in hydrochloric acid solution by application of Equation (4). The best average values of the velocity constant k_2 by the method of least squares was obtained from the logarithm of the iodine titers of the ascorbic acid remaining in the reaction mixtures *vs.* time plot, to the nearest tenth of a minute. For purposes of brevity only the data for a typical run are presented in Tables I and II. In Table I is given the progress and calculation of the transformation of 2-keto-L-gulonic acid into the corresponding L-ascorbic acid at 59.9°, and Table II records the data for the decomposition of L-ascorbic acid at 59.9°.

(7) Regna and Caldwell, THIS JOURNAL, 66, 243 (1944).

(8) Pasternack and Regna, U. S. Patent 2,165,184, July 4, 1939.

(9) Hitchcock and Robinson, "Differential Equations," John Wiley & Sons, Inc., New York, N. Y., 1936, p. 59.

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TABLE I

RATE CALCULATIONS FOR THE TRANSFORMATION OF 2-KETO-L-GULONIC ACID INTO L-ASCORBIC ACID AT 59.9°

Time, min.	Volume, ml., V_∞ = 42.17	$e^{-k_2 t}$	$k_1 \times 10^3$ min.$^{-1}$
43.6	4.28	0.97884	
77.6	7.42	.96262	2.55
114.7	10.32	.94528	2.53
166.0	13.45	.92178	2.44
208.7	16.58	.90268	2.57
278.3	19.89	.87236	2.55
361.9	22.73	.83730	2.50
442.3	25.11	.80492	2.55
480.9	25.98	.78980	2.56
516.8	26.41	.77602	2.53
556.1	27.14	.76120	2.56
602.7	27.56	.74398	2.53
658.0	27.98	.72407	2.53
742.8	28.30	.69457	2.51
770.7	28.04	.68495	2.41[a]
802.1	27.82	.67445	2.34[a]
843.8	27.65	.66080	2.27[a]
1436.6	19.48	Average	2.53
1548.8	17.94		
1576.1	17.50		
1601.1	16.95		
1635.0	16.40		
1688.2	16.00		
1760.4	15.20		
1840.1	14.58		
1944.0	13.96		
2887.5	9.05		
2930.5	8.80		

[a] Omitted in averaging.

TABLE II

THE DECOMPOSITION OF L-ASCORBIC ACID INTO FURFURAL AT 59.9°

Time, min.	Volume, ml., V_t	Log V_0/V_t	$k_2 \times 10^4$ min.$^{-1}$
0	V_0 = 42.02		
34.2	41.29	0.00656	4.41[a]
89.1	40.21	.01913	4.95[a]
113.8	39.81	.02347	4.75
146.7	39.20	.03017	4.74
172.0	38.72	.03556	4.76
237.2	37.53	.04901	4.76
272.8	36.92	.05620	4.75
309.5	36.26	.06403	4.77
382.6	34.92	.08039	4.84
427.3	34.06	.09122	4.91
467.6	33.42	.09945	4.90
505.5	32.83	.10719	4.88
539.6	32.20	.11560	4.93
579.1	31.77	.12144	4.83
642.7	30.90	.13350	4.92
683.0	30.10	.14489	4.89
720.0	29.40	.15511	4.96
773.8	28.84	.16347	4.87
810.3	28.15	.17398	4.95
1459.6	20.48	.31213	4.93
1517.4	19.89	.32483	4.93
1570.4	19.36	0.33752	4.95
1599.0	19.10	.34243	4.93
1715.0	18.02	.36339	4.88
1811.4	17.31	.38516	4.89
1907.9	16.46	.40703	4.91
		Av. by L. S.	4.91
2678.1	10.02	.61955	5.30[a]
2887.0	9.01	.66854	5.30[a]
2963.6	8.71	.68344	5.31[a]

[a] Omitted in averaging.

Column 2 in Table I gives the actual values of c_B in terms of the number of ml. of standard iodine solution at the times indicated in column 1. V_∞ is the theoretical volume of iodine which the original amount of 2-ketohydroxy acid would have required if it were quantitatively transformed into its ascorbic acid analog.

In Table II, V_0 is the ml. of iodine at $t = 0$ for the ascorbic acid. This is the reading obtained immediately after the flask was submerged into the thermostat and connected to the automatic pipet. V_t is the ml. of iodine which the remaining ascorbic acid required at time t. Tables III and IV give a summary of the average values of k_1 and k_2 for the other 2-keto acids at the temperatures of the experiments.

TABLE III

THE RATES OF THE TRANSFORMATIONS OF 0.05 *M* 2-KETOHYDROXY ACIDS INTO THEIR CORRESPONDING ASCORBIC ACID ANALOGS AT 59.9 AND 69.9°, IN 5 *M* HYDROCHLORIC ACID

2-Keto acids	k_1 min.$^{-1}$ at 59.9°	k_1 min.$^{-1}$ at 69.9°	E, kcal./mole
L-Gulonic	0.00253	0.00820	26.7
D-Gluconic	.000566	.00186	27.0
D-Galactonic	.000654	.00208	26.3
D-Glucoheptonic	.000478	.00164	28.0
D-Galactoheptonic	.000207	.000704	27.7

TABLE IV

THE RATES OF THE DECOMPOSITIONS OF 0.05 *M* ASCORBIC ACID ANALOGS IN 5 *M* HYDROCHLORIC ACID

Acids	k_2 min.$^{-1}$ at 59.9°	k_2 min.$^{-1}$ at 69.9°	E, kcal./mole
L-Ascorbic	0.000491	0.00141	23.9
D-Araboascorbic	.00162	.00388	19.9
D-Glucoascorbic	.000920	.00279	25.2
D-Galactoascorbic	.00329	.00943	23.9

In some cases there was evidence of slowly drifting k_1 values for the 2-keto acid rearrangements and this may be due to a portion of the keto acids decomposing without first going through the ascorbic acid rearrangement. This is quite small, however, because there was usually no darkening of the solutions due to furfural formation during the first six hours of the kinetic studies until an appreciable amount of ascorbic acid had already formed. The iodine titrations during the rearrangement of the 2-ketohexonic acids behaved more or less normally. Yet, in a number of cases the 2-ketoheptonic acids acted erratically and the

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experiments had to be discarded because there was no increased iodine consumption, but rather periods of stationary iodine readings followed by sharp increases of iodine consumption.

The k_2 values for the decomposition of the ascorbic acids exclude any effects due to the presence of the parent substances, namely, the 2-keto acids. However, the maximum amounts of all the ascorbic acids calculated by the equation

$$c_{B\,(max.)} = c_0 \left(\frac{k_2}{k_1}\right)^{\frac{k_2}{k_1 - k_2}} \qquad (8)$$

agree with the maxima obtained from the graphs when the volumes of the iodine titers were plotted against the times of the transformations of the 2-ketohydroxy acids. These results are given in Table V.

TABLE V

OBSERVED AND CALCULATED VALUES OF THE MAXIMUM YIELDS OF ASCORBIC ACIDS FROM 2-KETOHYDROXY ACIDS

Acid	Temp., °C.	Calcd., %	Observed, %
2-Keto-L-gulonic	59.9	67.5	67.6
	69.9	69.4	69.9
2-Keto-D-gluconic	59.9	20.5	20.8
	69.9	24.3	24.4
2-Keto-D-galactonic	59.9	42.1	41.7
	69.9	44.3	42.5
2-Keto-D-glucoheptonic	59.9	25.4	27.7
	69.9	27.6	28.2
2-Keto-D-galactoheptonic	59.9	6.3	6.1
	69.9	5.2	7.3

Activation Energy.—From the values of k_1 and k_2 obtained at the two temperatures, the energies of activation were determined in the usual way using the Arrhenius equation, and are shown in Columns 4 of Tables III and IV. The energies of activation of the 2-keto acids in the six and seven carbon series show a variance of not more than 1.7 kcal./mole, although their reaction velocities vary widely. This would indicate that essentially the same intramolecular mechanism is involved for all of the acids. However, this cannot be wholly the case since the two seven carbon 2-keto acids which we have studied possess the same arrangement of atoms with respect to the first four groups of the molecules. Were the same intramolecular mechanism involved we should expect their rates of transformations into their corresponding ascorbic acids to be very nearly the same, inasmuch as only the first four groups enter into the rearrangement. Yet, the specific rate constants have a 2.3/1 ratio. The only structural explanation for this wide difference lies in the *cis–trans* arrangement of the groups in the parts of the molecule which do not enter into the rearrangement.

A similar condition exists in the six carbon 2-ketoaldonic series. Although 2-ketogulonic and -gluconic acids have identical structures on all but the last two carbon atoms, this alteration accounts for more than a fourfold difference in their rates of transformation.

In the case of 2-ketogalactonic acid with *cis* arrangement of the hydroxy groups on carbon atoms 3 and 4 and 2-ketogluconic with the same hydroxy groups in *trans* position there result almost equal rates of rearrangement. These observations strongly suggest that the groups in the molecules which do not enter into the enolization and lactonization materially affect the rate of transformation.

Summary

1. The kinetics of the consecutive reactions of five 2-ketopolyhydroxy acids and the decomposition of their ascorbic acid analogs have been studied at 59.9° and 69.9° in 5 *M* hydrochloric acid.

2. The rates of rearrangement of 2-ketopolyhydroxy acids into their ascorbic acid analogs are affected by the groups on the carbon atoms outside the lactone ring.

3. The rate constants of the decomposition of the ascorbic acids are greater for molecules which exhibit *cis* arrangement of the hydrogen atoms on carbon atoms 4 and 5 than for those which have *trans* arrangement of the hydrogen atoms.

4. A method is given for calculating rate constants in a reaction A → B → C where only B can be experimentally determined.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

Hydrogenation–Dehydrogenation Reactions Involving Some Compounds of Ammono-aldehyde, Ammono-acetal and Aquo-ammono-aldehyde Types

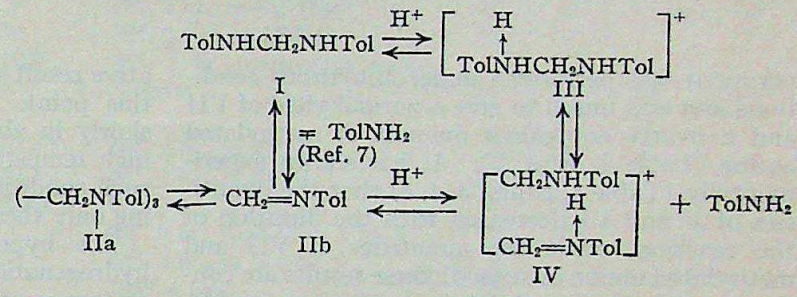
BY PAUL J. MCLAUGHLIN[1,2] AND E. C. WAGNER

In an earlier paper from this Laboratory Simons[3] showed that the incidental formation of methyl-*p*-toluidine which accompanies conversion of methylene-bis-*p*-toluidine (I) to 3-*p*-tolyl-6-methyl-3,4-dihydroquinazoline (VII) by warming with amine salt results by a complementary hydrogenation–dehydrogenation reaction, essentially

$$-NHCH_2N- + RNHCH_2NHR \longrightarrow -N{=}CHN- + RNH_2 + CH_3NHR.$$

Methylation has been observed also during interaction of *p*-substituted amines with formaldehyde in aqueous acid solution[4,5] to form dihydroquinazolines and other products, but the propriety of extending Simons' explanation to such cases is doubtful, as are explanations suggested by Maffei[4] and by Eisner and Wagner.[5] The formal resemblance of Simons' reaction to a crossed Cannizzaro reaction is obvious, and recalls some other hydrogenation–dehydrogenation reactions involving compounds of ammonoaldehyde type.[6]

This paper presents the results of a further study of the oxidation of 3-*p*-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline (VI) to the corresponding dihydroquinazoline (VII) by substances of aldehyde or acetal type in presence of acid, and an interpretation and rationalization of the findings. Though the reaction (at lower temperatures) requires presence of acid the environment is prevailingly basic, and the function of the acid is believed to be the cleavage of the methylene-bis-amines (compounds which can be regarded as ammono-aldehyde "hydrates" or ammono-acetals) to aldehydic structures, *i. e.*, to induce a reaction which is preliminary to the pseudo-Cannizzaro reaction which follows. It has been found that trimeric methylene-*p*-toluidine can function as hydrogen acceptor; in this case the acid may operate in a similar manner to open the triazine ring. These preliminary steps are shown in the scheme.



In acid-induced reactions the hydrogen acceptor is believed to be the Schiff base IIb or its cation IV, obtainable from the trimer or from the methylene-bis-amine *via* the Schiff base monomer, or from the methylene-bis-amine via its cation III, as shown in the scheme. In thermally induced reactions the hydrogen acceptor may be IIb. The several subsequent reactions which may be initiated in presence of acid were established in their proper relationships by Simons[3]: (1) formation of the *o*-aminobenzylarylamine base V,[8] presumably from IV and *p*-toluidine by ortho-coupling, (2) conversion of V to the diphenylmethane base VIII by action of acid in absence of I or II,[9] a reaction not encountered under the conditions of the present study, (3) conversion of V to the tetrahydroquinazoline VI, a reaction whose reversibility[3] in presence of acid was confirmed in the present study, though the reaction is not sensibly reversible in absence of acid,[10] and (4) the hydrogenation–dehydrogenation reaction which is the principal subject of study. These interrelated reactions are shown in the accompanying scheme. The extent of reaction 4 was estimated from the quantity of VII formed, and the nature of the reaction was inferred from the presence of methylated amine. The possibility cannot be excluded that the amine products of reaction 4 could enter the reaction system, with eventual formation of dimethylated amine of which, however, little or none has been encountered. The presence and amount of unmethylated amine, some of which may be liberated by incidental hydrolysis, are regarded as not diagnostic. To test the possibility that a small quantity of water, operating cyclically, might generate formaldehyde by hydrolysis of I or II and so modify the reaction series, an ex-

(1) This paper is constructed from the doctoral dissertation of Paul J. McLaughlin, University of Pennsylvania, 1943.

(2) Present address: Hercules Experimental Station, Hercules Powder Company, Wilmington, Delaware.

(3) Simons, THIS JOURNAL, **59**, 518 (1937).

(4) Maffei, *Gazz. chim. ital.*, **58**, 261 (1928).

(5) Eisner and Wagner, THIS JOURNAL, **56**, 1938 (1934).

(6) E. C. Franklin, "The Nitrogen System of Compounds," Reinhold Publishing Corp., New York, N. Y., 1935, p. 246; Mills, Harris and Lambourne, *J. Chem. Soc.*, **119**, 1294 (1921); Strain, THIS JOURNAL, **49**, 1558 (1927); **50**, 2218 (1928); Hinsberg and Koller, *Ber.*, **29**, 1499 (1896); Wheeler, *Am. Chem. J.*, **17**, 400 (1895); Fischer and Wrezinski, *Ber.*, **25**, 2711 (1892); Bischoff, *ibid.*, **31**, 3254 (1898); Cuisa and Zerbini, *Gazz. chim. ital.*, **50**, 1294 (1921); Cuisa and Musajo, *ibid.*, **59**, 796 (1929); Robinson and Bogert, *J. Org. Chem.*, **1**, 65 (1936); Crippa and Maffei, *Gazz. chim. ital.*, **71**, 194 (1941).

(7) Bischoff and Reinfeld, *Ber.*, **36**, 41 (1903).

(8) T. R. Miller and Wagner, THIS JOURNAL, **60**, 1738 (1938).

(9) Wagner, *ibid.*, **56**, 1944 (1934).

(10) Fellman and Wagner, *J. Org. Chem.*, **7**, 31 (1942).

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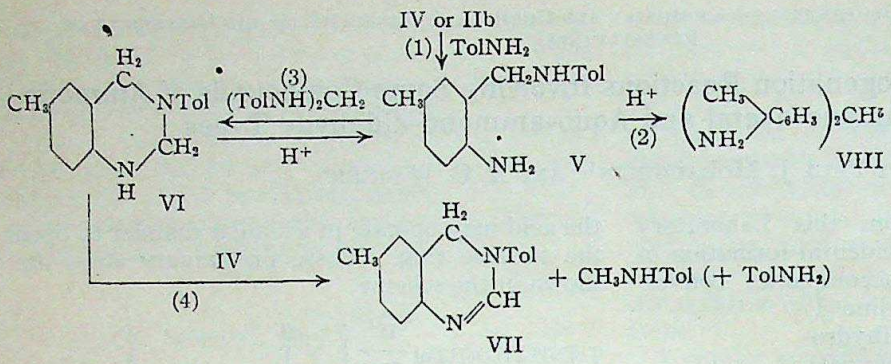

periment was performed under anhydrous conditions and was found to give a normal yield of VII and a nearly equivalent amount of methylated amine (Table I, expt. 6). It has shown experimentally (Table I, expts. 3, 4, 5) that the quantities of V and VI decreased with the duration of the reaction, while the quantities of VII and methylated amine increased; these results are consistent with the view that reaction 4 is irreversible.

Reaction 4 was realized with compound VI using as the second aldehydic reactant methylene-bis-*p*-toluidine, trimeric methylene-*p*-toluidine, methylene-bis-piperidine, and benzalaniline, and as the sources of acid *p*-toluidine hydrochloride, piperidine hydrochloride, trimethylamine hydrochloride, the hydrochloride of VII, and ammonium chloride. The salts named appeared to vary with respect to the effectiveness of each in promoting reaction 3 (ring opening–ring closure) and reaction 4 (hydrogenation–dehydrogenation). In experiments with salts of tertiary amines (trimethylamine and VII), which are not eligible to participate in ring opening with formation of V and I, both V and VII were formed (Table I, expts. 2, 5); the ring opening in each of these cases must be attributed to operation of the amines formed in reaction 4. The amine salts used all proved to be more effective than ammonium chloride with respect to reactions 3 and 4 (Table I, expts. 1–10), the order of decreasing effectiveness being *p*-toluidine hydrochloride, trimethylamine hydrochloride, the hydrochloride of VII, piperidine hydrochloride, and ammonium chloride. The comparative activities of these salts as proton donors should be related in an inverse sense to the dissociation constants of the bases represented. Results with *p*-toluidine hydrochloride, trimethylamine hydrochloride and piperidine hydrochloride are consistent with this view; the basicity of VII is not known. The low activity of ammonium chloride thus appears to be anomalous, but may be attributable to the low solubility of this salt in alcohol or in molten amine mixtures. Actually the identity of the salt used is not preserved, for the acid so introduced may be assumed to become distributed among all bases present in a manner determined jointly by the relative strengths and concentrations of the bases and by the relative solubilities of their salts in the reaction mixture.

The possibility that oxidation of VI to VII might be caused by ready loss of hydrogen[11] was tested (expt. 23) by heating VI in contact with air; no VII precipitable as picrate was present. The possibility that picric acid, used to precipitate VII in the experiments, might serve to some extent as oxidant was excluded by the negative result of an experiment (expt. 24) to test this point. Reaction 4 was found to proceed slowly in absence of added acid at a relatively high temperature (expt. 12), indicating that for such conditions an alternate mechanism, involving only thermal effects, must be admitted.

The hypothesis that the hydrogenation–dehydrogenation reaction is analogous to the Cannizzaro reaction was further tested by experiments in which the abilities of compounds of ammono-aldehyde or aldehyde types to serve as hydrogen acceptors were contrasted with those of similar nonaldehydic ammono-carbonyl or carbonyl compounds. The pairs of compounds tested were diphenylformamidine and diphenylacetamidine, formyl-*p*-toluidine and acetanilide, and formamide and acetamide. The first named of each pair possesses an aldehydic structure, and in each case only this compound was found to oxidize VI to VII (expts. 14–22). The behavior of diphenylformamidine, a derivative of ammono-formic acid and also an aldehyde in the sense that formic acid is an aldehyde, is of interest. Dains[12] reported diphenylformamidine to condense with reactive methylene compounds after the manner of aldehydes, and the conversion of VI to VII by formic acid has been recorded.[13] In the oxidation of VI to VII by diphenylformamidine the results showed the reaction to proceed in two stages, essentially

$$\mathrm{PhNHCH{=}NPh} \xrightarrow{\mathrm{VI}} \begin{cases} \mathrm{VII} \\ \mathrm{PhNHCH_2NHPh} \end{cases} \xrightarrow{\mathrm{VI}} \begin{cases} \mathrm{VII} \\ \mathrm{PhNH_2 + CH_3NHPh.} \end{cases}$$

In the experiments reported in Table I (expts. 14, 15, 16) the reactants were used in this over-all proportion. The reaction was favorably affected by presence of acid (expt. 14), but diphenylformamidine, form-*p*-toluidide and formamide all reacted in absence of added acid but at somewhat elevated temperatures (105–210°; expts. 15, 16, 18, 21). These conversions may be wholly thermal, or they may be induced in part by the acid characters of the compounds named; similar

(11) Mason, *Ber.*, **20**, 267 (1887); *J. Chem. Soc.*, **55**, 99 (1889); Lankelma and Sharnoff, THIS JOURNAL, **53**, 2654 (1931).
(12) Dains, *Ber.*, **35**, 2496 (1902).
(13) Wagner, *J. Org. Chem.*, **2**, 165 (1937).

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TABLE I

HYDROGENATION–DEHYDROGENATION REACTIONS INVOLVING 3-*p*-TOLYL-6-METHYL-1,2,3,4-TETRAHYDROQUINAZOLINE (VI) AND HYDROGEN ACCEPTORS

	Acceptor[a]	Acid[b]	Conditions[c]	VII, %	V, %	Steam-vol. amines: Methylated base, %	Steam-vol. amines: Unmethylated base, %
1	Methylene-bis-*p*-toluidine	$TolNH_2 \cdot HCl$	60°, 3 hr., in EtOH	62	9	50	40
2	Methylene-bis-*p*-toluidine	VII·HCl	78°, 3.5 hr., in EtOH	51	11	25	56
3	Methylene-bis-*p*-toluidine	Me_3NHCl[d]	78°, 3 hr., in EtOH	69	0	28	42
4	Methylene-bis-*p*-toluidine	Me_3NHCl[d]	78°, 2 hr., in EtOH	55	0		52
5	Methylene-bis-*p*-toluidine	Me_3NHCl[d]	78°, 0.5 hr., in EtOH	11	9		
6	Methylene-bis-*p*-toluidine	$TolNH_2 \cdot HCl$	85°, 3 hr., anhydrous conditions[e]	54	+[f]	49	37
7	Trimeric methylene-*p*-toluidine	$TolNH_2 \cdot HCl$	60°, 2 hr., in EtOH	52	10		
8	Methylene-bis-piperidine	$TolNH_2 \cdot HCl$	60°, 3 hr., in EtOH	91	5		
9	Methylene-bis-piperidine	Piperidine HCl·NH_4Cl	60°, 2 hr., in EtOH	38	29	[g]	
10	Methylene-bis-piperidine	Piperidine HCl·NH_4Cl	60°, 2 hr., then 100°, 1 hr.	33	0		
11	Methylene-bis-piperidine	None	65°, 2 hr., in MeOH	0			
12	Methylene-bis-piperidine	None	195°, 4 hrs.	32			
13	Benzalaniline	$PhNH_2 \cdot HCl$	60°, 2 hr., in EtOH	61[h]			
14	Diphenylformamidine[i]	$PhNH_2 \cdot HCl$	60°, 2 hr., in EtOH	61	3		
15	Diphenylformamidine[i]	None	105°, 2 hr.	30			
16	Diphenylformamidine[i]	None	210°, 1.5 hr.	53			
17	Diphenylacetamidine	None	190°, 2 hr.	0			
18	Form-*p*-toluidide	None	170°, 2 hr.	30			
19	Acetanilide	None	170°, 2 hr.	0			
20	Acetanilide	$PhNH_2 \cdot HCl$	170°, 2 hr.	0			
21	Formamide	None	150°, 2 hr.	21			
22	Acetamide	None	140°, 2 hr.	0			
23	None[j]	None	150°, 2 hr.	0			
24	Picric acid[k]	None	10°, 6 hr.	0			

[a] In most cases 0.005 mole each of VI and acceptor. [b] In experiments involving use of acid (amine salt or NH_4Cl) the amount was two molar equivalents with respect to the other reactants, unless specified otherwise. [c] When alcohol was used as solvent, the amount was 50 ml. [d] 0.009 mol. [e] All reagents were dried over sulfuric acid in a desiccator for a week. The glass apparatus was kept in an oven at 135° for four days. The return condenser was protected by a calcium chloride tube. No solvent was used. [f] Benzaldehyde gave a small precipitate, but the m. p. (162°) and the m. p. of a mixture with the benzal derivative of V (106°) indicates probable formation of some diphenylmethane base in the reaction.[3] [g] Presence of methyl piperidine was suggested by the nature of the picrate obtained following removal of piperidine as benzenesulfonyl derivative. Results of attempts to identify and determine methylpiperidine as hydrochloride were not satisfactory. The steam volatile bases were apparently only piperidine and methylpiperidine, for the refractive index of the mixture, redistilled over sodium, was $n^{20}D$ 1.4453, the values for pure specimens of piperidine and methylpiperidine being 1.4532 and 1.4376, respectively. [h] Only VII was determined, as the isolation of benzylaniline presented difficulties not wholly overcome. [i] The amount of diphenylformamidine was 0.5 equivalent with respect to the amount of VI. [j] Experiment to test possible thermal dehydrogenation of VI to form VII. The mass, after heating, was dissolved in ethanol, and picric acid solution was added. No precipitate appeared. [k] Experiment to test possible formation of some VII by oxidation of residual VI by picric acid added to precipitate VII. A solution of 0.6 g. of VI in 25 ml. of ethanol was treated with 15 ml. of a saturated solution of picric acid in ethanol, and the liquid was chilled in the refrigerator. After six hours only a scanty precipitate of picric acid had separated.

effects have been observed in certain reactions studied recently.[14]

The experimental results available show that the following structure types, all of which are aldehydic, can function as hydrogen acceptors in the reaction studied: (1) $-\overset{|}{N}CH_2\overset{|}{N}-$ (methylene-bis-amines), (2) $-N{=}CH-$ (methylene-amine, Schiff base), (3) $-NHCHO$ (formylamine), (4) $-NHCH{=}N-$ (substituted formamidine), and (5) formic acid. The following structures, respectively, homologous with 3 and 4 but lacking aldehydic structural characteristics, were found to be incapable of serving as hydrogen acceptors: CH_3CONH- and $-NHC(CH_3){=}N-$. It is concluded that, within the scope of this study, possession of a structure of aldehydic type is necessary in order that a compound may function as a dehydrogenating agent in the oxidation of VI to VII, and that the action is promoted at moderate temperatures by presence of acid or, in its absence and less effectively, by considerably higher temperatures.

Experimental

Starting Materials.—Methylene-bis-*p*-toluidine was prepared by the method of Eberhardt and Welter,[15] and methylene-bis-piperidine as described by Ehrenberg.[16]

(14) E. L. Hölljes, Jr., Thesis, University of Pennsylvania, 1942.

(15) Eberhardt and Welter, *Ber.*, **27**, 1808 (1894).

(16) Ehrenberg, *J. prakt. Chem.*, [2] **36**, 117 (1887).

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The tetrahydroquinazoline VI was made from *o*-amino-*m*-xylyl-*p*-toluidine (V),[8] prepared by the method of Miller and Wagner,[8] and the dihydroquinazoline VII was made from *p*-toluidine, formalin and formic acid.[13] Trimeric methylene-*p*-toluidine was prepared as described by Miller and Wagner,[17] and diphenylformamidine and diphenylacetamidine were made by the methods of Walther[18] and Sen and Ray,[19] respectively.

General Procedures.—For reactions at lower temperatures the reactants (0.005 mole each of tetrahydroquinazoline VI and hydrogen acceptor and 0.011 mole of amine salt in most experiments) were dissolved in ethanol (50 ml.) in a round-bottomed flask (200 ml.) fitted with a short return condenser, and the mixture was heated on a steam-bath. For reactions at higher temperatures the reactants, in a test-tube (25 × 200 mm.) provided with a short return condenser, were heated in a sand-bath. In each procedure temperatures were observed by means of a thermometer with its bulb in the reaction mixture. At the end of the heating period any acid present was neutralized with sodium hydroxide solution and the mixture was submitted to steam distillation to remove volatile amines.

Analysis of Reaction Mixtures.—The amines in the steam distillate were extracted in ether. The amines were fixed by conversion to hydrochlorides and the ether was removed by evaporation. The residue was analyzed by the Hinsberg–Kessler procedure[20] modified in one particular. Following the precipitation of the benzenesulfonamides these were dissolved in ether, and the solution was shaken with 10% sodium hydroxide solution to remove the monosulfonamide of any primary amine present. This improved the separation of primary and secondary amines; after the sodium and alcohol treatment the amount of primary amine derivative recovered was small, but the melting point of the secondary amine derivative was better than that observed when the unmodified procedure was used. The sulfonamides of the several amines were identified by mixed melting point tests.

For the analysis of the solid residue in the steam distillation flask a procedure similar to that of Simons[3] was used. The solid was separated by filtration and was dissolved in 25 ml. of ethanol. The solution was heated to boiling, 3 ml. of benzaldehyde was added, and the mixture was kept for ten hours in a refrigerator (about 10°), after which any precipitated benzal derivative of compound V was removed by filtration, dried, weighed and identified by mixed melting point test. The filtrate from the benzal derivative was heated to boiling and was treated with 15 ml. of a saturated solution of picric acid in ethanol. The mixture was chilled, and the picrate of VII was collected, dried, weighed, and identified by mixed melting point test and by its rather unique sensitivity to light, which changes its color from bright yellow to deep orange-red.

The accuracy of this separation procedure, tested by analysis of mixtures of known amounts of the substances named, is indicated by the following recoveries: dihydroquinazoline VII, 87%; *o*-amino-*m*-xylyl-*p*-toluidine (V), 89%; *p*-toluidine, 96%; N-methyl-*p*-toluidine, 82%. Appropriate corrections were thereafter applied to analytical data for reactions involving VI and I or trimeric II.

In the hope of avoiding the rather troublesome isolation and purification of the benzenesulfonyl derivative of methyl-*p*-toluidine a zinc chloride separation based on that of Frankland[21] was submitted to trial. The precipitate of *p*-toluidine zincichloride was found to be chalky and to occlude methyl-*p*-toluidine, recovery of which (as nitrosamine) was variable and did not exceed 79%. Trials of the 3-nitrophthalic anhydride procedure of Alexander and McElvain,[22] designed for use in qualitative analysis, showed the yields of the derivatives of both amines to be far from quantitative.

The separation of piperidine and methylpiperidine by the Hinsberg–Kessler procedure was satisfactory, but the determination of the latter as picrate proved to be inaccurate. Haase[23] reported methylpiperidine picrate to melt at 148°. Several yields of picrate obtained in the separations failed to melt at this temperature, the melting points being indefinite and diverse. The normal (1:1) picrate resulted only when methylpiperidine and picric acid were brought together in exactly equivalent amounts in alcohol. The product was a compound which melted sharply at 228° cor. as first precipitated, and at the same temperature after recrystallization from 95% ethanol; the yield was 87%. The use of methylpiperidine and picric acid in other proportions gave products which melted badly, and which are believed to be loose compounds of the 1:1 picrate and picric acid. Thus methylpiperidine and 2.5 equivalents of picric acid gave a product which melted in the range 146–180° as obtained, and in the range 147–179° after recrystallization; the yield was 118% of the amount calculated for the 1:1 picrate.

Significant data for the hydrogenation–dehydrogenation experiments are presented in Table I.

Summary

Study of the dehydrogenation of 3-*p*-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline to the corresponding dihydroquinazoline by action of methylene-bis-amine in presence of acid and at temperatures ordinarily not above 100°, the methylene-bis-amine being cleaved by hydrogenation to yield amine and methylated amine, was extended by use of methylene-bis-*p*-toluidine, trimeric methylene-*p*-toluidine and methylene-bis-piperidine with the acids *p*-toluidine hydrochloride, piperidine hydrochloride, trimethylamine hydrochloride and ammonium chloride. The results confirm the opinion that the over-all reaction is an acid catalyzed hydrogenation–dehydrogenation involving two compounds of ammono-aldehydic type, with formation of compounds of ammono-acidic and ammono-alcoholic types, the essential change having at least a formal resemblance to a crossed Cannizzaro reaction. This interpretation was supported by the demonstration that only compounds which possess an aldehydic structure are able to participate in the oxidation–reduction reaction. The structurally aldehydic compounds diphenylformamidine, form-*p*-toluidide, formamide and benzalaniline all reacted; the analogous non-aldehydic compounds diphenylacetamidine, acetanilide and acetamide failed to react.

The function of the acid appears to be the formation, either by cleavage of a methylene-bis-amine (considered as an ammono-acetal) or from a Schiff base (taken as such or derived from the methylene-bis-amine), of a reactive cation capable of serving as a hydrogen acceptor. Higher temperatures (*circa* 200°) force the reaction in absence of added acid. A general reaction scheme for the acid-induced reaction is presented which appears to be consistent with the observed facts.

PHILADELPHIA, PA. RECEIVED OCTOBER 1, 1943

(17) J. G. Miller and Wagner, THIS JOURNAL, **54**, 3698 (1932).

(18) Walther, *J. prakt. Chem.*, [2] **53**, 475 (1896).

(19) Sen and Ray, *J. Chem. Soc.*, 646 (1926).

(20) Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., Vol. II, 1916, p. 24.

(21) Frankland, *J. Chem. Soc.*, **115**, 198 (1919).

(22) Alexander and McElvain, THIS JOURNAL, **60**, 1280 (1938).

(23) Haase, *Ber.*, **37**, 3233 (1904).

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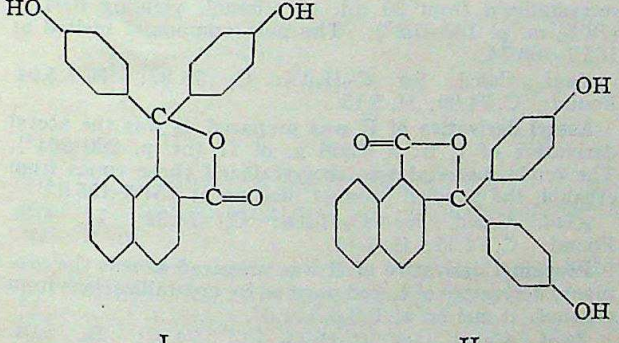
[CONTRIBUTION FROM THE RESEARCH LABORATORY OF EX-LAX, INC.]

The Phthaleins from Phenol and 1,2-Naphthalenedicarboxylic Acid

BY MAX H. HUBACHER

A study is being made in this Laboratory of the relationship, if any, between the molecular structure of aromatic compounds, especially of phthaleins, and their laxative potency.[1] Of the four theoretically possible phenolnaphthaleins, only one is known, the phenol-1,8-naphthalein.[2] Therefore, the synthesis of the phthaleins from phenol and 1,2-naphthalenedicarboxylic acid anhydride was undertaken. The two theoretically possible phthaleins were obtained. The main product (I) melted at 292° and yielded, on fusion with potassium hydroxide, 2-naphthoic acid and 4,4′-dihydroxybenzophenone. It is, therefore, the γ-lactone of the 1-(α,4,4′-trihydroxybenzohydryl)-2-naphthoic acid or the phenol-2,1-naphthalein. The by-product (II) melted at 268° and yielded, on treatment with potassium hydroxide, the 1-naphthoic acid and 4,4′-dihydroxybenzophenone. Therefore, it must be the γ-lactone of the 2-(α,4,4′-trihydroxybenzohydryl)-1-naphthoic acid or the phenol-1,2-naphthalein.



I II

According to Dr. W. W. Hartman, the *p*H range for both phthaleins is approximately identical, 8.6 to 10.5, the color change from colorless to red magenta. Based on the color density curves, compound I is about four times more intense in color than II. The tests indicate that phenol-2,1-naphthalein (I) is the better indicator of the two, with the advantage over phenolphthalein that it does not fade.

In contrast to that of phenolphthalein and many other phthaleins,[3] the color of solutions of either of the two phthaleins in dilute alkali does not fade. Likewise, phenol-2,1-naphthalein resists oxidation by hydrogen peroxide, while phenolphthalein is easily oxidized under the same conditions.

Acknowledgment.—The author is indebted to Dr. L. T. Capell of *Chemical Abstracts* for the nomenclature and to Dr. W. W. Hartman of the Eastman Kodak Company for the preparation of the transmission curves.

(1) S. Loewe and M. Hubacher, *Arch. intern. pharmacodynamie*, **65**, 297 (1941); M. H. Hubacher, THIS JOURNAL, **64**, 2538 (1942).

(2) H. P. Kaufmann, *Z. angew. Chem.*, **40**, 863 (1927); F. F. Blicke and R. A. Patelski, THIS JOURNAL **60**, 2284 (1938).

(3) M. H. Hubacher, *ibid.*, **65**, 2097 (1943).

Experimental[4]

Condensation of 1,2-Naphthalenedicarboxylic Anhydride with Phenol.—To 19.8 g. (0.1 mole) of 1,2-naphthalenedicarboxylic anhydride (m. p. 164–169°)[5] and 18.8 g. (0.2 mole) of phenol was added 8 ml. of stannic chloride and the mixture stirred for four hours at 113–116°. The reaction mass was treated with hot 0.1 *N* hydrochloric acid, filtered, and the residue dissolved in 300 ml. of 1 *N* sodium hydroxide. The red filtrate was saturated with carbon dioxide. The precipitated crude phthaleins weighed 16.4 g. (m. p. 240–270°). Separation into two compounds was effected by crystallization from acetic acid. The first crop consisted of the main product (I), crystallizing in fine needles arranged in star-like clusters. The by-product (II) was separated from subsequent fractions in the form of coarse, granular crystals. On heating a solution containing crystals of both compounds, the fine crystals of I dissolve first. This observation can be helpful in the separation; yield of I, 8.03 g. (22%) of m. p. 288–291°; of II, 1.82 g. (5%) of m. p. 261–267°.

Phenol-2,1-naphthalein.—Phthalein I was recrystallized for analysis from acetic acid (1 g. in 20 ml.) or from ethanol (1 g. in 4.5 ml.). It melts at 291.1–292.4°. One gram dissolves in 6.7 ml. of methanol (100%) and 16.5 ml. of ethanol (92.3%) at 20°. A 0.001 molar solution of I in 0.1 *N* sodium hydroxide is red magenta in color[6] or similar to that of a phenolphthalein solution of the same concentration. The solution has a maximum absorption at 562 λ. The color of such an alkaline solution, as well as that of phenol-1,8-naphthalein[2] in the same concentration, does not fade.[3] A 0.1 molar solution of I in 5 *N* sodium hydroxide is dark red and remains unchanged for months; a phenolphthalein solution of the same concentration turns to light red within a few minutes.

The color of I in concd. sulfuric acid is red.

Phenol-2,1-naphthalein turns from colorless to red at a *p*H of 8.6 to 10.5 or at a slightly higher *p*H than phenolphthalein. It is about one-third as strong in color as phenolphthalein and four times as strong as phenol-1,2-naphthalein (see Fig. 1).

By methylation of I with methyl iodide or dimethyl sulfate, an alkali-insoluble, non-crystallizable product was obtained.

Phenol-2,1-naphthalein could not be made to react with hydrogen peroxide, whereas phenolphthalein, under similar conditions, is oxidized readily.[3] Nor did I react with hydroxylamine.

Anal. Calcd. for $C_{24}H_{16}O_4$: C, 78.24; H, 4.37; mol. wt., 368. Found: C, 77.97; H, 4.34; mol. wt., 388, 366, 377, 322 (Signer method[7]).

Phenol-1,2-naphthalein.—The by-product was purified further by recrystallizations from acetic acid (1 g. in 16 ml.)

(4) All melting points are corrected and determined in a Hershberg precision melting point apparatus. Before analysis, the compounds were dried to constant weight at 110° and 10 microns pressure, with the exception of the dipropionate of II, which was dried at 80° and high vacuum. Analyses by William Saschek.

(5) E. B. Hershberg and L. F. Fieser, "Organic Syntheses," Vol. 18, 59 (1938).

(6) This color is called strong red or 4 R 4.5/18, according to the nomenclature of the Munsell Color System ("Method of Designating Colors," National Bureau of Standard Research Paper, RP 1239, Sept., 1939).

(7) E. P. Clark, *Ind. Eng. Chem., Anal. Ed.*, **13**, 820 (1941). Acetone was used as a solvent and azobenzene as a standard.

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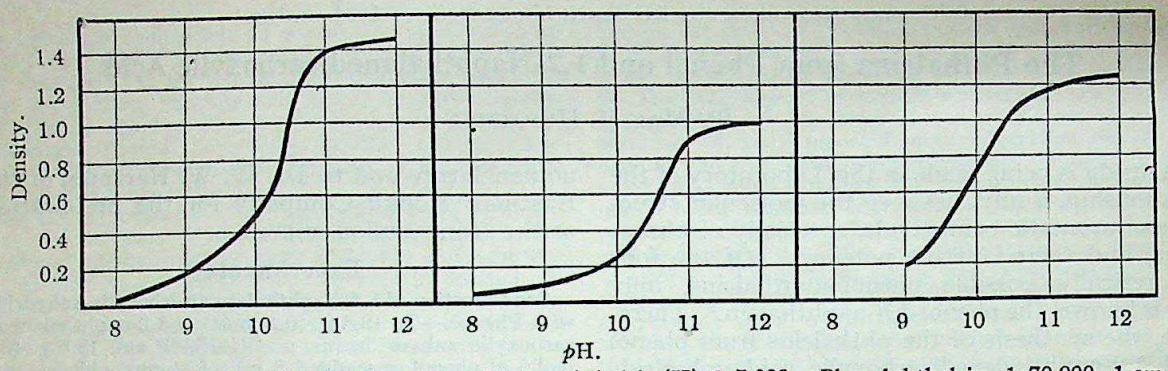

Phenol-2,1-naphthalein (I), 1:21,000, 1-cm. layer at λ 562. Phenol-1,2-naphthalein (II), 1:7,666, 1-cm. layer at λ 558. Phenolphthalein, 1:70,000, 1-cm. layer at λ 555.

Fig. 1.—Density–*p*H range characteristics.

and finally from ethanol. It melts at 267.5-269.5°. The color of a 0.001 molar solution in 0.1 *N* sodium hydroxide is red magenta[6] and orange in concd. sulfuric acid. The maximum of absorption is at 558 λ.

Anal. Calcd. for $C_{24}H_{16}O_4$: C, 78.24; H, 4.37; mol. wt., 368. Found: C, 78.06; H, 4.08; mol. wt., 352 (Rast in camphor).

Some 1,2-naphthalenedicarboxylic anhydride (8.1 g., m. p. 168–169°) was recovered from the mother liquor of the crude phthalein by acidification and sublimation of the precipitate at 160° in high vacuum.[8]

Fusion of I with Potassium Hydroxide.—Twenty grams of potassium hydroxide was heated in a nickel crucible to 240–245° (oil-bath temperature) and then 3.0 g. of I stirred in. After ten minutes, the melt was dissolved in water and treated for the separation of phenolic and acidic compounds by the usual method. The phenolic fraction was purified by sublimation at 180° and 20 microns pressure,[8] yielding 0.697 g. (40%) of 4,4′-dihydroxybenzophenone melting at 208–214° (no depression when mixed with a pure specimen of m. p. 216.8–217.2°).[9] The acidic fraction, likewise purified by sublimation at 150° and 10 microns, weighed 1.006 g. (72%) and melted at 181.5–184.4° (no depression when mixed with 2-naphthoic acid (Eastman Kodak Co.) of m. p. 183.2–184.8°).

Fusion of II with Potassium Hydroxide.—Seven grams of potassium hydroxide was stirred with 0.726 g. of II (m. p. 260–265°) for ten minutes at 240–245° (oil-bath temperature). The reaction product consisted of 0.270 g. (64%) of 4,4′-dihydroxybenzophenone (m. p. 208–215°) and 0.279 g. (82%) of 1-naphthoic acid (m. p. 161.7–162.8°) (no depression when mixed with 1-naphthoic acid (Eastman Kodak Co.) of m. p. 159.8–161.1°).

(8) In tube A of the apparatus described in *Ind. Eng. Chem., Anal. Ed.*, **15**, 448 (1943).

(9) Prepared according to A. Baeyer and J. B. Burkhardt, *Ann.*, **202**, 126 (1880).

Acetyl Derivative of I.—A solution of 1.84 g. (0.005 mole) of I, 1.50 g. (0.015 mole) of acetic anhydride, 5 ml. of acetic acid and one drop of concd. sulfuric acid was refluxed for one hour. The product weighed 2.22 g. (98%, m. p. 218–223°) and after two crystallizations from ethanol (1 g. in 100 ml.) melted at 223.8–225.9°.

Anal. Calcd. for $C_{28}H_{20}O_6$: C, 74.32; H, 4.46; mol. wt., 452. Found: C, 74.01; H, 4.52; mol. wt., 435, 409, 460 (Signer method[7]).

Propionyl derivative of I was prepared by refluxing for one hour 0.92 g. of I, 3.0 ml. of propionic anhydride and a trace of concd. sulfuric acid. The crude product was recrystallized from 20 ml. of ethanol, yielding 0.94 g. (78%, m. p. 159–162°). The pure compound melted at 162.7–163.7°.

Anal. Calcd. for $C_{30}H_{24}O_6$: C, 74.97; H, 5.04. Found: C, 74.99; H, 5.13.

Acetyl derivative of II was prepared as was the acetyl derivative of I, from 0.368 g. of II (m. p. 260–264°). The crude material was recrystallized three times from ethanol, the purified product melting at 154.5–155.6°.

Anal. Calcd. for $C_{28}H_{20}O_6$: C, 74.32; H, 4.46. Found: C, 74.11; H, 4.41.

Propionyl derivative of II was prepared as was the propionyl derivative of I, and purified by crystallizations from ethanol; it melted at 109.6–111.0°.

Anal. Calcd. for $C_{30}H_{24}O_6$: C, 74.97; H, 5.04. Found: C, 74.59; H, 4.83.

Summary

The two theoretically possible phthaleins from phenol and 1,2-naphthalenedicarboxylic acid anhydride were prepared and their structure proved. The corresponding acetyl and propionyl derivatives were made also.

Brooklyn, N. Y. Received September 17, 1943

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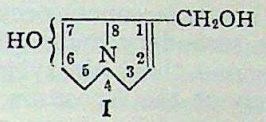
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Structure of Monocrotaline. XI. Proof of the Structure of Retronecine[1]

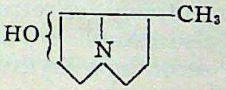
BY ROGER ADAMS AND N. J. LEONARD

Retronecine, the base obtained along with carbon dioxide and monocrotic acid upon alkaline hydrolysis of monocrotaline, has been postulated[2,3] as having structure I. The presence of the

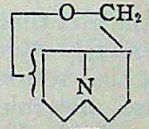


I

—CH_2OH group in the 1-position of the pyrrolizidine nucleus[3] and the location of the double bond in the 1,2-position[4] have been proved conclusively. The location of the secondary hydroxyl group in retronecine (I) or in retronecanol (II)[3] has been in doubt. The experimental evidence favors either the 6- or the 7-position. The degradation of retronecanol by bromocyanogen indicates that the 7-position is the more likely.[2] Corroborative evidence for the 7-position is obtained by construction of models representing anhydroplatynecine (III). When the secondary



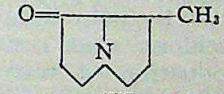
II



III

hydroxyl group is in the 7-position, the structural model of anhydroplatynecine involves somewhat less strain.

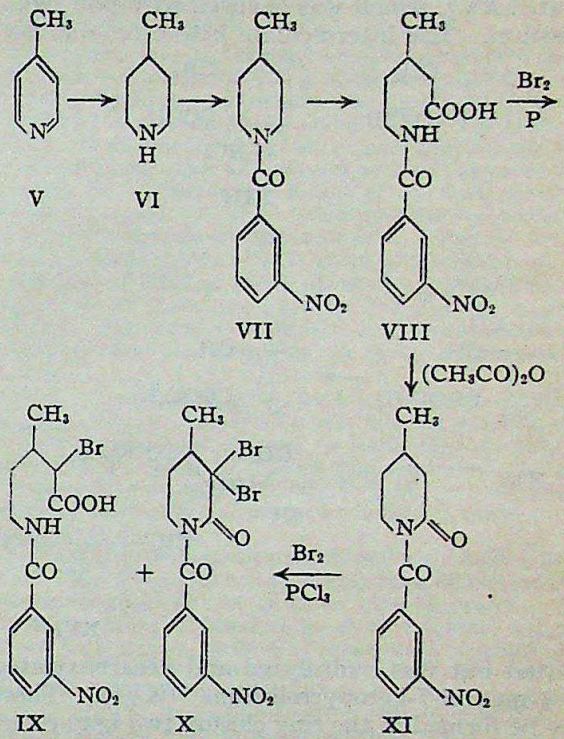
An optically active form of 1-methyl-7-ketopyrrolizidine has now been synthesized by an unequivocal method and found to be identical with the retronecanone (IV)[3] obtained by oxidation of



IV

retronecanol with aluminum *t*-butoxide. It has thus been proved that retronecine and its derivatives have the secondary hydroxyl group in the 7-position.

4-Methylpyridine (V) was reduced catalytically to 4-methylpiperidine (VI), which was converted into 1-*m*-nitrobenzoyl-4-methyl-piperidine (VII) by a Schotten–Baumann reaction with *m*-nitrobenzoyl chloride. Oxidation of compound VII with potassium permanganate according to the method of Schotten[5,6] and Fischer and Zemplén[7]



gave β-methyl-δ-*m*-nitrobenzoylaminovaleric acid (VIII), which would be formed by cleavage of either ring carbon–nitrogen bond. Bromination of this acid (VIII) in the presence of red phosphorus resulted in the formation of two products IX and X. Compound X was identified as N-*m*-nitrobenzoyl-γ-methyl-β,β-dibromo-α-piperidone by bromination of N-*m*-nitrobenzoyl-γ-methyl-α-piperidone (XI).[8] The structure of compound IX was accepted on the basis of the results of the researches of Fischer and Zemplén,[7] who prepared the analogous compound through a similar series of reactions from pyridine.

α-Bromo-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid (IX) was not obtained in a pure state but the crude product was converted to ethyl 3-methylpyrrolidine-2-carboxylate (XIV) through the intermediates XII and XIII. The formation of 1-*m*-nitrobenzoyl-3-methylpyrrolidine-2-carboxylic acid (XII) resulted from the reaction of alkali upon IX, and 3-methylpyrrolidine-2-carboxylic acid hydrochloride (XIII) was obtained by the hydrolysis of XII with hydrochloric acid. Owing to the difficulty in purifying either XII or XIII, compound XIII was esterified directly to XIV, which was obtained readily in pure form by distillation. The physical properties and analyses of XIV and its picrate indicated conclusively that the compound was ethyl 3-methylpyrrolidine-2-

(1) For previous paper see Adams and Wilkinson, THIS JOURNAL, 65, 2203 (1943).
(2) Adams, Carmack and Mahan, *ibid.*, 64, 2593 (1942).
(3) Adams and Hamlin, *ibid.*, 64, 2597 (1942).
(4) Adams and Mahan, *ibid.*, 65, 2009 (1943).
(5) Schotten, *Ber.*, 17, 2544 (1884).
(6) Schotten, *ibid.*, 21, 2235 (1888).
(7) Fischer and Zemplén, *ibid.*, 42, 2989 (1909).
(8) Sanicon and Marvel, THIS JOURNAL, 61, 2822 (1939).

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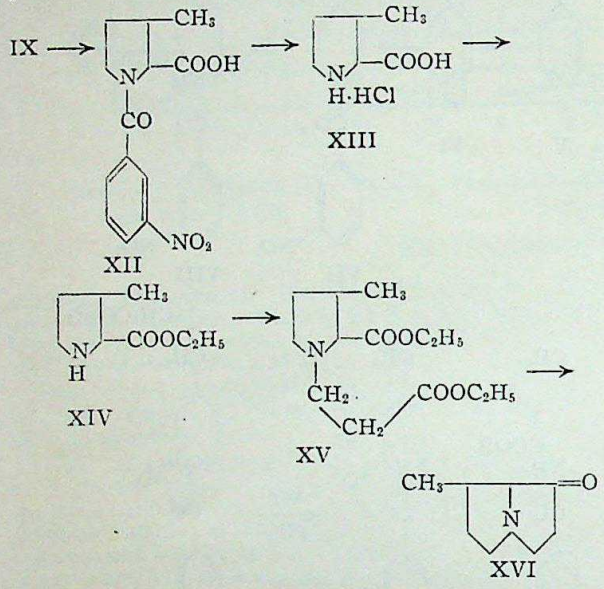
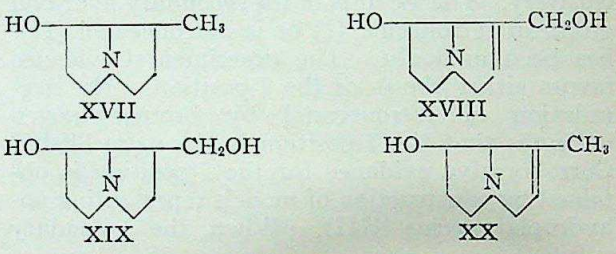
carboxylate. Proline has been made previously by a similar series of reactions.[7] Ethyl 3-methylpyrrolidine-2-carboxylate underwent practically quantitative addition to ethyl acrylate to give ethyl β-N-(3-methyl-2-carbethoxypyrrolidyl)-propionate (XV), which was cyclized with powdered potassium. The intermediate keto-ester was not



isolated but was hydrolyzed and decarboxylated to 1-methyl-7-ketopyrrolizidine (XVI). There may be formed in the ring closure two keto-esters depending upon which ethoxy group is eliminated as ethanol. Both of these, however, on hydrolysis and decarboxylation would yield the same ketone.

The picrate, methiodide and oxime of compound XVI were prepared. Although theoretically two racemic modifications might be present in the liquid XVI as synthesized only single derivatives were isolated in each case. An attempt was made to isolate an optically active 1-methyl-7-ketopyrrolizidine from the possible mixture of four forms by the use of *l*-menthydrazide. A pure *l*-menthydrazone was obtained but it proved to have a different melting point and specific rotation from the *l*-menthydrazone of retronecanone. Moreover, hydrolysis of the 1-methyl-7-ketopyrrolizidine *l*-menthydrazone and conversion of the ketone to the oxime gave an optically inactive product.

In order to decrease the stereochemical possibilities in the final product as a result of working with racemic modifications, a similar series of reactions was carried out using *l*-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid. This optically active acid was obtained by resolution through the quinidine salt of the racemic acid (VIII). There was thus obtained optically active 1-methyl-7-ketopyrrolizidine (XVI) which could not consist of a mixture of more than two forms. Like the product from the racemic acid this was an oil. When treated with hydroxylamine, however, a single, pure, optically active oxime was isolated. This proved to be identical in melting point, crystalline form as observed under the microscope, and specific rotation with retronecanone oxime, and the melting points of mixtures of the two compounds showed no depression. The picrates of the aminoketoximes obtained from natural and synthetic sources were also found to be identical and showed no depression of melting-decomposition point when mixed. Likewise, the picrolonates of the oximes were identical. Since the keto group in retronecanone occupies the same position as the secondary hydroxyl group in its parent, retronecanol, this hydroxyl group has been located definitely at the 7-position, and the precise structure of retronecanol may now be represented by XVII. Retronecine, therefore, has structure XVIII; platynecine,[9] structure XIX; and desoxyretronecine,[10] structure XX. Owing



to the fact that heliotridine and oxyheliotridane[11] are merely stereoisomers, respectively, of retronecine and retronecanol, it is also established that these molecules have the secondary hydroxyl group in the 7-position.

Monocrotaline, the acetyl and benzoyl esters of retronecine, and retronecine itself have been reduced to retronecanol.[10,12,13] These reductions have been carried out in solutions of widely different *p*H over palladium or platinum oxide catalysts, and retronecanol is the only 1-methyl-7-hydroxypyrrolizidine isomer which has been obtained, always in essentially quantitative yield. Likewise, the catalytic reduction of desoxyretronecine in hydrochloric acid resulted in almost quantitative production of retronecanol,[10] and isoheliotridene was reduced in ethanol over platinum oxide to heliotridane,[4] which is related to retronecanol through chlororetronecane,[14]

Reduction of all of these $\Delta^{1,2}$-unsaturated pyrrolizidines makes carbon atom-1 asymmetrical. There is the possibility of reduction proceeding to give a mixture of isomers in which the C_1-CH_3 would be both *cis* and *trans* with respect to the C_8-H; the other possibility would be asymmetric reduction proceeding to give *either* the *cis*- or the *trans*-C_1-CH_3 configuration. Asymmetric reduction is indicated because of the fact that synthetic (and, therefore, naturally-obtained) retronecanone possesses the C_1-CH_3 fixed in one stereo-

(9) Orekhov and Tiedebel, *Ber.*, **68**, 650 (1935).
(10) Adams and Rogers, THIS JOURNAL, **63**, 537 (1941).
(11) Menshikov, *Ber.*, **68**, 1051 (1935).
(12) Barger, Seshadri, Watt and Yabuta, *J. Chem. Soc.*, 11 (1935).
(13) Adams and Rogers, THIS JOURNAL, **61**, 2815 (1939).
(14) Adams and Rogers, *ibid.*, **63**, 228 (1941).

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chemical configuration. This may be deduced from the fact that the starting material for its preparation was *l*-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid, in which the C_{β}-CH_3 had a fixed configuration.

Reduction of retronecanone could yield a mixture of a maximum of four stereoisomeric 1-methyl-7-hydroxypyrrolizidines if C-8 were racemized in the aluminum *t*-butoxide oxidation of retronecanol to retronecanone. A maximum of two isomers, of which one would be retronecanol, could result on reduction of retronecanone if the latter possessed only one stereochemical configuration about C-8. Neither retronecanol nor its derivatives could be obtained by reduction of retronecanone over platinum oxide in ethanol or in ethanolic hydrochloric acid solution. The reaction products from reductions carried out both in neutral and acid solution were mixtures. In each of the two experiments it was possible to isolate a pure compound as a picrate, but these were not identical with each other or with retronecanol picrate. Upon acetylation of each reduction product mixture and then treatment with methyl iodide, the same pure acetyl methiodide was isolated in small yield. This methiodide was not identical but stereoisomeric with acetylretronecanol methiodide. As a consequence of these results no attempt was made to synthesize natural retronecanol from synthetic optically active 1-methyl-7-ketopyrrolizidine.

Experimental

4-Methylpiperidine (VI).—Hydrogenation of 482 g. (5.18 moles) of redistilled 4-methylpyridine (V) (b. p. 142–144°) was concluded after twenty-four hours at 210° and 150–300 atm. with 50 g. of Raney nickel catalyst. The product was fractionally distilled and the fraction boiling at 126–129° was collected[15]; $n^{20}D$ 1.4487; yield 283 g. (55%, or 90% on the basis of unrecovered 4-methylpyridine).

1-*m*-Nitrobenzoyl-4-methylpiperidine (VII).—To a well-stirred mixture of 265 g. (2.67 moles) of 4-methylpiperidine and 120 g. (3.00 moles) of sodium hydroxide in 630 cc. of water was added slowly, during the course of two hours, 500 g. (2.69 moles) of molten *m*-nitrobenzoyl chloride.[6] The temperature was maintained at 35–40°. When addition was complete the mixture was stirred for an additional hour and then cooled in ice. The yellow crystals were filtered, washed with water and dried; yield of crude product, 582 g. (88%). After recrystallization from aqueous ethanol, 550 g. of large colorless prisms was obtained, m. p. 72–73°. The compound may be recrystallized also from benzene–ligroin (b. p. 90–110°).

Anal. Calcd. for $C_{13}H_{16}N_2O_3$: C, 62.89; H, 6.49. Found: C, 63.00; H, 6.50.

***dl*-β-Methyl-δ-*m*-nitrobenzoylaminovaleric Acid (VIII).**—A total of 520 g. (2.1 moles) of 1-*m*-nitrobenzoyl-4-methylpiperidine was oxidized in thirteen batches of 40 g. each. The amide (40 g.) was dissolved in 2.5 liters of boiling water and a solution of 60 g. of potassium permanganate in 500 cc. of hot water was added during one hour, while stirring vigorously and refluxing. The reaction mixture was filtered hot and the alkaline filtrate was cooled and extracted with ether. The combined ether extracts of thirteen runs furnished 88 g. of crude starting material which again was subjected to permanganate oxidation. The aqueous solution (above) was acidified with dilute sulfuric acid and cooled in ice. The colorless crystalline product which separated was collected on a filter; extraction of the acidic filtrate with ether furnished additional product. The total combined yield was 340 g. (57%) which was purified by recrystallization from dilute acetic acid or aqueous ethanol; colorless elongated prisms, m. p. 103–105°.

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.78; H, 5.93; N, 9.84.

Resolution of *dl*-β-Methyl-δ-*m*-nitrobenzoylaminovaleric Acid.—A mixture of 100 g. of the *dl*-acid and 116 g. of anhydrous quinidine was dissolved in hot absolute ethanol, boiled with Darco and Norite and filtered. The ethanolic filtrate, which amounted to 450 cc., was diluted with 1300 cc. of anhydrous ether and allowed to stand at room temperature for several days. Rosets of colorless elongated prisms separated and these were isolated by filtration, washed with anhydrous ether and dried (Fraction 1); m. p., 125.0–126.5° (cor.); yield 77 g. (36% of total).

Rotation. 0.2286 g. made up to 5 cc. with absolute ethanol at 28° gave αD +5.10°; *l*, 1; $[\alpha]^{28}D$ +111.5° (±0.5°). Further recrystallization from absolute ethanol–anhydrous ether altered neither the melting point nor the rotation.

After removal of 77 g. of the most insoluble quinidine salt (Fraction 1), the filtrate was diluted further with anhydrous ether and allowed to stand in the cold. A further 48 g. (22%) of yellow, semicrystalline material separated, leaving approximately 42% of the total salt in solution (Fraction 2). The more soluble salt could not be obtained crystalline.

***l*-β-Methyl-δ-*m*-nitrobenzoylaminovaleric Acid.**—Fraction 1 (75 g.) was shaken thoroughly with 500 cc. of 2 *N* sulfuric acid and 200 cc. of ether, then separated. The mixture of dilute acid and undissolved quinidine salt was shaken with 200-cc. portions of ether until no more solid material remained. The ethereal extracts were combined, dried over anhydrous magnesium sulfate, and evaporated to give 30 g. of crystalline *l*-acid. This was purified by recrystallization from aqueous ethanol: colorless rods, m. p. 113–114°.

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.96; H, 6.02; N, 9.92.

Rotation. 0.2040 g. made up to 5 cc. with absolute ethanol at 30° gave αD −0.205°; *l*, 1; $[\alpha]^{30}D$ −5.0° (±0.2°).

***d*-β-Methyl-δ-*m*-nitrobenzoylaminovaleric Acid.**—The ethereal solution containing Fraction 2 was shaken with 2 *N* sulfuric acid, and 34 g. of the *d*-acid was obtained by the same procedure as that outlined above. Purification was accomplished by recrystallization from chloroform–ligroin (b. p. 90–110°): colorless elongated prisms, m. p., 113–114°.

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.71; H, 5.75; N, 9.99. Found: C, 55.94; H, 5.84; N, 10.09.

Rotation. 0.2164 g. made up to 5 cc. with absolute ethanol at 25° gave αD +0.23°; *l*, 1; $[\alpha]^{25}D$ +5.3° (±0.2°).

Bromination of *dl*-β-Methyl-δ-*m*-nitrobenzoylaminovaleric Acid.—An intimate mixture of 50 g. (0.18 mole) of *dl*-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid and 8 g. of red phosphorus was protected from moisture, cooled in ice, and stirred manually during the thirty-minute addition of 51.5 cc. (*ca.* 0.94 mole) of dry bromine. When addition was complete the mixture was stirred at room temperature for thirty minutes, warmed to 90° during ten minutes, and kept at 90° for a further ten minutes. The reaction mixture was cooled in ice and ice-water was added gradually. Excess bromine was reduced by passing a slow stream of sulfur dioxide into the cold solution. After addition of excess sodium carbonate solution the mixture was stirred vigorously and filtered. The sodium carbonate-insoluble material weighed 15 g. It was purified by recrystallization from ethanol, from which it separated in leaf-like aggregates of colorless elongated prisms, m. p. 152–153° (cor.). It proved to be N-*m*-nitrobenzoyl-γ-methyl-β,β-dibromo-α-piperidone (X).

(15) Ladenburg, *Ann.*, **247**, 1 (1888).

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Anal. Calcd. for $C_{13}H_{12}Br_2N_2O_4$: C, 37.17; H, 2.88; N, 6.67. Found: C, 37.36; H, 3.08; N, 6.62.

After removal of the alkali-insoluble material the filtrate was cooled, acidified with 1 *N* sulfuric acid and extracted thoroughly with ether. The ethereal solution was dried over anhydrous magnesium sulfate, and the ether was removed to leave a residue of 42 g. of straw-colored oil which could not be crystallized. The crude α-bromo-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid (IX) was not purified but was used directly in the next step (ring-closure).

N-*m*-Nitrobenzoyl-γ-methyl-α-piperidone (XI).—A solution of 2 g. of *dl*-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid (VIII)[6] in 25 cc. of acetic anhydride was refluxed for two and one-half hours in all-glass apparatus. The acetic anhydride was removed *in vacuo* and the residue was recrystallized from aqueous ethanol: colorless elongated prisms, m. p. 102–103°. The melting point of a mixture of this product and the starting material (m. p. 103–104°) was depressed to 85–95°.

Anal. Calcd. for $C_{13}H_{14}N_2O_4$: C, 59.53; H, 5.38; N, 10.68. Found: C, 59.71; H, 5.44; N, 10.82.

N-*m*-Nitrobenzoyl-γ-methyl-β,β-dibromo-α-piperidone (X).—To 0.25 g. of N-*m*-nitrobenzoyl-γ-methyl-α-piperidone in 5 cc. of dry chloroform were added three drops of phosphorus trichloride and 0.6 g. of bromine.[8] The solution was illuminated by a bright electric light for forty-eight hours, then the reaction mixture was treated with water and sufficient sodium bisulfite to decompose the excess bromine. The chloroform layer was separated and evaporated to dryness, leaving 0.10 g. of product which was recrystallized from ethanol: colorless elongated prisms, m. p., 152–153° (cor.). When this product was mixed with the alkali-insoluble material obtained in brominating *dl*-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid, there was no depression of melting point.

Bromination of *l*-β-Methyl-δ-*m*-nitrobenzoylaminovaleric Acid.—The bromination was carried out in a manner identical with that used for the *dl*-acid. The quantities employed were 25 g. (0.09 mole) of *l*-acid, 3.5 g. of red phosphorus, and 20 cc. of bromine (*ca.* 0.36 mole), and two products were obtained. The alkali-insoluble bromination product was recrystallized from ethanol: colorless prisms, m. p., 167–168° (cor.). This was *l*-N-*m*-nitrobenzoyl-γ-methyl-β,β-dibromo-α-piperidone.

Anal. Calcd. for $C_{13}H_{12}Br_2N_2O_4$: C, 37.17; H, 2.88; N, 6.67. Found: C, 37.33; H, 3.05; N, 6.54.

Rotation. 0.1211 g. made up to 5 cc. with pyridine at 30° gave α_D −0.49°; *l*, 1; $[\alpha]^{30}_D$ −20.2° (±0.2°).

The alkali-soluble product of bromination weighed 19 g. but was not obtained crystalline. It was crude optically active α-bromo-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid and was used directly in the next step.

1-*m*-Nitrobenzoyl-3-methylpyrrolidine-2-carboxylic Acid (XII).—A solution of 42 g. of crude α-bromo-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid (IX) in 350 cc. of 1 *N* sodium hydroxide was kept at 37° for forty-eight hours. The red solution was nearly neutralized with 1 *N* sulfuric acid and concentrated *in vacuo* to 100 cc. The solution was cooled, acidified strongly with sulfuric acid and extracted with five 100-cc. portions of ether. The combined ether extracts were washed with a small quantity of water, dried over anhydrous magnesium sulfate, and the ether was removed. The residue amounted to 29 g. of thick yellow oil which could not be induced to crystallize.

The crude 1-*m*-nitrobenzoyl-3-methylpyrrolidine-2-carboxylic acid was esterified directly.

Optically Active 1-*m*-Nitrobenzoyl-3-methylpyrrolidine-2-carboxylic Acid.—This compound was prepared in the same manner as the above acid, starting with a solution of 19 g. of crude optically active α-bromo-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid in 160 cc. of 1 *N* sodium hydroxide. The product was obtained as 14 g. of yellow oil which was used directly in the next step in the synthesis.

Ethyl 3-Methylpyrrolidine-2-carboxylate (XIV).—A solution of 27.5 g. of crude 1-*m*-nitrobenzoyl-3-methylpyrrolidine-2-carboxylic acid in 1 l. of 3 *N* hydrochloric acid was refluxed for four hours. The solution was cooled, and the *m*-nitrobenzoic acid was removed by filtration. The filtrate was concentrated to small volume *in vacuo*, cooled and filtered free of additional precipitated *m*-nitrobenzoic acid. This filtrate was extracted with three portions of ether and evaporated to dryness *in vacuo* to yield 9 g. of crude 3-methylpyrrolidine-2-carboxylic acid hydrochloride (XIII) as a viscous oil. This amino acid hydrochloride was esterified by a method analogous to that used for preparing the ethyl ester of *l*-proline.[16] The crude material was suspended in 150 cc. of freshly distilled absolute ethanol. The suspension was saturated with dry hydrogen chloride which brought about complete solution. The solution was refluxed gently for ten minutes, allowed to stand for several hours protected from moisture, and then evaporated *in vacuo*. The residue was redissolved in 100 cc. of absolute ethanol and again saturated with dry hydrogen chloride, with natural refluxing. After standing overnight the solution was evaporated to dryness *in vacuo*. The brown viscous residue was dissolved in 25 cc. of warm absolute ethanol and 175 cc. of anhydrous ether was added. The solution was cooled in an ice–salt-bath and dry ammonia was passed through, slowly at first, then in a rapid stream until the solution was saturated. It was allowed to stand overnight and, after filtration and removal of the ether, the residue was distilled under diminished pressure; b. p. 90–91.5° (17.5 mm.), 96–97° (21 mm.); $n^{20}D$ 1.4470; d^{20}_4 0.993. The yield was 4 g., or an over-all yield of 14% of the theoretical amount, based upon 50 g. (0.18 mole) of *dl*-β-methyl-δ-*m*-nitrobenzoylaminovaleric acid (VIII).

Anal. Calcd. for $C_8H_{15}NO_2$: C, 61.13; H, 9.61; N, 8.91; MR_D, 42.36. Found: C, 61.18; H, 9.60; N, 8.92; MR_D, 42.31.

Picrate.—Prepared in and recrystallized from dry benzene, the picrate formed long yellow prisms, m. p. 112.5–114°.

Anal. Calcd. for $C_{14}H_{18}N_4O_9$: C, 43.53; H, 4.69. Found: C, 43.67; H, 4.81.

Optically Active Ethyl 3-Methylpyrrolidine-2-carboxylate.—The same procedure was followed as for the optically inactive compound. The hydrolysis was carried out by refluxing a solution of 14 g. of crude optically active 1-*m*-nitrobenzoyl-3-methylpyrrolidine-2-carboxylic acid in 400 cc. of 3 *N* hydrochloric acid for five hours. The crude optically active 3-methylpyrrolidine-2-carboxylic acid hydrochloride weighed 4.7 g. and was esterified with absolute ethanol saturated with dry hydrogen chloride as described above. The ethyl ester boiled at 97–98° (23 mm.); $n^{20}D$ 1.4458; yield, 1.2 g.

Anal. Calcd. for $C_8H_{15}NO_2$: N, 8.91. Found: N, 8.76.

Rotation. 0.0686 g. made up to 5 cc. with absolute ethanol at 28° showed no measurable rotation.

Ethyl β-N-(3-Methyl-2-carbethoxypyrrolidyl)-propionate (XV).[17]—A solution of 3.8 g. (24 millimoles) of ethyl 3-methylpyrrolidine-2-carboxylate and 8 cc. (*ca.* 70 millimoles) of ethyl acrylate containing a trace of hydroquinone was heated under reflux for twenty-four hours on the steam-bath, protected from moisture. The clear yellow solution was fractionally distilled *in vacuo*. The boiling point of the colorless product was 163.5–165.5° (18 mm.), 126–127° (4 mm.); $n^{20}D$ 1.4523; d^{20}_4 1.032; yield, 6.0 g. (97%).

Anal. Calcd. for $C_{13}H_{23}NO_4$: C, 60.69; H, 8.98; N, 5.44; MR_D, 67.46. Found: C, 60.73; H, 8.96; N, 5.36; MR_D, 67.27.

Picrate.—Prepared in anhydrous ether and recrystallized from dry benzene, the picrate formed glistening yellow platelets, m. p., 98–99°.

Anal. Calcd. for $C_{19}H_{26}N_4O_{11}$: C, 46.92; H, 5.39. Found: C, 47.07; H, 5.50.

(16) Kapfhammer and Matthes, *Z. physiol. Chem.*, **223**, 43 (1933).

(17) The procedure used here is similar to that followed by Dr. M. Carmack in the addition of ethyl *l*-pyrrolidine-2-carboxylate to

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Optically Active Ethyl β-N-(3-Methyl-2-carbethoxypyrrolidyl)-propionate.—A solution of 1.2 g. of the ethyl 3-methylpyrrolidine-2-carboxylate prepared from optically active starting material and 4 cc. of ethyl acrylate was refluxed on a steam-bath for twenty hours, protected from moisture. The product boiled at 170–171° (25 mm.); $n^{20}D$ 1.4512; yield, 1.5 g.

Anal. Calcd. for $C_{13}H_{23}NO_4$: C, 60.69; H, 8.98; N, 5.44. Found: C, 60.88; H, 9.16; N, 5.69.

Rotation. 0.1038 g. in 2.5 cc. of absolute ethanol at 30° gave αD −1.45°; *l*, 1; $[\alpha]^{30}D$ −34.9° (±0.5°).

1-Methyl-7-ketopyrrolizidine (XVI).—Metallic potassium (2.5 g.) was finely powdered under 20 cc. of dry xylene. The mixture was cooled and 10 cc. of dry benzene was added. With vigorous stirring, a solution of 6 g. (23 millimoles) of optically inactive ethyl β-N-(3-methyl-2-carbethoxypyrrolidyl)-propionate and 10 cc. of dry benzene was added dropwise over a period of thirty-five minutes. The residual diester solution was washed in with an additional 10 cc. of dry benzene and the reaction mixture was heated under reflux on the steam-bath for four and one-half hours, protected from moisture. The mixture was cooled and the excess potassium was decomposed by the addition of 8 cc. of ethanol, followed by 20 cc. of distilled water. The mixture was separated and the benzene–xylene solution was extracted with four 5-cc. portions of water. To the combined aqueous extracts was added 30 cc. of concentrated hydrochloric acid, and the solution was heated under reflux for two and one-half hours on the steam-bath. After the hydrochloric acid had been removed by distillation *in vacuo*, the dark reddish residue was taken up in 20 cc. of water, basified with saturated sodium hydroxide solution, and extracted five times with ether. The ethereal solution was dried, the ether removed, and the residue distilled under reduced pressure. The optically inactive 1-methyl-7-ketopyrrolizidine was obtained as a colorless mobile liquid which rapidly darkened; b. p. 96.5–98° (18 mm.), 79–80° (8 mm.); $n^{20}D$ 1.4770; yield, 1.9 g. (59%).

Anal. Calcd. for $C_8H_{13}NO$: C, 69.03; H, 9.41. Found: C, 68.91; H, 9.33.

Picrate.—Prepared in anhydrous ether and recrystallized from absolute ethanol, the picrate formed yellow, feathery elongated prisms which melted, with decomposition, at 189–190° (cor.).

Anal. Calcd. for $C_{14}H_{16}N_4O_8$: C, 45.65; H, 4.37. Found: C, 45.73; H, 4.49.

Methiodide.—Prepared in and recrystallized from dry benzene the methiodide formed colorless prisms, m. p. 149.5–150.5° (cor.).

Anal. Calcd. for $C_9H_{16}INO$: C, 38.46; H, 5.73. Found: C, 38.33; H, 5.94.

***l*-Menthydrazone.**—A solution of 1.9 g. of optically inactive 1-methyl-7-ketopyrrolizidine and 2.25 g. of *l*-menthydrazide[18] in the minimum amount of absolute ethanol (containing 2 g. of fused sodium acetate and 1 g. of glacial acetic acid per 100 cc. of absolute ethanol) was heated under reflux on the steam-bath for twenty-five hours, protected from moisture. After standing at room temperature, crystals separated. These were collected on a filter, washed with a little absolute ethanol, and recrystallized from ligroin (b. p. 90–110°). After the first recrystallization, 160 mg. of colorless elongated prisms was obtained; these melted at 169.5–171° (cor.) and the melting point was unchanged after three more recrystallizations from ligroin.

Anal. Calcd. for $C_{19}H_{33}N_3O_2$: C, 68.02; H, 9.92; N, 12.53. Found: C, 68.09; H, 9.79; N, 12.64.

Rotation. 0.0658 g. made up to 5 cc. with absolute ethanol at 27° gave αD −0.52°; *l*, 1; $[\alpha]^{27}D$ −39.5° (±0.5°).

After the above crystals had been removed by filtration, the ethanolic filtrate was heated and diluted with water. When the solution was allowed to cool slowly, 2.7 g. of crystals was obtained and submitted to a systematic six-stage fractionation from ligroin. The melting points of all of the fractions remained nearly identical and the specific rotations of widely separated fractions also were identical within the precision of measurement. Chromatographic adsorption of a dilute ligroin solution of the *l*-menthydrazone on activated alumina brought about no recognizable separation of the diastereoisomers. In order to check the assumption that no resolution was being accomplished through this derivative, the most insoluble fraction of *l*-menthydrazone obtained at the sixth fractional recrystallization stage was converted to the oxime.

Oxime.—Approximately 0.6 g. of the most insoluble portion of *l*-menthydrazone was refluxed for one hour in 20 cc. of 2 *N* sulfuric acid. The solution was cooled, extracted with ether and the ether extract discarded. The aqueous solution was made strongly basic with sodium hydroxide and extracted again with ether. The combined ether extracts of the alkaline solution were dried over anhydrous magnesium sulfate and evaporated to small volume. Addition of excess picric acid in dry ether resulted in the precipitation of yellow crystals. This picrate, after one recrystallization from absolute ethanol, melted at 189–190° (cor.) and gave no depression of melting point when mixed with the picrate of optically inactive 1-methyl-7-ketopyrrolizidine. The picrate was decomposed in hydrochloric acid solution, and the picric acid was removed by extraction with ether. The aqueous solution was evaporated to dryness *in vacuo*. The residue was redissolved in 3 cc. of water and treated with 3 cc. of 5 *N* sodium hydroxide and 0.25 g. of hydroxylamine hydrochloride. The oxime was formed and isolated in the same manner as described for the oxime of retronecanone.[3] Recrystallization from chloroform–petroleum ether (b. p. 40–60°) gave colorless prisms, m. p. 128–130° (cor.). The compound showed no optical activity.

Anal. Calcd. for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.54; H, 9.16; N, 18.26.

Optically Active 1-Methyl-7-ketopyrrolizidine.—Cyclization of levorotatory ethyl β-N-(3-methyl-2-carbethoxypyrrolidyl)-propionate was carried out under the same conditions employed in the formation of the optically inactive 1-methyl-7-ketopyrrolizidine (XVI). A suspension of 0.6 g. of finely powdered potassium in 6 cc. of dry xylene and 3 cc. of dry benzene was treated with a solution of 1.3 g. of the levorotatory diester and 6 cc. of benzene added dropwise during one-half hour. The aminoketone was obtained as 0.4 g. of light amber-colored oil which was not distilled but was converted directly to the oxime in the usual manner, by treating with 0.6 g. of hydroxylamine hydrochloride in 6 cc. of 2.5 *N* sodium hydroxide. The **oxime** was purified by recrystallization from chloroform–petroleum ether (b. p. 40–60°), from which it separated as colorless elongated prisms, m. p. 166–167° (cor.).

Anal. Calcd. for $C_8H_{14}N_2O$: C, 62.31; H, 9.15; N, 18.17. Found: C, 62.44; H, 9.06; N, 18.08.

Rotation. 0.0659 g. made up to 5 cc. with absolute ethanol at 32° gave αD −1.02°; *l*, 1; $[\alpha]^{32}D$ −77.3° (±1.5°).

The melting point was not depressed when the oxime was mixed with varying proportions of authentic retronecanone oxime (reported m. p. 167–168° (cor.)). The crystalline form of the synthetic oxime was identical with that of retronecanone oxime as observed under the microscope. Furthermore, the specific rotation of this synthetic oxime was identical, within the precision of measurement, with that recorded for retronecanone oxime ($[\alpha]^{24}D$ −76.0° ±2.5°).

Picrate of Optically Active 1-Methyl-7-ketopyrolizidine Oxime.—Prepared in anhydrous ether, from the oxime of optically active 1-methyl-7-ketopyrrolizidine and dry picric acid, and recrystallized from absolute ethanol, the picrate formed yellow elongated prisms which melted, with decomposition, at 188–190° (cor.).

Anal. Calcd. for $C_{14}H_{17}N_5O_8$: C, 43.86; H, 4.47; N, 18.27. Found: C, 43.97; H, 4.66; N, 18.23.

(18) Woodward, Kohman and Harris, THIS JOURNAL, 63, 120 (1941).

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The melting–decomposition point was not depressed when the synthetic picrate was mixed with the picrate of retronecanone oxime.

Picrolonate of Optically Active 1-Methyl-7-ketopyrrolizidine Oxime.—Prepared in absolute ethanol and recrystallized from ethanol–benzene solution, the picrolonate formed clusters of yellow elongated prisms which melted, with decomposition, at 209–211° (cor.).

Anal. Calcd. for $C_{18}H_{22}N_6O_6$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.83; H, 5.48; N, 20.02.

The melting–decomposition point was not depressed when the picrolonate was mixed with the picrolonate of retronecanone oxime.

Retronecanone Picrolonate.—Prepared in and recrystallized from absolute ethanol, the picrolonate formed yellow elongated prisms which melted, with decomposition and foaming, at 195–196° (cor.).

Retronecanone Methiodide.—Formed by warming retronecanone with excess methyl iodide in benzene solution and recrystallized from absolute ethanol, the methiodide formed colorless elongated prisms, m. p. 160–161° (cor.).

Retronecanone *l*-Menthydrazone.—An absolute ethanol solution of 0.8 g. of retronecanone and 0.95 g. of *l*-menthydrazide was heated on the steam-bath for twenty-four hours under reflux. When the reaction mixture was cooled and diluted with water, 0.8 g. of fine elongated prisms separated in a closely adhering mass. After seven recrystallizations from ligroin (b. p. 90–110°) the product melted at 175.5–176.5° (cor.).

Anal. Calcd. for $C_{19}H_{33}N_3O_2$: C, 68.02; H, 9.92; N, 12.53. Found: C, 68.20; H, 9.95; N, 12.65.

Rotation. 0.0655 g. made up to 5 cc. with absolute ethanol at 28° gave α_D −1.09°; *l*, 1; $[\alpha]^{28}D$ −83.2° (±0.5°); $[M]^{28}D$ −279°.

Hydrolysis of Retronecanone *l*-Menthydrazone.—A representative sample was boiled with 20 cc. of 1 *N* sulfuric acid for one hour. The solution was cooled and extracted with ether, which removed most of the coloration. After the aqueous solution had been made strongly basic, it was thoroughly extracted with ether, the combined ether extracts dried, and the ether solution concentrated to 10 cc. Picric acid in anhydrous ether was added until there was no further yellow precipitation. The solid picrate was collected on a filter and recrystallized from ethanol, from which it separated as fine elongated prisms, m. p. 195° (cor.), with decomposition. There was no depression of melting point when the sample was mixed with retronecanone picrate.

Picrate of Retronecanone Oxime.—Formed in anhydrous ether from picric acid and retronecanone oxime[3] and recrystallized from absolute ethanol, the picrate formed yellow elongated prisms which melted, with decomposition, at 188–190° (cor.).

Picrolonate of Retronecanone Oxime.—Prepared in absolute ethanol and recrystallized from ethanol–benzene, the picrolonate formed clusters of yellow elongated prisms which melted, with decomposition, at 209–211° (cor.).

Acetylretronecanol Methiodide.—This derivative of retronecanol was prepared according to the method of Barger, Seshadri, Watt and Yabuta,[12] but the stout colorless prisms from acetone were found to melt at 215–216° (cor.) instead of 207–208° as reported.

Rotation. 0.0709 g. made up to 5 cc. with absolute methanol at 28° gave α_D −1.24°; *l*, 1; $[\alpha]^{28}D$ −87.4° (±1.0°).

Reduction of Retronecanone

(a) Neutral Solution.—A solution of 366 mg. of retronecanone in 20 cc. of absolute ethanol was hydrogenated at normal pressure over 50 mg. of platinum oxide catalyst. The theoretical volume of hydrogen was absorbed in one hour. The reduction product was not obtained crystalline but the impure oil obtained exhibited a specific rotation in absolute ethanol of $[\alpha]^{33}D$ −9.5° (c = 1.266). This differs widely from that reported for retronecanol (−91.1°).[13]

The methiodide, obtained crystalline at first from acetone solution, was extremely hygroscopic (unlike retronecanol methiodide) and could not be recrystallized.

The picrate, formed in ether solution and recrystallized from absolute ethanol, separated as yellow elongated prisms which melted, with decomposition, at 218–219° (cor.). Retronecanol picrate melts, with decomposition, at 210° (cor.).[13]

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.41; H, 4.89. Found: C, 45.51; H, 4.96.

The reduction product of retronecanone was acetylated by heating under reflux on the steam-bath for four hours with excess acetyl chloride. The acetyl chloride was removed *in vacuo*, leaving a brown semicrystalline residue which was dissolved in 5 cc. of water. The aqueous solution was made alkaline with potassium carbonate and the acetylated base was extracted with ether. The ethereal solution was dried, decolorized and the ether removed. The residue did not crystallize, but the **methiodide** was obtained crystalline from benzene. After repeated fractional crystallization from acetone, the least-soluble fraction, obtained as colorless elongated prisms, possessed a maximum constant melting point of 210–212° (cor.). No other methiodide was obtained pure in the fractional crystallization process.

Anal. Calcd. for $C_{11}H_{20}INO_2$: C, 40.62; H, 6.20. Found: C, 40.79; H, 6.37.

Rotation. 0.0234 g. made up to 2.5 cc. with absolute methanol at 28° gave α_D +0.07°; *l*, 1; $[\alpha]^{28}D$ +7.5° (±1.5°).

The rotation differs widely from that of acetylretronecanol methiodide (−87.4°), and a melting point of a mixture of the two methiodides is depressed to 135–190°.

(b) Acid Solution.—Reduction of retronecanone over platinum oxide catalyst was carried out in 20 cc. of absolute ethanol containing 1 cc. of concentrated hydrochloric acid. The reduction was complete after nine hours. The reduced free base was liberated but was not obtained crystalline.

The methiodide, obtained crystalline at first from acetone solution, was hygroscopic and could not be recrystallized.

The picrate, formed in and recrystallized from absolute ethanol, separated as yellow platelets which melted, with decomposition, at 230–232° (cor.). The picrate differed from the picrate of the reduction product of retronecanone in neutral solution, and also from retronecanol picrate and oxyheliotridane picrate.[11]

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: N, 15.13. Found: N, 15.23. Carbon and hydrogen values are not reported since the analytical sample exploded.

Acetylation of the reduced product was carried out as before and **the picrate** of the acetylated reduction product was formed in anhydrous ether and recrystallized from absolute ethanol: yellow elongated prisms, m. p. 178.5–179.5° (cor.).

Anal. Calcd. for $C_{16}H_{20}N_4O_9$: C, 46.60; H, 4.89. Found: C, 46.64; H, 4.91.

The methiodide of the acetylated reduction product was formed in benzene and subjected to repeated fractional crystallization from acetone. The least-soluble methiodide fraction was finally obtained as colorless elongated prisms, m. p. 210.5–211.5° (cor.). This was identical with the methiodide of the acetylated reduction product of retronecanone in neutral solution and gave no melting point depression when mixed with it. Mixing with acetylretronecanol methiodide again produced a sharp depression of melting point. No other methiodide could be obtained pure in the fractional crystallization process.

Reduction of 1-Methyl-7-ketopyrrolizidine: 1-Methyl-7-hydroxypyrrolizidine.—Hydrogenation of 520 mg. of optically inactive 1-methyl-7-ketopyrrolizidine in 20 cc. of absolute ethanol was carried out at atmospheric pressure in the presence of 50 mg. of platinum oxide catalyst. The theoretical volume of hydrogen was taken up in one-half hour, after which the ethanol solution was filtered free of catalyst and used directly for the formation of derivatives.

Neither the picrate nor the methiodide was ob-

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tained pure because both were very hygroscopic. The picrate and picrolonate were obtained as well-characterized crystalline salts.

Picrate.—Prepared in and recrystallized from absolute ethanol, the picrate formed yellow elongated prisms which softened at 210° and melted, with decomposition, at 218.5–219.5° (cor.).

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.41; H, 4.89. Found: C, 45.57; H, 5.06.

Picrolonate.—Prepared in and recrystallized from absolute ethanol, the picrolonate formed yellow elongated prisms, m. p. 182.5–183.5° (cor.). It is interesting that the melting point of the racemic 1-methyl-7-hydroxypyrrolizidine picrolonate is almost the same as that of retronecanol picrolonate, m. p. 184–185°.[19] These picrolonates, of course, are not identical.

Anal. Calcd. for $C_{18}H_{23}N_5O_6$: C, 53.33; H, 5.72; N, 17.28. Found: C, 53.26; H, 5.71; N, 17.32.

Summary

1. 1-Methyl-7-ketopyrrolizidine has been synthesized through ethyl 3-methylpyrrolidine-2-carboxylate (obtained from γ-picoline) by addition to ethyl acrylate followed by a Dieckmann cyclization and hydrolysis. The final product probably was a mixture of two racemates. By condensation with *l*-menthydrazide a single pure 1 - methyl - 7 - ketopyrrolizidine - *l* - menthydrazone was isolated. This was different from the *l*-menthydrazone of retronecanone in melting point and rotation.

2. Optically active ethyl 3-methylpyrrolidine-2-carboxylate was converted to the corresponding optically active 1-methyl-7-ketopyrrolizidine by a similar series of reactions. By treatment of the reaction mixture with hydroxylamine, a pure optically-active 1 - methyl - 7 - ketopyrrolizidine oxime resulted, which was identical with retronecanone oxime in melting point and rotation. The identity was verified further by the preparation of identical picrates and picrolonates.

3. It has been proved that the keto group in retronecanone is in the 7-position. From this it may be deduced that the secondary hydroxyl group in retronecanol, retronecine, platynecine, desoxyretronecine, heliotridine, and oxyheliotridane is in the 7-position.

4. It has been shown that in the reduction of desoxyretronecine, retronecine, and esters of retronecine to give retronecanol, asymmetric reduction has taken plaec with the exclusive formation of one stereochemical configuration of the C_1-CH_3.

5. Reduction of retronecanone in neutral and acid solutions gave a mixture of corresponding hydroxy compounds, from which retronecanol could not be isolated.

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(19) Konovalova and Orekhov, *Bull. soc. chim.*, [5] **4**, 1285 (1937).

[CONTRIBUTION FROM THE BURROUGHS WELLCOME & CO. U. S. A. EXPERIMENTAL RESEARCH LABORATORIES]

The Preparation of N-Mono-substituted and Unsymmetrically Disubstituted Piperazines

BY RICHARD BALTZLY, JOHANNES S. BUCK, EMIL LORZ AND WILLIAM SCHÖN

The direct alkylation of piperazine produces a mixture of substitution products from which the isolation of mono-substituted compounds is difficult or impossible when the substituting group is relatively small. Because of this the belief has arisen that mono-substitution products are not formed, although examination of reported experiments shows only that they were not isolated. A similar situation has prevailed in regard to acylation, although even mono-acetylpiperazine can be obtained easily by logical manipulation.

In Table I are shown the yields of mono- and di-substituted piperazines from a number of reactions, together with the reaction conditions. It seems indicated that in the ideal case where the entire reaction takes place in one homogeneous phase, equimolecular proportions of reactants result in the 1:2:1 proportions of piperazine, mono-substituted piperazine and di-substitution product predicted on general considerations.

Major deviations from these proportions would be expected if a salt of piperazine itself (such as the dihydrochloride which is sparingly soluble in absolute ethanol) were to precipitate during the reaction, or if the acylating or alkylating agent were to form a second liquid phase, thus tending to extract preferentially mono-substituted piperazine already present.

The yields here recorded compare favorably with those claimed for more involved procedures.[1] The argument by which Moore[1a] was led to operate at low *p*H is probably valid. The second benzylation recorded in Table I, run at *p*H about 3.5 gave a proportion of mono-benzyl to dibenzyl piperazine of about 5–1. Similarly a proportion of 2.7–1 was observed in the carbethoxylation, where a low *p*H must have existed toward the end of the reaction. As a preparative method with moderately priced chemicals, however, the buffering procedures seem unprofitable.

From the mono-substituted piperazines that were thus rendered available a number of unsymmetrically disubstituted derivatives have been prepared. These are characterized in Table II.

(1) (a) Moore, Boyle and Thorn, *J. Chem. Soc.*, 39 (1929); (b) Jacobi, *Ber.*, **66**, 113 (1933). The methods described in these papers are two-phase acylations at low *p*H. The conditions are difficult to reproduce exactly and it is doubtful if yields significantly above 50% should be expected from them.

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TABLE I

PRODUCTS OF REACTION OF PIPERAZINE WITH VARIOUS REAGENTS

Reagent	Moles of reagent	Moles of piperazine	Solvent	Reaction time, hr.	Reaction temp., °C.	Mono-substituted piperazine: Moles obt.	B. p., °C.	Pressure, mm. Hg	Moles of disubstituted piperazine obt.
$C_6H_5CH_2Cl$	0.5	0.5[a]	300 cc. abs. EtOH	20	25–30	0.15–0.16	154–160	18	0.1[a]
							145–147	12	
$C_6H_5CH_2Cl$	.5	.5[b,c]	500 cc. 50% MeOH	80	65	.26	127–130	2	.05
p-$ClC_6H_4CH_2Cl$	.5	.5[a]	300 cc. abs. EtOH	20	25–30	.20	140–142	2.5	.1
p-$MeOC_6H_4CH_2Cl$	.5[d]	.5[a]	250 cc. abs. EtOH	20	25–30	.14	150	2.5	..[e]
$C_6H_5CH_2CH_2Br$	.5	.5[a]	300 cc. abs. EtOH	40	80	.09	150–152	8	..[e]
n-$C_{12}H_{25}Br$	.12	.17[b]	170 cc. 90% EtOH	20	80	.05	140	1/4	.017
$CH_2—CH_2$ \ O /	.33	.5[a]	500 cc. abs. EtOH	72	25	.17	122–123	10	.06
$CH_2—CH_2$ \ O /	.30	.60[b]	300 cc. abs. EtOH	72	25	.16	122–123	10	..[e]
ClCOOEt	.5	.5[b]	350 cc. 85% EtOH	1[f]	40–50	.27	.....	..	.1[g]
$(CH_3CO)_2O$	.5	.5[b]	300 cc. HAc	1[f]	50	.2	.....	..	..[e]

[a] Piperazine hexahydrate used. [b] Anhydrous piperazine used. [c] This run was made at about the *p*H specified by Moore.[1a] [d] 0.5 mole of anisyl alcohol was treated with gaseous HCl and the crude but dry and neutral product used directly. [e] Disubstituted product not isolated. [f] At end of hour soln. was allowed to cool and stand overnight. [g] 15% of original piperazine recovered.

Since, further, the benzyl group can be removed by catalytic hydrogenation,[2] preferably with palladium, a variety of mono-substituted piperazines that would be difficult to separate from a reaction mixture can be obtained pure. The lower alkyl piperazines can also be prepared by alkylating N-piperazine ethyl carboxylate, but this intermediate is unsuitable with more labile systems for which the debenzylation procedure appears preferable.

Experimental

Benzylations.—Data on the preparations are given in Table I. On completion of the reaction, the solution was evaporated *in vacuo*, and the residue partitioned between ether and sodium hydroxide solution. After drying over potassium hydroxide or potassium carbonate the ethereal extract was evaporated and the residual oil distilled *in vacuo*.

In the preparations with *p*-chlorobenzyl and anisyl chlorides and in one run with benzyl chloride considerable solid separated toward the end of the reaction. These solids were filtered off and recrystallized from alcohol; the mother liquors added to the filtrate, and the whole worked up as indicated above. The recrystallized solids were the fairly pure dihydrochlorides of the respective disubstituted piperazines. In these cases very little disubstituted compound was found in the distillation.

In some cases a small amount of piperazine was present in the first fraction of the mono-benzyl derivative. This could be removed by washing in ether solution with water or dilute alkali.

In view of the considerable reaction of benzyl chlorides with water and alcohols, it is likely that the yields could be improved by additon of excess benzyl chloride, possibly with sodium acetate for buffering.

In the reactions of piperazine with lauryl and phenethyl bromides heating was required. The poor yield of phenethylpiperazine was presumably due to loss of hydrogen bromide. The corresponding di-substituted piperazines were very high-boiling and the *bis*-phenethylpiperazine decomposed at the pressure used instead of distilling.

Reaction with Ethylene Oxide.—The only significant differences from the procedure of Kitchen and Pollard[3] were in the proportions of reactants (see Table I) and the reaction temperature.

Carbethoxylation.—One-half mole (43 g.) of anhydrous piperazine was dissolved in 300 cc. of 95% ethanol. To this was added, with mechanical stirring, 54 g. (0.5 mole) of ethyl chlorocarbonate. The solution warmed itself fairly rapidly (thirteen minutes) to 50° whereupon water cooling was used to keep the temperature below 50°. At this point solid began to separate and 50 cc. of water was added to restore it to solution. The addition of the ethyl chlorocarbonate required about thirty minutes. Shortly thereafter solid was again observed and two types of crystal were apparent. The solution was allowed to stand overnight. The solid was filtered off and washed with 10 cc. of absolute ethanol. The undissolved crystals were piperazine dihydrochloride.

The filtrate, which was acid to congo red, was evaporated *in vacuo*. The residue was dissolved in water and extracted twice with ether. The ethereal extract, on evaporation, yielded 24 g. of N,N'-piperazine *bis*-ethylcarboxylate, a gum that crystallized from hexane and then melted at 49°. The aqueous layer was again taken down *in vacuo* and extracted with a minimum of absolute alcohol, a small residue of piperazine dihydrochloride being again separated. The yellow solution on addition of ethyl acetate and ether, and cooling deposited flesh-colored crystals of piperazine N-ethylcarboxylate hydrochloride. Recrystallization from absolute alcohol with charcoaling gave a colorless product melting at 145°.

Acetylation.—One-half mole (43 g.) of anhydrous piperazine was dissolved in 300 cc. of glacial acetic acid. To this was added with stirring 51 g. (0.5 mole) of acetic anhydride. The addition took fifteen minutes during which the temperature rose from 48 to 54°. Stirring was continued for one-half hour and the solution was allowed to stand overnight. Fifty cc. of concentrated hydrochloric acid was then added and the solution was evaporated *in vacuo*. The residue, a thick, red-brown sirup was extracted with 300 cc. of hot benzene to remove the diacetylpiperazine. The benzene-insoluble material was treated with absolute ethanol and the resulting solution filtered off from piperazine dihydrochloride. On addition of ether and standing in the refrigerator the acetylpiperazine hydrochloride crystallized. The crude product weighed 33 g. and melted at 150°. After three recrystallizations from alcohol–ether mixture the melting point was 183°.[1b]

From the intermediates whose preparation is described above a variety of unsymmetrical piperazines has been

(2) *Cf.* among others Buck and Baltzly, THIS JOURNAL, 63, 1964 (1941).

(3) Kitchen and Pollard, *J. Org. Chem.*, 8, 338 (1943).

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TABLE II

No.	R	R′	Appearance,[a] crystallizing solvent[b]	M. p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
			Mono-alkylpiperazine dihydrochlorides $RN\langle CH_2—CH_2 \rangle NH\cdot 2HCl$						
I	$C_6H_5CH_2$—	.....	Flat needles, A	253	$C_{11}H_{18}N_2Cl_2$	53.00	7.28	53.14	7.54
II	*p*-$MeOC_6H_4CH_2$—	.....	A	263 dec.	$C_{12}H_{20}ON_2Cl_2$	51.61	7.23	51.49	7.55
III	*p*-$ClC_6H_4CH_2$—	.....	Flat needles, A	296 dec.	$C_{11}H_{17}N_2Cl_3$	46.55	6.04	46.46	6.23
IV	$C_6H_5CH_2CH_2$—	.....	A	252	$C_{12}H_{20}N_2Cl_2$	54.75	7.66	54.83	7.90
V	*n*-$C_{12}H_{25}$—	.....	Slender needles, AA-E	Dec. >220	$C_{16}H_{36}N_2Cl_2$	58.69	11.09	58.96	10.97
VI	$HOCH_2CH_2$—	.....	A	189.5	$C_6H_{16}ON_2Cl_2$	35.48	7.94	35.37	7.87
VII	CH_3—	.....	Aq-M	110 (hydrate)	$C_5H_{14}N_2Cl_2$	34.69	8.16	34.62	8.58
VIII	C_2H_5—	.....	AA	203–205	$C_6H_{16}N_2Cl_2$	38.48	8.62	38.27	8.70
			Mono-alkylpiperazine amide hydrochlorides $RN\langle CH_2—CH_2 \rangle NCOR'\cdot HCl$						
IX	$C_6H_5CH_2$—	C_6H_5—	Prisms, A	245	$C_{18}H_{21}ON_2Cl$	68.27	6.69	68.24	6.79
X	$C_6H_5CH_2CH_2$—	C_6H_5—	Leaflets, A	246	$C_{19}H_{23}ON_2Cl$	68.96	7.01	69.19	6.81
XI	*p*-$ClC_6H_4CH_2$—	C_6H_5—	Leaflets, A	265	$C_{18}H_{20}ON_2Cl_2$	61.52	5.74	61.79	5.96
XII	*p*-$MeOC_6H_4CH_2$—	C_6H_5—	A-E	234	$C_{19}H_{23}O_2N_2Cl$	65.78	6.69	65.92	7.08
XIII	*p*-$MeOC_6H_4CH_2$—	$C_6H_5CH_2$—	Silky leaflets, A-E	225	$C_{20}H_{25}O_2N_2Cl$	66.56	6.98	66.64	6.95
XIV	*p*-$ClC_6H_4CH_2$—	$C_6H_5CH_2$—	A	241	$C_{19}H_{22}ON_2Cl_2$	62.47	6.08	62.63	6.38
			Dialkylpiperazine dihydrochlorides $RN\langle CH_2—CH_2 \rangle NR'\cdot 2HCl$						
XV	$C_6H_5CH_2$—	Me—	M	250 dec.	$C_{12}H_{20}N_2Cl_2$	54.73	7.66	54.70	7.81
XVI	$C_6H_5CH_2$—	Et—	AA	250 dec.	$C_{13}H_{22}N_2Cl_2$	56.29	8.00	56.03	7.93
XVII	$C_6H_5CH_2$—	*n*-$C_{12}H_{25}$—	Waxy solid, AA	Dec. >250	$C_{25}H_{42}N_2Cl_2$	66.16	10.13	66.23	10.09
XVIII	Dimethiodide of XVII		AA	225 dec.	$C_{25}H_{46}N_2I_2$	47.76	7.38	47.97	7.48
XIX	$C_6H_5CH_2$—	—CH_2CH_2OH	Platelets, A-Æ	225	$C_{13}H_{22}ON_2Cl_2$	53.23	7.60	53.18	7.81
XX	*n*-$C_{12}H_{25}$—	*n*-$C_{12}H_{25}$—	A	....	$C_{28}H_{60}N_2Cl_2$	67.82	12.21	67.64	12.33
XXI	$C_6H_5CH_2$—	3,4-$(MeO)_2$-$C_6H_3CO\cdot CH_2$—	Glittering leaves, A	Dec. 250–270	$C_{21}H_{28}O_3N_2Cl_2$	59.00	6.61	59.08	6.85
XXII	$C_6H_5CH_2$—	3,4-$(OH)_2$-$C_6H_3CO\cdot CH_2$—	A	Dec. 255	$C_{19}H_{24}O_3N_2Cl_2$	57.13	6.06	57.30	6.07
XXIII	*p*-$ClC_6H_4CH_2$—	3,4-$(OH)_2$-$C_6H_3COC\cdot H_2$—	A	Dec. >200	$C_{19}H_{23}O_3N_2Cl_3$	52.59	5.35	52.54	5.71
XXIV	*p*-$MeOC_6H_4CH_2$—	3,4-$(HO)_2$-$C_6H_3COCH_2$—	A-Æ	230–231	$C_{20}H_{25}O_4N_2Cl_2$	61.12	6.42	61.41	6.64
XXV	$C_6H_5CH_2$—	3,4-$(HO)_2$-$C_6H_3CHOH\cdot CH_2$—	A-E	Dec. >210	$C_{19}H_{26}O_3N_2Cl_2$	56.84	6.54	56.97	6.86
XXVI	*p*-$MeOC_6H_4CH_2$—	3,4-$(HO)_2$-$C_6H_3CHOH\cdot CH_2$—	AA-Æ	175	$C_{20}H_{28}O_4N_2Cl_2$	55.67	6.55	55.45	6.65
			N-Alkyl-N′-benzoyloxyethylpiperazine dihydrochlorides $RN\langle CH_2—CH_2 \rangle NCH_2CH_2OCO\langle C_6H_4 \rangle R'\cdot 2HCl$						
XXVII	H	H	Aq-Ac	208–210	$C_{12}H_{20}O_2N_2Cl_2$	50.80	6.56	50.54	6.76
XXVIII	Et	H	Needles, AA	245 dec.	$C_{15}H_{24}O_2N_2Cl_2$	53.73	7.22	53.86	7.48
XXIX	$C_6H_5CH_2$—	H	Platelets, AA	245	$C_{20}H_{26}O_2N_2Cl_2$	60.44	6.60	60.59	6.57
XXX	$C_6H_5CH_2$—	Cl	Needles, AA	242	$C_{20}H_{25}O_2N_2Cl_3$	55.60	5.84	55.78	6.08
XXXI	$C_6H_5CH_2$—	NO_2	Meshed needles, Aq-Ac-HCl	236–237	$C_{20}H_{25}O_4N_3Cl_2$	54.29	5.71	54.19	6.00
XXXII	$C_6H_5CH_2$—	$NH_2\cdot HCl$	Buff crystals, Aq-M-Æ	258–260 dec.	$C_{20}H_{28}O_2N_3Cl_3$	53.49	6.29	53.50	6.39
XXXIII	$C_6H_5CH_2$—	—$NHCOCH_3$	Plates, A-E	229 dec.	$C_{22}H_{29}O_3N_3Cl_2$	58.12	6.44	58.60	6.77
			Mono-alkylpiperazine urea hydrochlorides $RN\langle CH_2—CH_2 \rangle NCONHR'\cdot HCl$						
XXXIV	$C_6H_5CH_2$—	H	Leaflets, A	238.5–239	$C_{12}H_{18}ON_3Cl$	56.35	7.10	56.46	7.03
XXXV	*p*-$ClC_6H_4CH_2$—	H	Leaflets, A	264	$C_{12}H_{17}ON_3Cl_2$	49.65	5.91	49.59	5.86
XXXVI	*p*-$ClC_6H_4CH_2$—	C_6H_5—	Leaflets, A	258 dec.	$C_{18}H_{21}ON_3Cl_2$	59.00	5.78	59.05	5.90
XXXVII	$HO\cdot CH_2CH_2$—	H	AA-E	177	$C_7H_{16}O_2N_2Cl$	40.10	7.69	40.10	7.35
XXXVIII	$C_6H_5COOCH_2CH_2$—	H	AA-E	205 dec.	$C_{14}H_{23}O_4N_3Cl$	53.59	6.42	53.87	6.63

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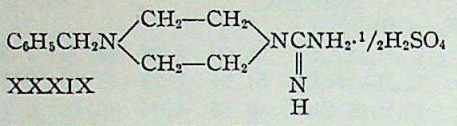
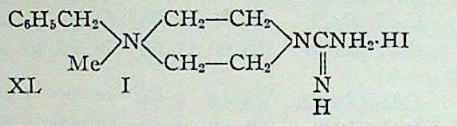
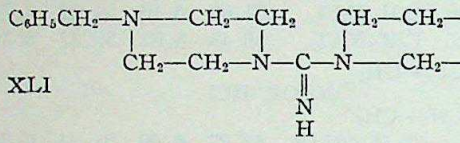
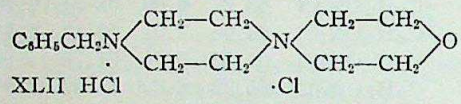
TABLE II (*Concluded*)

No.	Compounds	Appearance,[a] crystallizing solvent[b]	M. p., °C.	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
	Miscellaneous piperazine derivatives							
XXXIX		Glossy plates, A-Ac	220 dec.	$C_{12}H_{19}N_4O_2S_{1/2}$	53.91	7.17	54.15	7.38
XL		Hexagonal plates, M	219–220 dec.	$C_{13}H_{22}N_4I_2$	(N)	11.48	(N)	11.60
XLI		AA-E	229	$C_{23}H_{32}N_5Br$	60.24	7.02	60.00	7.11
XLII		A-E	Solid to 280	$C_{15}H_{24}ON_2Cl_2$	56.41	7.58	56.59	7.78

[a] Appearance is given only when form is macroscopically characteristic. [b] A = 95% EtOH, AA = absolute EtOH, M = MeOH, E = Et_2O, Æ = ethyl acetate, Ac = acetone, Aq = H_2O.

prepared. Pertinent data on these substances are given in Table II. Most are characterized as hydrochlorides.

Aralkylpiperazine Amides.—The benzoates of benzyl, *p*-chlorobenzyl, anisyl and phenethyl piperazines (IX–XII) were prepared by the Schotten–Baumann method. The phenylacetyl derivatives (XIII, XIV) of anisyl and *p*-chlorobenzyl piperazines were obtained by the action of phenylacetyl chloride in boiling benzene on the appropriate bases.

Di-alkylpiperazines.—Benzylpiperazine was reacted in alcoholic solution with methyl and ethyl iodides and with lauryl bromide. The latter required heating to complete the reaction. The methylated and ethylated bases (XV and XVI) were obtained by distillation of the liberated and benzoylated bases from the reaction. Benzyl laurylpiperazine was crystallized as the hydrochloride (XVII). Methylbenzylpiperazine is better prepared from benzylpiperazine by the Clarke–Eschweiler method.[4] Unlike dibenzylpiperazine, benzyl laurylpiperazine forms a dimethiodide (XVIII) without much difficulty. Presumably this is because the monomethiodide (on the lauryl end?) is relatively soluble and is not withdrawn from reaction whereas dibenzylpiperazine forms a rather insoluble monomethiodide that precipitates from solution and reacts further only on prolonged treatment.

Benzyl β-hydroxyethylpiperazine (XIX) resulted from the action of ethylene oxide on benzylpiperazine.

The substituted benzylphenacylpiperazines (XXI–XXIV) were produced by the reaction of the appropriate monosubstituted piperazines with chloroacetocatechol and bromo-acetoveratrone in ethyl acetate solution. Reduction of XXII and XXIV with platinum oxide platinum black at room temperature gave the amino-alcohols, XXV and XXVI.

Catalytic reduction of methylbenzylpiperazine and ethylbenzylpiperazine hydrochlorides with palladized charcoal removed the benzyl group forming methyl and ethyl piperazine dihydrochlorides (VII and VIII).

Similarly, hydrogenation of N-benzyl-N′-benzoyloxyethylpiperazine dihydrochloride (XXIX) (made by benzoylation of XIX) gave benzoyloxyethylpiperazine, XXVII.

Ethylation of β-hydroxyethylpiperazine with ethyl iodide followed by benzoylation of the total bases by the Schotten–Baumann method yielded ethylbenzoyloxyethylpiperazine (XXVIII).

Benzylhydroxyethylpiperazine (XIX) reacted with *p*-chloro and *p*-nitrobenzoyl chlorides in ether or benzene solution to give XXX and XXXI. Reduction of the latter gave the corresponding *p*-amino compound, XXXII which was acetylated to form the acetamido derivative, XXXIII.

Urea Derivatives.—Phenyl isocyanate and *p*-chlorobenzylpiperazine formed the urea, XXXVI. The other ureas recorded in Table II were prepared by the reaction of nitrourea on the appropriate mono-substituted piperazines.

Guanidines and Quaternary Salts.—Benzylpiperazine and S-methylisothiourea sulfate in 65% alcohol yielded the guanidine sulfate, XXXIX. The corresponding hydroiodide, m. p. 155–155.5°, was formed from benzylpiperazine and S-methylisothiourea hydroiodide in absolute alcohol and reacted with methyl iodide in methanol to form the guanidine quaternary salt, XL.

The symmetrical guanidine, XLI, resulted when 2 mols of benzylpiperazine and 1 mol of cyanogen bromide were mixed cautiously in absolute ether solution, the ether blown off and the residual mixture heated at 150–160° (oil-bath) for two and one-half hours.

The spiro-quaternary salt, XLII, was prepared by heating benzyl piperazine with β,β′-dichloro-ethyl ether.

The melting points below 250° given in Table II are corrected.

The authors wish to express their gratitude to Mr. W. S. Ide for the many micro-analyses performed in this study.

Summary

1. When piperazine reacts with acylating and alkylating agents satisfactory yields of monosubstitution product can be isolated provided the substituting group is of moderate size.

2. By catalytic debenzylation of suitable derivatives of monobenzylpiperazine a further variety of mono-substituted piperazines can be prepared.

3. A number of mono-substituted and unsymmetrically disubstituted piperazines have been prepared and characterized.

(4) Clarke, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

TUCKAHOE, NEW YORK RECEIVED AUGUST 4, 1943

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[CONTRIBUTION FROM THE UNIVERSITY OF TEXAS, BIOCHEMICAL INSTITUTE, AND THE CLAYTON FOUNDATION FOR RESEARCH]

Folic Acid. I. Concentration from Spinach[1a]

BY HERSCHEL K. MITCHELL, ESMOND E. SNELL AND ROGER J. WILLIAMS

In a preliminary note[1] it was announced that we had concentrated a nutrilite from spinach that had a high degree of activity in stimulating the growth of certain strains of bacteria. Because of its unusual abundance in numerous leaves, we suggested the name "folic acid" for the substance and defined it as the material responsible for growth stimulation of *Streptococcus lactis R* on a given medium.[2]

For purposes of convenience in concentration a sample of Wilson liver fraction "B" was established as a standard of "potency = 1." For comparison of folic acid assay values with those of other vitamins, results have been expressed in terms of micrograms of material of "potency 40,000" per gram of tissue.[3] Fraction "B" is required in concentrations 40,000 times as great as such material in order to produce the same amount of growth stimulation. One milligram of such a concentrate has been designated by Williams[4] to contain "one milligram unit," and this unit has been used throughout this paper.

Experimental

The following typical example best demonstrates the application of the concentration procedure.

Preparation of Extract.—One thousand pounds of raw spinach was ground in a hammer mill and transferred to a jacketed pot with sufficient water to bring the volume to about 350 gallons. The suspension was stirred vigorously and the temperature raised to 30–35°. After thirty-six hours standing the mixture was heated at the boiling temperature for fifteen minutes and the pulp strained out by allowing the solution to drain overnight through muslin bags. The resulting solution was adjusted to *p*H 3.0 to 3.2 with sulfuric acid, followed by addition of 4 gallons of super-cel filter aid. The solution was heated and held at the boiling temperature for about five minutes followed by rapid cooling with cold water in the jacket of the pot. The suspension was filtered in a plate and frame press coated with filter aid to obtain a brilliantly clear filtrate. This material contained 2,700 mg. units; potency of solids = 2.5.

Adsorption on Charcoal 1.—Twelve pounds of charcoal (Darco S-51) was added and the suspension stirred for thirty minutes. Following the addition of 2 gallons of super-cel the suspension was filtered and washed and the filtrate discarded.

Elution from Charcoal 1.—The charcoal containing the adsorbed activity was added to a boiling solution of one gallon of 28% ammonia in 10 gallons of distilled water. The suspension was maintained at boiling temperature for fifteen minutes and filtered while hot. The elution was repeated and the combined filtrates cooled rapidly to 25°. The charcoal was discarded; yield, 1,700 mg. units; potency of solids = 60.

Adsorption on Charcoal 2.—Three pounds of pretreated charcoal[4a] was added to the cooled ammonia solution and the suspension stirred twenty minutes. After addition of 1 gallon of super-cel the suspension was filtered and washed, discarding the filtrate.

Elution from Charcoal 2.—The charcoal with the adsorbed activity was added to a boiling mixture of 500 g. of aniline in 6 liters of water and the boiling continued for fifteen minutes. The suspension was filtered hot and the elution repeated. The charcoal was discarded. After cooling the solution was extracted twice with 20% of its volume of ether and then adjusted to *p*H 3.0 to 3.2 with sulfuric acid. A slight precipitate was removed by filtration with filter aid; yield, 1,400 mg. units; potency = 200.

Adsorption of Charcoal 3.—The solution was stirred twenty minutes with 180 g. of pretreated charcoal which was then filtered off and washed.

Elution from Charcoal 3.—The charcoal containing the activity was added to a boiling solution of 75 g. of aniline in 1 liter of water and the boiling continued for fifteen minutes. The elution was repeated and the combined eluates cooled and extracted twice with ether to remove the aniline; yield, 1,270 mg. units; potency = 800.

Lead Precipitation.—A solution of 37 g. of lead acetate trihydrate in 100 ml. of water was added to the aqueous solution from eluate 3 with vigorous stirring. The resulting precipitate was collected and washed by centrifugation. The activity was regenerated by suspension of the precipitate in 3 liters of water containing 150 g. of ammonium sulfate. The solution was boiled twenty minutes, cooled and filtered, and the filtrate retained; yield, 850 mg. units.

Silver Precipitation.—The filtrate from the lead regeneration step was diluted to 6 liters and a solution of 35 g. of silver nitrate in 100 ml. of water was added. The *p*H was adjusted to 6.5 with ammonium hydroxide with vigorous stirring of the suspension. The precipitate was collected and washed by centrifugation. The folic acid was regenerated from the silver precipitate by five minutes boiling with a solution of 25 g. of ammonium chloride in 150 ml. of water. After cooling the suspension was acidified to *p*H 6 with hydrochloric acid followed by filtration and washing. The precipitate was discarded; yield, 600 mg. units.

Adsorption on Lloyd Reagent.—The solution from the silver regeneration which contained a high concentration of salts was cooled below 10° and acidified to *p*H 1.0 with hydrochloric acid. The cold solution was shaken a few minutes with 15 g. of Lloyd reagent. The suspension was filtered and washed and the filtrate discarded.

Elution from Lloyd Reagent.—The Lloyd reagent was shaken with 50-ml. portions of 5% ammonium hydroxide three times. The volume of this combined eluate (150 ml.) was conveniently reduced to a few ml. by addition of 5 volumes of ether and sufficient ethanol to cause the separation of an aqueous layer of 5 to 10 ml. This product was then evaporated rapidly in a vacuum desiccator over sulfuric acid. The dry ammonium salt obtained in this fashion is stable and was stored as such; yield, 380 mg. units; potency = 5,200.

Products obtained from different batches treated as indicated varied in potency from 2,000 to 10,000 depending largely on the amount of activity in the original spinach.

Fractionation on Alumina.—Further purification was effected by fractional elution from alumina and by precipi-

(1a) Nearly all of the large scale concentration work was carried out by Mr. Elmer H. Stuart through the very generous coöperation of the Eli Lilly Co., Indianapolis, Indiana.

(1) Mitchell, Snell and Williams, THIS JOURNAL, **63**, 2284 (1941).

(2) Snell and Mitchell, *Proc. Natl. Acad. Sci.*, **27**, 1 (1941).

(3) Mitchell and Snell, *Univ. Texas Pub.*, **4137**, 36 (1941).

(4) Williams, *J. Am. Med. Assoc.*, **119**, 1 (1942).

(4a) This charcoal (Darco S-51) was pretreated by heating to boiling with 1.5 parts of aniline and 5 parts of water, followed by filtration and washing with hot water.

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tation of the acid from a concentrated solution of the ammonium salt. This is best illustrated by the following examples.

A sample (1.86 g.) of potency 3,500 (162 mg. units) was dissolved in 8 ml. of water and 6 ml. of methanol and adsorbed on a column of alumina (Merck according to Brockman) which had been washed with 40% methanol in water. The column was 2 cm. in diameter and 15 cm. long, packed dry. Following adsorption of the sample, the column was washed with 40% methanol. Fourteen 10-ml. fractions were collected followed by a fraction obtained by washing with 50 ml. of 2% ammonia in 40% methanol. Fractions 4–12 were combined giving 330 mg. of potency = 13,000 (143 mg. units). Fractions 1–4 and 13–15 were combined, evaporated and fractionated in an alumina column as before, giving 64.5 mg. of potency 11,000 (17.7 mg. units) and a considerable quantity of low potency material.

The two products, potency 13,000 and potency 11,000, were combined and again subjected to a fractionation on alumina. The sample was dissolved in 40% methanol (5 ml.) and adsorbed on an alumina column 1.5 cm. in diameter by 10 cm. long. Nine fractions of 5 to 10 ml. each were collected followed by one of 30 ml. containing 2% ammonia. Fractions 3–6 were combined giving 148 mg. of potency 25,000. The fractions 1–2 and 7–10 were combined and refractionated giving 36 mg. of potency 25,000 (total activity: 115 mg. units).

Acid Precipitation.—The combined sample of 184 mg. (potency = 25,000) of ammonium folate was triturated with 0.6 ml. of water, centrifuged and the precipitate washed 4 times with 0.1 ml. of water each time. The solution was acidified with 0.06 ml. of concentrated hydrochloric acid and mixed thoroughly. The solution was cooled to 0°, centrifuged and the precipitate washed 3 times with 0.1-ml. portions of ice water. The precipitate was dissolved in dilute ammonia and the solution evaporated in vacuum. The product weighed 88.3 mg., contained 110 mg. units, and had a potency of 46,000.

Fractionation on Alumina.—The sample with potency 46,000 was dissolved in 1 ml. of 40% methanol and adsorbed on a 1.5 × 10 cm. column of alumina as before. The column was washed with 40% methanol containing 1 drop of concentrated ammonium hydroxide per 100 ml. Nine fractions of from 4 to 6 ml. were collected followed by one obtained by using 40 ml. of 2% ammonia in 40% methanol. Fraction number 6 contained 5.8 mg. of solids and had a potency of 105,000. The remaining fractions were recombined and fractionated again under the same conditions. One fraction of 10.9 mg. had a potency of 75,000 (20.5 mg. units) and the remaining high potency fractions contained 28 mg. of potency 48,000 (33.5 mg. units). The total product at this point represented a 42.5% yield of the activity contained in the starting material of 3,500 potency.

Acid Precipitation from Cold Water.—A sample of 9.1 mg. of potency 71,000 (16.1 mg. units) prepared in the same fashion as that described, was dissolved in 0.2 ml. of ice water and 0.1 ml. of concentrated hydrochloric acid added. After a thorough mixing the precipitate was centrifuged and washed twice with 0.05 ml. of ice water. The supernatant liquid and washings contained 6.25 mg. units. The precipitate was triturated with 1 ml. of water at 50°, centrifuged and decanted. The precipitate weighed 1.4 mg. and had a potency of 85,000 (3.0 mg. units). The decanted solution was allowed to cool slowly in the dark to 25° and the resulting amorphous precipitate centrifuged off. It weighed 1.2 mg. and had a potency of 137,000 (4.1 mg. units). The supernatant liquid was cooled to 0° and centrifuged at that temperature. The product contained 0.6 mg. of potency 100,000 (1.5 mg. units). The remaining solution contained 1.5 mg. of material with 45,000 potency (1.67 mg. units).

Discussion

The illustrations cited represent the best single method of concentration that we have developed in this Laboratory though a great many variations have been tried. The problem was complicated by instability of the active principle to oxidation, reduction, acid, alkali, light and heat, as well as a high degree of reactivity with many organic reagents. One of the most complex processes, that of adsorption and elution from charcoal, involved extended study, and this phase of the work will be reported in a separate paper.

In addition to charcoal, alumina and Lloyd reagent we have utilized many kinds of fuller's earths, amberlites, barium carbonate, bentonites, florisil, floridin and permutite with successful adsorptions and elutions. We have also successfully utilized many precipitants other than lead and silver. Among these were salts of copper, mercury, iron, uranium oxide, phosphotungstic acid, alum, zinc, rhodanilic acid and barium. Recoveries of activity from the precipitates were poor in most cases.

A number of attempts to obtain crystalline products resulted unsatisfactorily. All samples prepared having a potency of 110,000 or greater precipitated in an amorphous state from acid solution and recrystallization attempts from warm water also gave amorphous products. Quinine, brucine, or even ammonium salts gave semicrystalline material on evaporation of the solvent on samples of potency 20,000 and up, but satisfactory recrystallization was not accomplished. Adsorption and fractionation from alumina has been a highly effective means of concentration only after the preliminary steps. This method has been most useful in the potency range of 2,000 to 80,000. Higher potency samples are readily adsorbed by the alumina but are not easily eluted. A preliminary treatment of the alumina with aniline allowed easy elution but no concentration was effected. Other eluants than ammonia such as triethanolamine, triisopropylamine, brucine, aniline, pyridine and quinine were tried with mediocre success.

Summary

A concentration procedure is described whereby folic acid has been concentrated from spinach to such an extent that the product is about 137,000 times as active as a standard material (liver extract).

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Folic Acid. II. Studies on Adsorption

BY EDWARD H. FRIEDEN,[1a] HERSCHEL K. MITCHELL AND ROGER J. WILLIAMS

The procedure for the concentration of folic acid described in a previous paper[1] is based to a considerable extent upon successive adsorptions upon and elutions from activated charcoal. During the early stages of the work on this problem it was observed that while the active principle from crude extracts adsorbed upon either norite or Darco could readily be eluted by treatment with hot ammonia, the principle from purified preparations, similarly adsorbed, was eluted to a negligible extent with this reagent. This rather peculiar behavior has been subjected to a more extended investigation in order to understand better the phenomenon and make use of it in concentration processes.

Experimental

Elution Experiments.—For preliminary quantitative experiments two extracts of spinach were prepared, one by hot water (110°) extraction of fresh spinach macerate for one-half hour and one by autolysis under toluene at 37° for two days. After the preliminary treatment, the samples were autoclaved for fifteen minutes at 15 lb. pressure. Both samples were then adjusted to *p*H 3.0 and filtered to remove precipitated protein material. Finally, each sample was adjusted to *p*H 6.5–7.0, sterilized, and stored. A concentrate of potency 280 was used as indicated.

The following experimental procedure was used. Aliquots of solution containing known amounts of folic acid were adjusted to *p*H 3.0 and shaken with weighed amounts of Darco S-51 (1 mg. Darco per mg. unit). The shaking was repeated several times during the course of one hour. The suspensions were then centrifuged, and the supernatant liquid removed. The residue was eluted with 5% ammonia (equal in volume to the supernatant liquid) at 90° for ten minutes, filtered while hot, and both filtrate and the supernatant solution assayed for folic acid. Folic acid assays were performed essentially according to the method of Mitchell and Snell,[2] and in all cases adsorption, as measured by the folic acid content of the supernatant solution, was found to be nearly complete (92–100%).

The results of the elution experiments are indicated in Table I.

TABLE I

ELUTION OF FOLIC ACID FROM DARCO S-51 BY 5% AMMONIA

Source of sample	Folic acid concentration, mg. units/ml. ($\times 10^{-4}$)	Eluted, %
Spinach autolysate	8.7	54
Spinach autolysate	3.35	69
Spinach autolysate	0.87	92
Spinach autolysate	.32	91
Spinach water extract	6.7	74
Spinach water extract	3.35	70
Spinach water extract	0.67	89
Spinach water extract	.67	92
Concentrate potency = 280	6.9	4.0
Concentrate potency = 280	3.4	5.4
Concentrate potency = 280	1.7	6.8
Concentrate potency = 280	0.69	25.6

Table I shows that at comparable concentrations the elution of folic acid from crude preparations is considerably more complete than when purified samples are used. It appeared, therefore, that the extent of elution with ammonia was dependent upon the concentration of substances present that interfered in the adsorption. This conclusion was verified by an experiment. A sample of the water extract referred to in Table I was exposed to ultraviolet light at *p*H 1 in order to destroy the folic acid present. This folic acid-free solution was then used as the solvent in the preparation of a solution of concentrate, and the adsorption-elution procedure repeated as described. The results are indicated in Table II.

TABLE II

EFFECT OF THE ADDITION OF FOLIC ACID FREE EXTRACT UPON THE EXTENT OF ELUTION BY AMMONIA

Source of sample	Folic acid concentration, mgu./ml. ($\times 10^{-4}$)	Eluted, %
Concentrate potency = 280	9.6	41
Concentrate potency = 280	4.4	65
Concentrate potency = 280	2.4	100
Concentrate potency = 280	0.96	100

Comparison of the data of Table II with those of Table I indicates the considerably increased elution yields due to the presence of added material. Results like those of Table II were also obtained when the irradiated material, instead of being added to folic acid solutions, was used to pretreat samples of charcoal. When this charcoal was used for adsorption and subsequent elution of purified folic acid, increased yields again resulted. A ten-fold dilution of irradiated extract was as effective in facilitating elution as was the undiluted material.

It seemed reasonable to suppose that the action of irradiated extract in facilitating elution of folic acid could be duplicated by known compounds. This hypothesis was tested by experiment. Samples of norite were shaken with 10 parts of 10% solutions of aniline, hippuric acid, allantoin, and triethanolamine at boiling temperature. The suspensions were filtered, washed with a small volume of water, and air dried overnight. The treated charcoals so

TABLE III

EFFECT OF PRETREATMENT OF NORITE UPON THE ELUTION OF FOLIC ACID

Description	Folic acid concentration, mgu./ml. ($\times 10^{-4}$)	Eluted, %
Norite, untreated	1.15	13
Norite, untreated (added irradiated extract)	1.15	88
Aniline-treated norite	1.15	100
Hippuric acid-treated norite	1.15	71
Allantoin-treated norite	1.15	55
Triethanolamine-treated norite	1.15	44

(1a) Lalor Foundation Fellow, University of Texas, 1942–1943. Present address: Department of Biochemistry, The University of Texas School of Medicine, Galveston, Texas.

(1) Mitchell, Snell and Williams, THIS JOURNAL, 66, 267 (1944).

(2) Mitchell and Snell, *Univ. Texas Pub.*, 4137, 36 (1941).

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obtained were tested for adsorption and subsequent elution of concentrate as before. The results are indicated in Table III.

This increase in elution yields by pretreatment of adsorbent with aniline has been found useful in large-scale concentration processes.

Adsorption Isotherms.—From the quantitative adsorption and elution experiments it appeared probable that two different mechanisms of adsorption of folic acid were involved. Since this difference should be evident from adsorption isotherms, the problem was considered from that standpoint. Only two studies of adsorption isotherms at extremely low concentrations were found in the literature. In 1914, Trumpler[3] studied the adsorption of fluorescein upon activated charcoal at equilibrium concentrations ranging upward from 10^{-7} g. per liter. He found that adsorption was essentially complete in one and a half hours, but that slow adsorption continued over a period of thirty hours. For a "reaction time" of one and a half hours, the isotherm was found to be linear from log x/m = -1.6 to log x/m = 0.5, where the symbols have their usual significance.[4] More recently, Cheldelin and Williams[4] reported adsorption studies for a large number of ampholytes upon Darco G-60. Of the substances studied only calcium pantothenate, biotin, pyridoxin hydrochloride and thiamin hydrochloride were investigated at very low concentrations. In all cases, linear log x/m − log C relations were found. No dependence of adsorption on time was noted.

Experiments were carried out on a folic acid concentrate of potency 10,000 using norite charcoal as the adsorbent. The concentration of folic acid was varied from 0 to 0.05 mgu. per ml. and the charcoal concentration was 0.2 mg. per ml. The adsorptions were carried out at *p*H 3. The suspensions were centrifuged, and the supernatant solution assayed for folic acid. The data are given in Fig. 1, plotted according to the Freundlich equation. Quantities of folic acid are expressed in milligram units.

Despite the scattering noted, the curve obtained does appear to exhibit the dual character predicted.

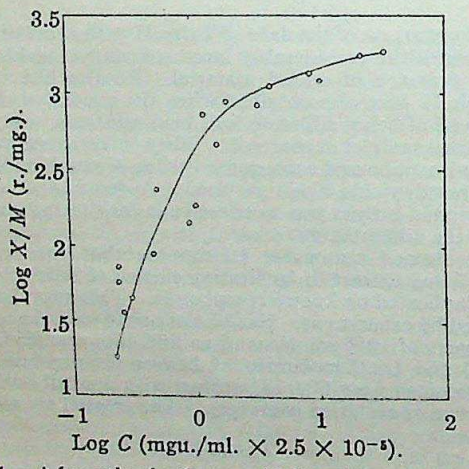

Fig. 1.—Adsorption isotherms of folic acid on norite at 25°.

Since a considerable part of the uncertainty probably lies in the use of a partially purified substance as well as the inherent limitations of microbiological assay methods, the studies were continued using riboflavin and thiochrome, analyses being made fluorometrically. Merck riboflavin was used, and the same Company very generously supplied sufficient pure thiochrome. Fluorescence was determined with a Pfaltz and Bauer fluorophotometer, equipped with a very sensitive triple mirror galvanometer. Equipped with suitable filters, the instrument is sensitive to 3×10^{-4} γ/ml. of riboflavin, and to 2×10^{-4} γ/ml. of thiochrome per galvanometer division.

(3) Trumpler, *Kolloid-Z.*, **15**, 10 (1914).

(4) Cheldelin and Williams, THIS JOURNAL, **64**, 1513 (1942).

Preliminary experiments followed the procedure used for folic acid. Erratic results were obtained, and were traced to a definite dependence of adsorption on time. Accordingly, the following procedure was adopted. Mixtures of norite and the compound being studied were prepared, and placed in an automatic shaking machine. At stated intervals, aliquots were withdrawn, centrifuged, and the supernatant fluid analyzed. The data obtained are shown in graphical form in Figs. 2 and 3.

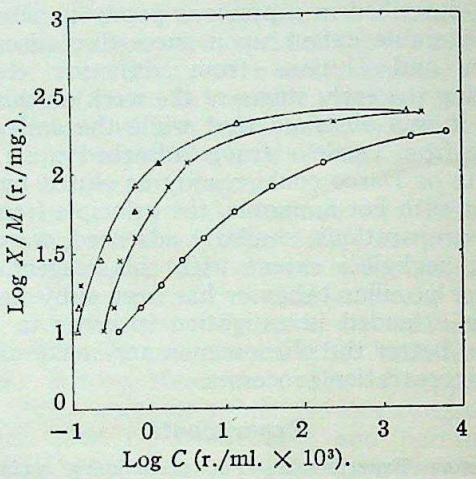

Fig. 2.—Adsorption isotherms for riboflavin at 25°: ⊙—⊙—⊙, after 1.1 hours; ×—×—×, after 17 hours; Δ—Δ—Δ, after 42 hours.

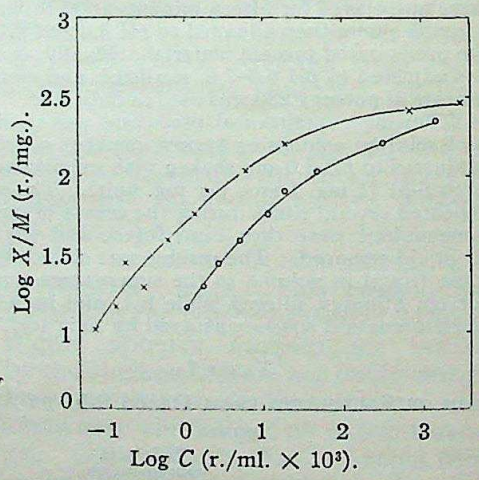

Fig. 3.—Adsorption isotherms for thiochrome on norite at 25°: O—O—O, after 1.5 hours; ×—×—×, after 22 hours.

Discussion

Quantitative elution and adsorption experiments suggest that adsorption of folic acid and presumably some other ampholytes occurs in two steps. From relatively pure solutions of folic acid the active principle is adsorbed in such a way that the resulting union is a very firm one and not readily reversible. If part or all of the charcoal surface is blocked by pretreatment, or by preferential adsorption of another compound, another type of binding manifests itself. In contrast to the initial "primary" adsorption, this "secondary" adsorption appears less tenacious, and its reversibility is more readily effected.

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Further evidence of the dual nature of the adsorption was obtained from adsorption isotherms (Figs. 1, 2 and 3). The fact that the change in slope of these curves occurs at very low concentrations may indicate that this behavior is related to the change in energy of adsorption which occurs when the adsorbing surface is covered with a single layer of molecules, and further adsorption involves the formation of secondary layers. Further studies relating the amount of material adsorbed to the surface area of adsorbent exposed might shed light upon the exact mechanism involved.

The slow rate of equilibrium of adsorption is rather surprising, requiring at least forty-two hours in the case of riboflavin. From the shapes of the adsorption curves after different lengths of time (Figs. 2 and 3) it appears that the primary irreversible adsorption is the slow step since this step becomes more sharply defined with increasing time. Data not shown indicated that the equilibrium was nearly reached in forty-two hours with riboflavin and in twenty-two hours with thiochrome.

From a practical standpoint the value of these observations is evident. In dealing with concentration of substances which adsorb and do not readily elute from the adsorbent it appears highly advantageous to pretreat the adsorbent, for a considerable period of time, with a solution of one or more compounds that will block the irreversible adsorption. A dilute solution of a crude tissue extract often may be effective.

Summary

Quantitative studies of charcoal adsorption of folic acid from crude preparations and from concentrates with subsequent elutions have been described. Elution of folic acid after adsorption from crude preparations is much easier than from relatively pure solutions. It has been found that this behavior is apparently due to the presence of interfering substances which affect the manner of adsorption. A working hypothesis of the mechanism of adsorption is proposed.

A study of the adsorption isotherms of folic acid, riboflavin, and thiochrome upon charcoal at low concentrations is reported. There is evidence that the adsorption process is of a dual nature, since the slopes of the isotherms change markedly in the range covered.

The application of these observations to concentration procedures using charcoal is pointed out.

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[CONTRIBUTION FROM THE UNIVERSITY OF TEXAS, BIOCHEMICAL INSTITUTE, AND THE CLAYTON FOUNDATION FOR RESEARCH]

Folic Acid. III. Chemical and Physiological Properties

BY HERSCHEL K. MITCHELL AND ROGER J. WILLIAMS

In order to better evaluate methods of concentration, various studies on stability, reactions and physical properties of folic acid were carried out. For most of this work the alteration of physiological activity of concentrates by various treatments was used as a criterion of reaction. Obviously a lack of destruction of activity by a given reagent does not prove the absence of a reaction since the product might be physiologically active. However, the destruction of activity does indicate a reaction.

Experimental

Esterification.—Two 1-mg. samples of ammonium folate, potency = 11,000, were each suspended in 1 ml. of methanol containing 0.01 ml. of fuming sulfuric acid. After ten minutes at 30° one sample was diluted with ice water and neutralized. After thirty minutes the other sample was treated in a similar fashion and both assayed for folic acid content using *S. lactis R.* The destruction of activity was 90 and 96%. In spite of considerable experimentation on means of hydrolysis of the ester, no consistently satisfactory method has been devised. Treatment with 1 *N* alcoholic potassium hydroxide at 30° for ten minutes usually gave a 60 to 80% recovery of activity.

Fractional adsorption and solubility experiments indicated the properties of the compound were not changed to any great extent by formation of the methyl ester. That the methyl ester was still acidic in nature was demonstrated by the fact that it could be more readily extracted from acid solution with butanol than from neutral or basic solution.

Acylation.—Acetylations using acetic anhydride and sodium acetate or acetic anhydride and pyridine at 100° for twenty minutes resulted in complete destruction of activity. Acetyl chloride as well as ketene (thirty minutes treatment at room temperature) also caused complete destruction of physiological activity. No method was found for regeneration of activity from any of these reaction products. Benzoyl chloride and β-naphthyl-sulfonyl chloride caused similar irreversible destruction of activity.

Solubility characteristics of acylation products were not markedly different than those of the original starting material.

Methylation.—Attempts to esterify folic acid using methyl iodide plus silver folate resulted in a product with no physiological activity. No activity could be recovered by methods used for hydrolysis of esters produced by acid–alcohol esterification. Similar results were obtained using benzyl chloride instead of methyl iodide, but the products in both cases did not show any great difference in solubility as compared to the starting material.

Solubility.—The solubility of free folic acid is very limited. In water it was found to be in the order of 2 mg. per ml. at 30° and about 1 mg. per ml. at 0°. The acid is slightly soluble in glacial acetic acid and liquid ammonia but essentially insoluble in dry methanol, ethanol, butanol, acetone, ether, dioxane, benzene, petroleum ether and chloroform. The ammonium salt is quite soluble in aqueous alcohols and is very soluble in water.

Stability to Various Treatments.—Frequent losses of activity during concentration processes necessitated studies of the stability of the concentrates at various

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stages of purification. It was observed repeatedly that the activity of higher potency fractions disappeared under milder conditions than that from crude extracts. Numerous tests for stability were performed. Treatments which involved about 50% destruction of activity included: material of potency 75,000, treated with 1 *N* sulfuric acid one-half hour at 100°, or with 1 *N* sodium hydroxide for one and one-half hours at 100°, or with 1 *N* sodium hydroxide for twenty-four hours at 28°. More or less vigorous treatment yielded results about as would be expected on the basis of the above results.

The material in the form of the ammonium salt (potency 17,000) was relatively stable in the neutral condition (even when exposed to ultraviolet light) but was destroyed slightly (17% in twenty minutes) at the boiling temperature in the presence of oxygen gas. Material of even higher potency (45,000) was stable at room temperature when kept at a *p*H of 3, but was destroyed to a considerable extent when exposed at this *p*H to ultraviolet light either in the presence of nitrogen or oxygen. At *p*H of 1, folic acid (potency 2,000–3,000) was readily destroyed by contact with an atmosphere containing ozone. By standing at room temperature for an hour in the presence of 1% hydrogen peroxide, it was about 90% destroyed.

Bubbling hydrogen sulfide through a solution either in 0.1 *N* ammonium hydroxide or at *p*H 4 resulted in 30–40% destruction in a half hour. Nitrous acid under Van Slyke conditions for thirty minutes caused about 90% destruction. Dry heat (98°) caused moderate destruction and heating in the neutral condition in the presence of zinc dust for fifteen minutes caused 50% destruction even in the case of low potency material. In 50% acetic acid at 100° for fifteen minutes, 100% destruction resulted from adding zinc dust, whereas in the presence of the acetic acid alone no destruction took place. Folic acid activity was completely destroyed by bromine, hypobromite and hydroxylamine in the presence of sodium acetate.

Analyses.—Qualitative elementary analyses were carried out at several stages of purification indicating the presence of C, H, O and N, and the absence of halogens, P and S. Following the work on absorption spectra of various fractions some C, H and N determinations were made on highly fractionated material having different physiological activities. It was considered probable that such fractions were made up principally of folic acid and inactivated folic acid and it was therefore expected that analyses of materials of different activities would give similar results.

Potency	C, %	H, %	N, %
80,000	45	3.6	19.2
28,000	46	5.0	..
3,000	45	5.1	..

Micro-Kjeldahl determinations on the potency 80,000 and 28,000 samples gave N values of 10 to 12%. It was found that micro-Kjeldahl determination on xanthopterin under the same digestion conditions accounted for only about three-fifths of the theoretical amount of nitrogen present.

Determination of Glycols.—The apparent high oxygen content of the folic acid concentrates analyzed suggested the possibility of a sugar group being present. Five-micromole samples of erythritol, mannitol, dextrose, riboflavin, xanthopterin, folic acid of potency 80,000 (assuming a molecular weight of 400) and folic acid of potency 28,000 were placed in small test-tubes with 0.5 ml. of solution containing 5 mg. of potassium periodate. One-half ml. of 0.4 *N* sulfuric acid was added and the mixture allowed to stand for twenty-four hours. The formaldehyde produced was distilled into 1 ml. of Schiff reagent. No formaldehyde was obtained from the xanthopterin and the folic acid samples, but strong positive tests were obtained with the rest of the compounds. The absence of a glycol was thus indicated.

Quantitative Acetylation.—As a check on the absence of polyhydroxy groups in folic acid, quantitative acetylations were carried out on 5-micromole samples of folic acid concentrate of potency 28,000 (assuming an average molecular weight of 400 for its ingredients), xanthopterin, mannitol, and riboflavin. The samples were weighed into 0.3 × 5 cm. Pyrex tubes followed by 0.039 ml. of 20% acetic anhydride in pyridine. The reagent was measured with a calibrated capillary pipet and the rinsings from each tube placed in a labeled erlenmeyer flask. The tubes were sealed, heated for one hour at 100°, placed in the proper flasks and the tubes crushed with the end of a glass rod. All samples except the xanthopterin had dissolved in the hot reaction mixture. Five ml. of water was added and the samples titrated with 0.01 *N* sodium hydroxide after standing thirty minutes. The number of moles of acetic acid used per mole of compound is given as follows: mannitol, 5.95; riboflavin, 4.05; folic acid, 1.15; xanthopterin, 0.5.

Since hydroxyl groups were found not to be abundant and since analysis indicated that a concentrate of this potency contained as high a percentage oxygen as a concentrate of potency 80,000, it appears probable that the high oxygen content of folic acid is due to structural features other than polyhydroxy groups.

Molecular Weight.—The determination of molecular weight by diffusion has been previously described and applied.[1,2] An application of this method to low potency fractions of folic acid gave the molecular weight as about 500. Results of more recent studies are described as follows: A sample of ammonium folate, potency = 65,000, was diluted to 20 micrograms per ml. with 0.1 *N* potassium chloride and the solution placed in one compartment of each of three calibrated diffusion cells. The other compartment of the cells contained 0.1 *N* potassium chloride. After twenty hours of diffusion time at 35°, samples were removed from both sides of the cells and the concentration of folic acid determined by biological test. Concentration of material in the solutions was also determined by fluorescence in a Pfaltz and Bauer fluorophotometer. The results are summarized below in terms of diffusion coefficients calculated in sq. cm. per day.

Cell	Physiological test *D* (sq. cm./day)	Fluorometric *D* (sq. cm./day)
E	0.453	0.495
F	.445	.449
J	.396	.462

The molecular weight was determined by comparison of these diffusion coefficients with those obtained from studies of a number of compounds of known molecular weight.[2a] The molecular weight appears to be 400 ± 50.

In order to test further the hypothesis that highly fractionated concentrates are made up of molecules of the same type as folic acid (folic acid plus products of its inactivation) a diffusion experiment was carried out on a sample of potency 10,000. This sample had been subjected to extensive chromatographic and solvent fractionation without appreciable increase in potency of products. Concentrations of the material in the solutions after diffusion were determined in

(1) Moquin and Cathcart, THIS JOURNAL, **57**, 1571 (1935).

(2) Williams, Lyman, Goodyear, Truesdail and Holaday, *ibid.*, **55**, 2912 (1933).

(2a) The experimental work involved in these diffusion experiments was carried out by E. H. Frieden and will be published later.

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parallel by (1) physiological test, (2) fluorescence and (3) ultraviolet light absorption at various wave lengths. Results are given as follows

	D (sq. cm./day)
Physiological test	0.48
Fluorescence	.47
Light absorption	.49

It appears from these results that the concentrate either was composed of molecules of very nearly the same molecular weight (about 380) or else the impurities involved showed no fluorescence or light absorption. Since 9 micrograms of this sample (potency 10,000) was found to be equivalent to 7 micrograms of potency 63,000 in ultraviolet light absorption the second possibility is ruled out.

Physiological Properties.—Folic acid was originally defined[3] as the active principle required for the growth of *S. lactis R* under specified conditions.[4] A considerable number of known compounds have been tested for activity under these conditions. One compound, thymine, replaces folic acid if present in sufficient quantity (1 γ per ml. of culture medium). This activity is not sufficient to cause interference with the test for folic acid. A considerable number of other compounds show a slight activity at very high concentrations (10 γ per ml. of culture medium). Among these are hypoxanthine, alloxazine, alloxantine, guanidine, theobromine, xanthopterin, alloxan, allantoin and uric acid. Compounds tested that were completely inactive were: nicotinic acid, pyridoxin, pantothenic acid, ascorbic acid, taurine, asparagin, biotin, riboflavin, *p*-aminobenzoic acid, creatine, inositol, phytin, 4-carboxy - uracil, 4 - carboxy - thymine, 5 - carboxy-uracil, uracil, adenylic acid, indolbutyric acid, cozymase, cystine, theophylline and caffeine.

Until pure folic acid becomes available, specific physiological properties of the compound must necessarily remain uncertain. However, a number of indications as to these physiological activities have been obtained using highly purified concentrates.

In this Laboratory activity of concentrates (potency 400) on four strains of yeast was demonstrated. In the very early stages of concentration "Old Process" yeast was used as a test organism but it was discarded in favor of the more specific and otherwise superior test using *S. lactis R*. Concentrates were found essential for *L. casei*, *L. delbruckii*, and *Clostridiun tetanii*,[5] and stimulated the growth of *L. arabinosus*.[3] The "eluate factor" of Snell and Peterson[6] has been identified with folic acid on the basis of a test using *L. casei* but the exact relationship between the two factors is not yet clear. In view of the recent findings of Pfiffner, *et al.*,[7] and of Stokstad,[8] it appears certain that pure compounds promote the growth of both *S. lactis R* and *L. casei*, but the relative activity of preparations from different sources differs for the two organisms. Keresztesy, *et al.*,[9] have reported isolation of a material of extremely high activity for *S. lactis R* which is almost without activity for *L. casei*. We have found concentrates from spinach acting in a somewhat similar fashion to those from liver described by Keresztesy, *et al.*,[9] *e. g.*, a sample of concentrate of potency 30,000, by *S. lactis R* test had only a potency of 15,000 by *L. casei* test, both being referred to the same standard. These findings support the conclusion drawn here and in a subsequent paper[10] that very minor changes in structure may produce great changes in activity for various organisms.

Antianemia properties of liver concentrates for chicks were reported by Hogan,[11] and this active principle was recently identified with folic acid though some uncertainty still exists.[7]

Early experiments on rats in this Laboratory indicated a higher erythrocyte count with animals receiving a folic acid concentrate than with controls. The difference was about 10% but an insufficient number of animals was used. Consequently, through the very generous coöperation of Dr. Earl R. Norris of the University of Washington, a sample of potency 75,000 folic acid concentrate was tested for antianemia activity on trout. The material was found to be one-fifth as active as xanthopterin for this purpose, since 10 micrograms per g. of fish was required to produce a good response in erythrocyte regeneration.

Concentrates high in folic acid were demonstrated to stimulate growth of chicks[12] and indications were obtained of stimulation of the growth of rats.[3] In both cases the concentrates used were of too low a potency to be certain of the biological specificity of the preparations. That intestinal bacteria can serve as a source of folic acid for the rat was demonstrated in this Laboratory[13] while several investigators have been able to produce a deficiency[14,15,16] by impairment of intestinal production with succinylsulfathiazole. In one case[14] this deficiency was cured by administration of a highly purified concentrate of folic acid obtained from this Laboratory.

Discussion

Investigation of stability of folic acid to a number of reagents and conditions demonstrated

(3) Mitchell, Snell and Williams, THIS JOURNAL, **63**, 2284 (1941).
(4) Snell and Mitchell, *Proc. Natl. Acad. Sci.*, **27**, 1 (1941).
(5) Mueller and Miller, *Proc. Soc. Expll. Biol. Med.*, **49**, 211 (1942).
(6) Snell and Peterson, *J. Bact.*, **39**, 273 (1940).
(7) Pfiffner, *et al.*, *Science*, **97**, 404 (1943).
(8) Stokstad, *J. Biol. Chem.*, **149**, 573 (1943).
(9) Keresztesy, Rickes and Stokes, *Science*, **97**, 465 (1943).
(10) Frieden, Mitchell and Williams, THIS JOURNAL, **66**, 269 (1944).
(11) Hogan and Parrott, *J. Biol. Chem.*, **132**, 507 (1940).
(12) Hutchings, Bohonos, Hegsted, Elvehjem and Peterson, *ibid.*, **140**, 681 (1941).
(13) Mitchell and Isbell, *Univ. Texas Pub.*, **4237**, 125 (1942).
(14) Nielson and Elvehjem, *J. Biol. Chem.*, **145**, 713 (1942).
(15) Martin, *Proc. Soc. Expll. Biol. Med.*, **51**, 353 (1942).
(16) Wright, Welton and Welch, *Science*, **97**, 426 (1943).

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a marked instability of the active principle to oxidation, reduction, acid, alkali, light, dry heat, acylation, esterification, methylation, benzylation, nitrous acid, bromine, hypobromite and certain other specific reagents. There is considerable evidence that some of these reactions involve structural changes that are of a minor nature with respect to the whole complex molecule. For example, partial destruction of physiological activity with alkali takes place very rapidly and with dilute reagents but a long and vigorous treatment is necessary for complete destruction. A similar situation appears to exist in the case of light destruction. With acid destruction physiological activity is lost rapidly but absorption spectra data[10] indicate that only minor modifications of the folic acid molecule are involved. It therefore appears evident that folic acid may be converted by various treatments to other very closely related substances which may have quite different physiological properties than the original.

A summation of analyses of our concentrates combined with information on molecular weight indicated that the formula of folic acid may be approximated by $C_{15}H_{15}O_8N_5$. Absorption spectra data[17] indicate the presence of a structural unit similar to xanthopterin. Side chains or other rings of an unknown nature but lacking nitrogen or a sugar residue, are indicated according to our evidence. The explanation of the high oxygen content must await further investigation.

Summary

Reactions and stability of folic acid are considered with reference to concentration problems.

The probability is pointed out that a large proportion of the impurities in purified concentrates are of a very similar nature to folic acid. On the basis of analyses of some of these concentrates an approximate empirical formula of $C_{15}H_{15}O_8N_5$ is given.

The absence of a sugar or poly hydroxy group, and the probable presence of a xanthopterin-like structural unit are indicated.

(17) Mitchell, THIS JOURNAL, 66, 274 (1944).

AUSTIN, TEXAS RECEIVED SEPTEMBER 14, 1943

[CONTRIBUTION FROM THE UNIVERSITY OF TEXAS, BIOCHEMICAL INSTITUTE, AND THE CLAYTON FOUNDATION FOR RESEARCH]

Folic Acid. IV. Absorption Spectra

BY HERSCHEL K. MITCHELL

It became evident from precipitation reactions, in the early stages of concentration, that folic acid was probably related to the pyrimidines, which show a strong absorption of ultraviolet light. There appeared to be a good possibility that such absorption might serve as a basis for quick quantitative determinations of the substance as well as an aid to chemical identification by showing specific absorption bands. It was also hoped that modification of folic acid by various chemical reactions would alter its absorption spectrum in such fashions as to yield information on the structure of the substance.

For comparative purposes (Figs. 1–4) the absorption data for concentrates are given in terms of extinction for a 1-cm. layer of 1% solution. This is represented according to the notation of Morton[1] by $E^{1\%}_{1\,cm.}$. The data in Figs. 5–11 are plotted in terms of molecular extinction coefficients since most of the substances concerned are pure compounds. In Fig. 11 the molecular weight of the folic acid sample is assumed to be 400.[2]

All of the absorption work was carried out using a Beckman spectrophotometer and a 1-cm. cell.

(1) Morton, "The Application of Absorption Spectra to the Study of Vitamins, Hormones and Coenzymes," Adam Hilger, Ltd., Camden Road, London, 1942, p. 10.

(2) Mitchell and Williams, THIS JOURNAL, 66, 271 (1944).

Experimental

Absorption Curves of Different Concentrates.—The absorption curves for folic acid concentrates covering a wide range of physiological potency are given in Fig. 1. These are illustrative only and represent materials of widely diversified treatment. It is evident that there is little parallelism between absorption and physiological activity. In certain high potency preparations, however, such a parallelism was found. In many low potency preparations, especially among those whose lack of physiological activity was probably due to destruction during fractionation rather than a lack of sufficient fractionation, a high degree of absorption was shown. This is illustrated in Fig. 1 by the two samples of potency 2,400 and 12,000, both of which had undergone more fractionation than the potency 28,000 sample and weight for weight represented much more raw material than either of the high potency samples. It therefore appears probable that concentration processes cause partial inactivation of the folic acid without altering the complex molecule sufficiently to cause a great change in light absorption. This supposition was corroborated by purposely destroying the physiological activity and following the treatment by a determination of the absorption spectra of the products.

Absorption of Inactivated Folic Acid.—Samples of folic acid of potency 33,000 were treated with 1 *N*, 4 *N* and 16 *N* sulfuric acid for one hour at 100°. All of the treatments are sufficient to destroy the folic acid activity. The absorption spectra of these products are compared with the original untreated sample in Fig. 2. It is evident that the molecular structure responsible for the light absorption is not destroyed by these treatments though some changes are produced.

Light absorption curves for products of treatment of folic acid with ultraviolet light in the presence of oxygen

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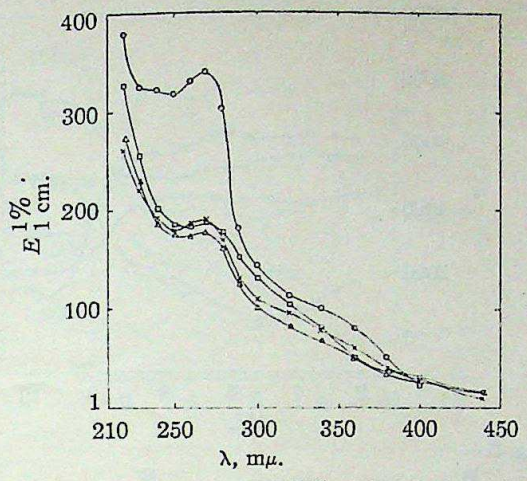

Fig. 1.— ⊙-⊙-⊙, potency 75,000; ×—×—×, potency 30,000; Δ—Δ—Δ, potency 12,000; □—□—□, potency 2,400.

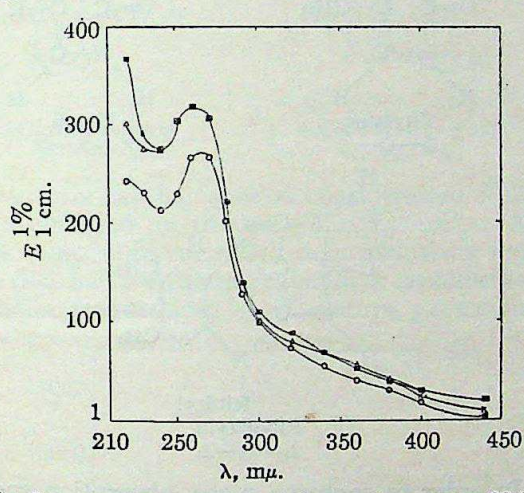

Fig. 2.— ⊙—⊙—⊙, untreated sample, potency 33,000; ×—×—×, 1 *N* H_2SO_4, potency 33,000; □—□—□, 4 *N* H_2SO_4, potency 33,000; Δ—Δ—Δ, 16 *N* H_2SO_4, potency 33,000.

and in the absence of oxygen are given in Fig. 3. The physiological activity was destroyed in both cases. A curve in Fig. 3 represents the absorption curve for a benzylated sample of folic acid. This was prepared by heating 10 mg. of silver folate (potency 12,000) for two hours at 100° with 1 ml. of benzyl chloride. The excess benzyl chloride was removed in vacuum. The product was physiologically inactive.

From these representative curves it appears probable that in spite of easy destruction of the physiological activity of folic acid the nucleus of the molecule is quite stable to varied treatments. The complete destruction by ultraviolet light in the presence of oxygen is attributed to the presence of ozone as well as to the light energy itself. Ozone in the dark produces the same effect though much more slowly. The supposition previously set forth that a large portion of the impurity in many folic acid concentrates consists of inactivated folic acid that still maintains its general structure, seems to be supported by these findings on absorption spectra of concentrates in which the folic acid has been purposely destroyed.

Absorption Spectra of Similar Compounds.—Only one compound has been found that has absorption characteristics with a marked similarity to these folic acid concentrates. A comparison of the absorption spectrum of this compound (xanthopterin) with that of a folic acid concentrate of potency 63,000 is given in Fig. 4. This indicates a probable similarity in structure.

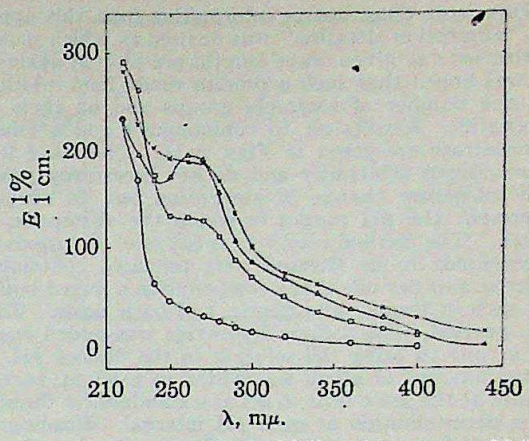

Fig. 3.—Δ—Δ—Δ, untreated folic acid, potency 28,000; ⊙—⊙—⊙, ultraviolet light and oxygen, potency 28,000; ×—×—×, ultraviolet light and nitrogen, potency 28,000; □—□—□, benzylfolic acid, potency 12,000.

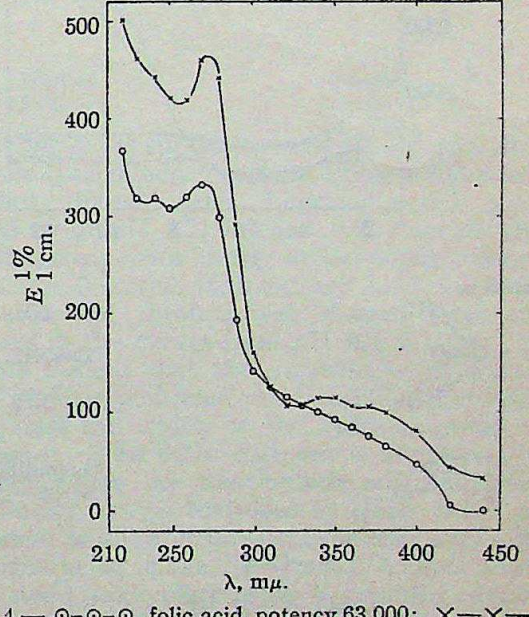

Fig. 4.— ⊙-⊙-⊙, folic acid, potency 63,000; ×—×—×, xanthopterin.

Effect of *p*H on Absorption Spectra.—A number of investigators have studied and adequately reviewed recent work on the effects of acid and alkali on the absorption spectra of solutions of several purines and pyrimidines.[3,4,5] Considerable shifts in absorption bands were observed in compounds containing tautomeric structures which are affected by *p*H. Evidence has been presented by Stuckey[6,7] showing that in certain barbituric acids ionization takes place followed at once by a tautomerism with its accompanying change in absorption.

The absorption spectra of xanthopterin and folic acid (potency 63,000) were determined in 0.1 *N* acid, at neutrality and in 0.1 *N* alkali. Considerable changes were observed as a result of the *p*H differences but both substances changed in a very similar fashion. In order to

(3) Loofbourow, Stimson and Hart, THIS JOURNAL, **65**, 148 (1943).
(4) Stimson and Reuter, *ibid.*, **65**, 151 (1943).
(5) Stimson and Reuter, *ibid.*, **65**, 153 (1943).
(6) Stuckey, *Quart. J. Pharm. Pharmacol.*, **15**, 370 (1942).
(7) Stuckey, *ibid.*, **15**, 377 (1942).

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obtain more quantitative information from this approach an "absorption titration" was devised in which molecular extinctions at given wave lengths are plotted against pH. It was hoped that such a process would lend information on the number of ionizable groups and on their acidic strengths. Results on 16 compounds[7a] and a folic acid concentrate are given in Figs. 5–11. The wave lengths were chosen arbitrarily and do not necessarily represent the maximum change in absorption but do adequately represent the pH ranges in which the absorption takes place. The method used was as follows. Solutions of the compounds to be titrated were prepared containing 10 micrograms per ml. of the compound in a mixed buffer 0.1 M each in formic, phosphoric, and boric acids. To a 50 ml. portion, 40% sodium hydroxide was added one drop at a time to bring the solution to the desired pH. The same amount of alkali was added to a 50-ml. portion of buffer at the same time to act as a standard for the absorption determination at each pH interval. Readings were taken at five or six arbitrarily chosen wave lengths in the range of absorption of the compound.

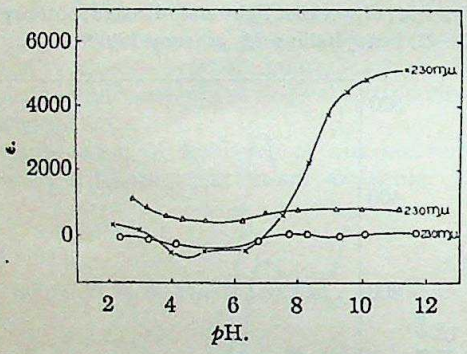
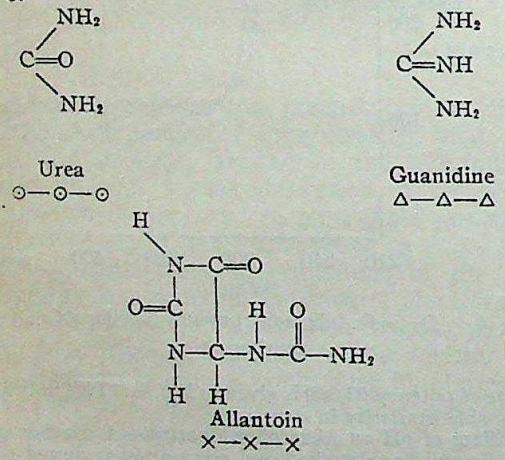


Fig. 5.—



Discussion

Studies of absorption of ultraviolet light by solutions of folic acid concentrates have indicated that the pure substance has an absorption spectrum similar to that of xanthopterin but it appears to have a much higher molecular extinction coefficient. No significant interpretation of that difference can be made at the present time other than the suggestion that the folic acid may contain more carbon to carbon, or carbon to oxygen double bonds.

(7a) The author is indebted to his colleague, E. E. Snell, for samples of thymine, 5-carboxy-uracil, 4-carboxy-thymine, 4-carboxy-uracil ethyl ester, which had been previously prepared by him in this Laboratory.

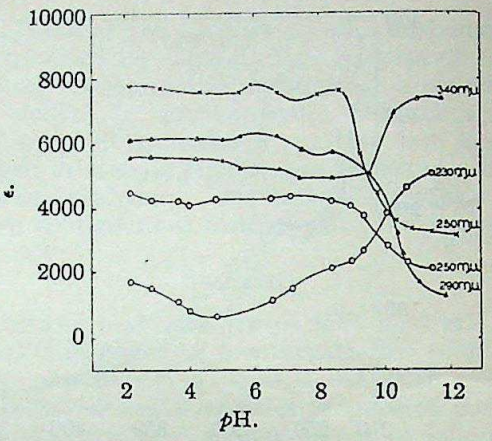
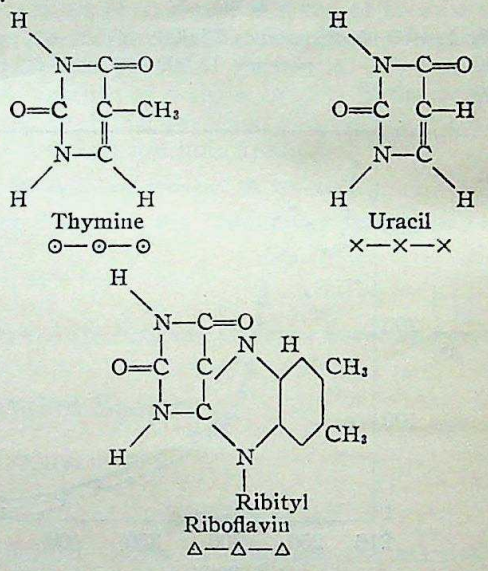


Fig. 6.—



In order to conserve space, absorption spectra on only a few concentrates are given here and all are on samples that have been highly fractionated by processes already described.[8] Low potency fractions that have not been subjected to extensive fractionation do not show a high degree of absorption as do the samples of potency 12,000 and 2,400 in Fig. 1 (Curves 3 and 4). It appears probable that these samples consist of folic acid plus a considerable proportion of folic acid with the structure modified to the extent of destroying the physiological activity of the compound. In view of the ease of destruction of this physiological activity[2] and the stability of the absorbing nucleus, as shown in Figs. 2 and 3, this hypothesis is given considerable support and offers a good explanation for difficulties involved in obtaining fractions of high physiological activity from many low potency concentrates.

The "absorption titrations" given in Figs. 5–11 suggest a strong similarity between the folic acid concentrate and the xanthopterin except for intensity of absorption. Both show two marked inflections in the curves, at about pH 2.5 and at about pH 9.0. Some reasonable interpretations

(8) Mitchell, Snell and Williams, THIS JOURNAL, 66, 267 (1944).

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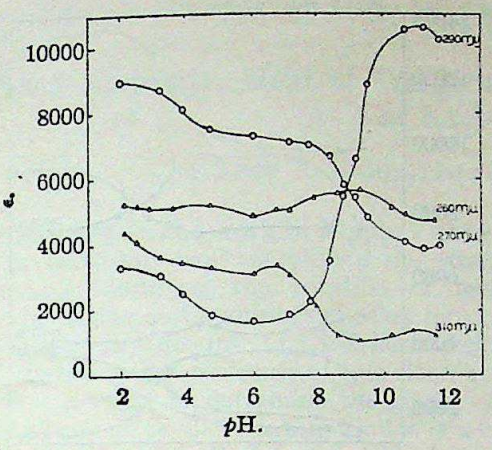
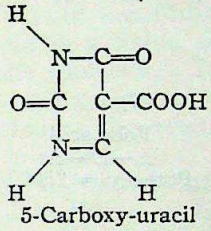
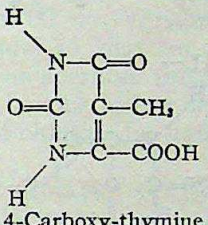


Fig. 7.—



5-Carboxy-uracil
⊙—⊙—⊙



4-Carboxy-thymine
△—△—△

of these data can be made on consideration of the curves obtained on the known compounds. All of the compounds on which determinations were made that had a structure capable of tautomerism in position 6 as induced by *p*H change, gave major

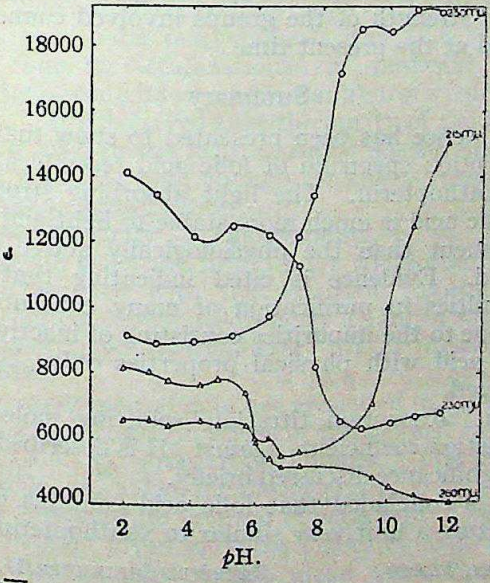
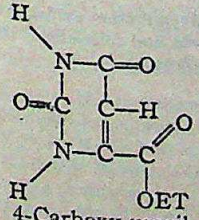
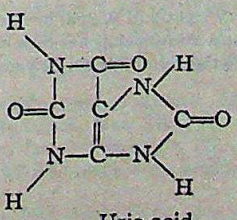


Fig. 8.—



4-Carboxy-uracil
(Ethyl ester)
⊙—⊙—⊙



Uric acid
△—△—△

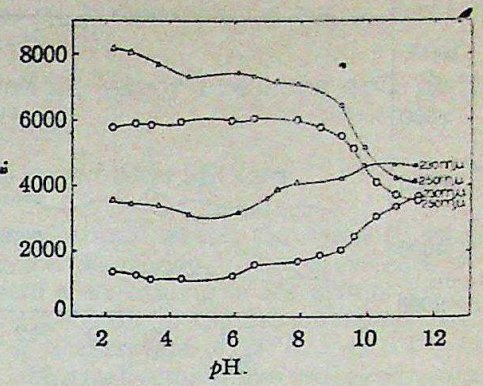
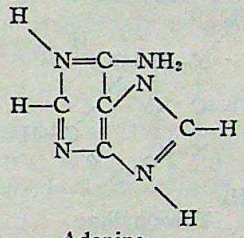
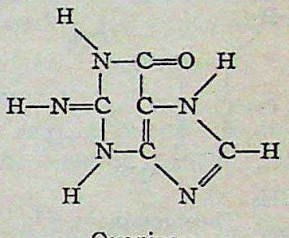


Fig. 9.—



Adenine
⊙—⊙—⊙



Guanine
△—△—△

inflections in the curves between *p*H 7.5 and 10.4. Of these compounds, 4-carboxy-uracil ethyl ester, 4-carboxy-thymine and 5-carboxy-uracil gave inflections at *p*H 7.5, 7.9 and 8.9, respectively. Six other compounds having similar configurations in position 6 (uracil, thymine, uric acid, guanine, riboflavin and theobromine) showed large inflections in the curves from *p*H 9.6 to 10.4. It appears evident that the substitution of a carboxyl group in position 5 and especially in position 4 increases the acidity of the ionizable group in position 6. Two other compounds of interest in this connection are theophylline and allantoin. The former has no hydrogen in either the 1 or 5 position to allow enolization, the only available hydrogen being in the 7 position. A three-atom shift could take place with a resulting major change in absorption characteristics. The ionization could be direct at position 7 but according to Stuckey's work on barbituric acids,[6,7] the ionization alone would not be expected to produce the large absorption changes. Allantoin represents a different series of compounds which appear to have more acidic enolic forms than the pyrimidines. The large inflections in the absorption curves of xanthopterin and folic acid at *p*H 9 appear to represent enolizable groups at position 6 with acidic strength influenced by both an amino group in position 3 and a relatively strong acidic group at some position closer to 6 (position 8 in xanthopterin).

Inflections in the curves in the acid range are not as easily explained as those on the alkaline side since a neutralization of a weak acid is not involved and the changes in absorption necessitate marked changes in electronic structure but do not necessarily involve ionization. Nearly all of the compounds including urea and guanidine

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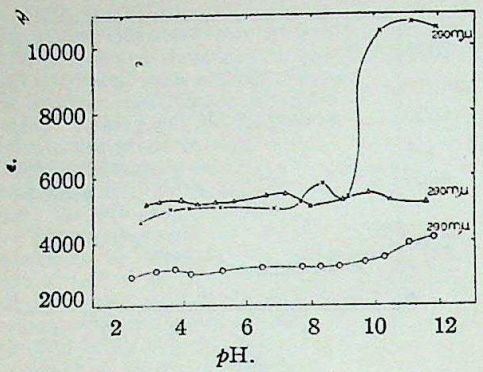
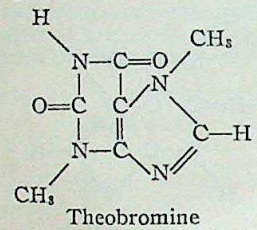
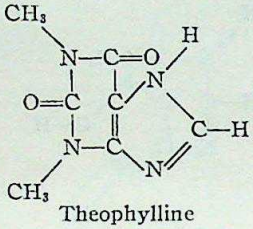


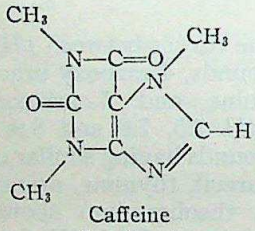
Fig. 10.—



Theobromine
⊙—⊙—⊙



Theophylline
×—×—×



Caffeine
△—△—△

show minor changes in absorption between *p*H 3.0 and 7.0 at short wave lengths. These changes can therefore be attributed to the urea or guanidine portion of the molecules but are insignificant with the more complex compounds. Five compounds, 5-carboxy-uracil, 4-carboxy-thymine, uric acid, xanthopterin and folic acid, show marked inflections in the curves in the acid *p*H range at many wave lengths over the entire wave length scale of absorption. In the cases of the two carboxy compounds it appears evident that the absorption changes are due to electronic shifts involving the carboxyl groups themselves since no such inflection was evident with 4-carboxy-uracil ethyl ester. The uric acid similarly must be involved at the strongly acid group in position 8. The changes in absorption of xanthopterin in the acid range must also be due to electronic changes around position 8 though this change is at a much more acidic *p*H than with uric acid and is in the opposite direction. By inference folic acid also contains an acidic enol in position 8 implying

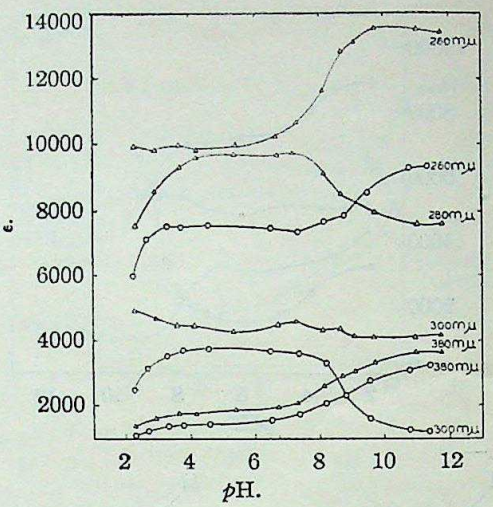
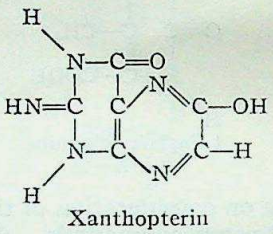


Fig. 11.—



Xanthopterin
⊙—⊙—⊙

Folic acid
△—△—△
Potency = 75000

a further similarity in its structure to that of xanthopterin.[8a] Whether or not these changes in absorption in the acid *p*H range are related to acidic strength of the groups involved cannot be stated at the present time.

Summary

Evidence has been presented to show that the absorption spectrum of folic acid resembles that of xanthopterin. The light absorbing structure in folic acid is much more stable to light and acid treatment than the physiologically active compound. Evidence is cited indicating that the difficulties in purification of many concentrates are due to the impurities consisting of inactivated folic acid with physical properties only slightly changed.

An "absorption titration" plotting molecular extinction coefficients against *p*H is described and its significance discussed briefly.

It is concluded that folic acid contains in its structure a unit very similar to xanthopterin.

AUSTIN, TEXAS RECEIVED SEPTEMBER 14, 1943

(8a) Wright and Welch[9] have recently given further evidence of a structural relationship between xanthopterin and folic acid.

(9) Wright and Welch, *Science*, **97**, 426 (1943).

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[CONTRIBUTION NO. 935 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY]

The Heat Capacity, Heat of Transition, Vaporization, Vapor Pressure and Entropy of 1,1,1-Trichloroethane

BY THOR R. RUBIN,[1] BLAINE H. LEVEDAHL AND DON M. YOST

Introduction.—The work of Kemp, Pitzer and other investigators has[2] established the existence of barriers hindering the rotation of methyl groups in ethane and a number of other molecules containing methyl groups. 1,1,1-Trichloroethane, CH_3CCl_3, is another molecule of this class, and it seemed important to determine the height of its barrier since one of the rotating groups is a completely substituted methyl group. The height of the barrier was found to be 2700 ± 350 calories per mole, a value almost equal to that for the ethane molecule. It is of considerable interest that the magnitude of the barrier is but little affected by the substitution of chlorine for hydrogen in ethane.

An additional interesting property of 1,1,1-trichloroethane is that dipole moment studies[3] indicate that its molecules begin to rotate in the solid at a temperature of 224.3°K. The heat capacity data reported here establish the existence of a transition at this temperature.

Material.—Eastman Kodak Co. "methyl chloroform" was purified by fractional distillation and subsequent repeated fractional crystallization. The corrected boiling range of the fraction which was to be recrystallized was 73.8–74.0°. After four recrystallizations the material was dried by passing its vapor over anhydrous calcium sulfate. It is believed that the purity of the final fraction used in the heat capacity measurements is easily 99.7%, high enough for the purposes of the present investigation.

Heat Capacity Measurements.—The heat capacity of solid and liquid 1,1,1-trichloroethane was determined with the adiabatic calorimeter (Gold-plated copper calorimeter I, and a strain-free resistance thermometer CT-2) described elsewhere.[4]

The experimental data are presented in Table I. They are expressed in terms of the defined calorie equal to 4.1833 international joules. The value 273.16°K. was taken for the ice point.

The temperature interval of each heat capacity measurement given in Table I may be estimated from the spacing of the mean temperatures, since there were no gaps between measurements in any series. The data are shown plotted in Fig. 1; the measurements were reproducible at all of the temperatures where the various series of measurements overlap. The deviations of the data from a smooth curve are within 0.2%; the probable accuracy of the measurements is about 1% at a temperature of 15°K. and 0.2% above 25°K. Thermal equilibrium was easily attained even for measurements taken at temperatures in the immediate neighborhood of the peaks shown in Fig. 1.

TABLE I

THE MOLAL HEAT CAPACITY OF 1,1,1-TRICHLOROETHANE

0°C. = 273.16°K.; molecular weight = 133.415; 1.7383 moles in the calorimeter.

T, °K.	C_p, cal./deg. mole	T, °K.	C_p, cal./deg. mole	T, °K.	C_p, cal./deg. mole
Series 1		Series 4		Series 8	
82.58	13.81	207.17	31.61	245.40	33.35
86.17	14.22	212.28	33.19	251.61	33.47
93.33	14.90	216.96	40.10	257.80	33.57
101.84	15.76			263.81	33.72
109.86	16.48	Series 5		269.77	33.61
117.74	17.29	227.80	35.86	275.85	33.91
125.73	18.12	231.91	43.38	281.85	34.07
133.84	18.89	234.98	96.3	287.70	34.23
141.86	19.66			293.71	34.35
157.05	21.26	Series 6		299.59	34.49
164.26	22.01	190.22	24.87		
171.27	22.62	195.29	25.98	Series 9	
178.08	23.42	199.19	27.47	12.29	1.40
		202.84	31.57	13.33	1.90
Series 2		206.18	34.98	14.37	2.34
177.23	23.24	209.51	31.32	15.68	2.86
183.83	24.04	212.88	33.94	17.50	3.52
190.24	24.92	216.01	38.09	19.61	4.29
196.43	26.28	218.81	45.16	21.68	4.98
				24.04	5.706
Series 3		Series 7		27.02	6.686
183.64	24.03	226.13	34.70	30.36	7.461
189.98	24.84	228.91	37.60	33.83	8.175
196.13	26.13	230.82	40.70	37.75	8.853
201.88	29.93			42.43	9.517
207.03	35.28			47.60	10.22
211.99	33.02			53.40	10.89
				59.56	11.49
				65.83	12.13
				73.22	12.86
				81.09	13.69
				89.59	14.55
				98.57	15.44

The peak at 206°K. is believed to be due to an eutectic resulting from the presence of a small amount of impurity, since similiar data taken with another sample of 1,1,1-trichloroethane by

(1) A. A. Noyes Fellow in Chemistry, present address: Chemistry Department, Cornell University, Ithaca, New York.

(2) J. D. Kemp and K. S. Pitzer, THIS JOURNAL, 59, 276 (1937). See E. Bright Wilson, *Chem. Rev.*, 27, 17 (1940), for a summary of references to this work.

(3) A. Turkevich and C. P. Smyth, THIS JOURNAL, 62, 2468 (1940).

(4) Don. M. Yost, C. S. Garner, D. W. Osborne, T. R. Rubin and H. Russell, *ibid.*, 63, 3488 (1941).

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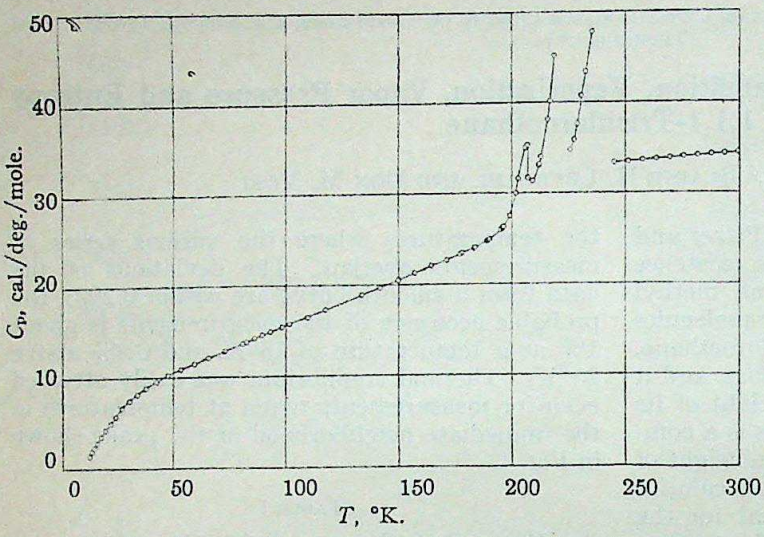

Fig. 1.—The molal heat capacity of 1,1,1-trichloroethane.

Professor E. A. Long showed no such maximum.[5]

Immediately below the melting point, premelting effects obscure the course of the true heat capacity curve. It is obvious that the effect is large for relatively little impurity, since the heat of fusion is small. A correction based on Raoult's law applied in a manner given by Pitzer[6] could not be made, because of the close proximity of the transition temperature to the melting point.

Transition Temperature and Melting Point.—The transition temperature and melting point were carefully measured, and the results are presented in Table II, together with the values obtained by other observers. The melting point value is an extrapolated one, corresponding to a completely melted system in which the mole fraction of dissolved impurities is small.

TABLE II

MELTING AND TRANSITION TEMPERATURES FOR 1,1,1-TRICHLOROETHANE

0°C. = 273.16°K.

Melting point, °K.	Transition temperature, °K.	Observer
240.5	224.3	Turkevich and Smyth[3]
241.0	...	Van de Vloed[7]
242.8		Henne and Hubbard[8]
240.2 ± 0.5	224.20 ± 0.03	This Research

Heats of Transition and Fusion.—The heat of transition of 1,1,1-trichloroethane was observed to be 1785 cal./mole and 1787 cal./mole from measurements over a temperature range of 214.785–225.716°K. and 210.983–227.301°K., respectively; the average value is 1786 ± 2 cal./mole. Each value of the heat of transition contains a correction for the normal heat capacity of the solid obtained by extrapolating the heat capacity curve below 206°K. to the transition temperature. The uncertainty in the heat of transition given includes all calorimetric errors, but errors in the extrapolated heat capacity values at temperatures above 206°K. may increase this uncertainty fivefold. The total entropy and heat content are not affected appreciably by this latter possibility, since errors in the extrapolated heat capacity values are compensated almost completely by the resulting errors in the heat of transition.

An accurate value of the heat of fusion was not determined because of the errors in the heat capacity of the solid just above the transition point. A rough value for the heat of fusion of 1,1,1-trichloroethane of 450 ± 300 calories per mole was calculated from the total heat absorbed over the melting range and from the estimated heat capacity of the solid; it was assumed that the latter were about equal to the heat capacity of the liquid.

Neither this rough value of the heat of fusion nor the melting point given above is used in the calculation of the total entropy, and uncertainties in these quantities do not affect the uncertainty in the total entropy.

Heat of Vaporization.—The heat of vaporization of 1,1,1-trichloroethane was determined in a Giauque type calorimeter fitted with a strain-free platinum resistance thermometer.[4] The usual corrections were made for the heat lost by the calorimeter to its surroundings by radiation and the heat carried off by the vapor. A constant measured pressure was maintained for every determination in a manner described elsewhere.[4] The temperatures of vaporization were calculated from the pressure data using the vapor pressure equation given below.

The observed molal heat of vaporization of 1,1,1-trichloroethane at 284.34°K. and a pressure of 6.899 cm. was 7988 cal./mole and at 286.53°K. and 7.686 cm. was 7969 cal./mole. These values when corrected to 286.53°K. and 7.686 cm. become 7955 and 7969 cal./mole, respectively, with an average value of 7962 ± 12 cal./mole. The correction to 286.53°K. was made using (a) the heat capacity of the gas from spectroscopic data, (b) the heat capacity of the liquid from this research and (c) Berthelot's equation with reasonable estimates for the critical constants of T_c = 533°K. and P_c = 50 atm.

Vapor Pressure.—The vapor pressure of 1,1,1-trichloroethane at various temperatures is given in Table III together with pressures calculated from the derived vapor pressure equation presented below. The temperature of the liquid was measured in the Giauque type calorimeter

(5) E. A. Long, private communication.
(6) K. S. Pitzer, THIS JOURNAL, 62, 331 (1940).
(7) Van de Vloed, *Bull. Soc. Chim. Belg.*, 48, 229 (1940).
(8) A. L. Henne and D. M. Hubbard, THIS JOURNAL, 58, 404 (1936).

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used for determining the heat of vaporization. The pressure was measured with a mercury manometer by means of a Gaertner meter bar and a Henson cathetometer. Corrections for the capillary depression were made from the measured height of the menisci and the data of Cawood and Patterson.[9]

TABLE III

THE VAPOR PRESSURE OF 1,1,1-TRICHLOROETHANE

0°C. = 273.16°K., pressures in int. cm.

T, °K.	P, obs., cm.	P,[a] calcd., cm.	P, calcd. − P, obs.
267.796	2.88	2.91	+0.03
272.943	3.87	3.85	− .02
278.269	5.05	5.09	+ .04
284.464	6.93	6.95	+ .02
290.083	9.12	9.12	− .00

[a] $\log_{10} P_{cm.} = -(1729/T) + 6.92013$.

Vapor pressure values were not determined above 17°C. since in this region condensation of vapor in the manometer would result. The uncertainty in any of the pressure values is estimated to be ±0.05 cm. It was not deemed essential, in this case, to measure the vapor pressures with high precision.

The Entropy of 1,1,1-Trichloroethane.—The entropy from the calorimetric data is summarized in Table IV. The entropy of the solid below a temperature of 15°K. was calculated by a Debye extrapolation with three degrees of freedom and $\Theta_D = 78°$; the entropy over the temperature interval from 224.20°K. to 241.00°K., was calculated by graphical evaluation of $\int C_p$ d ln T from 224.20°K. to a known intermediate temperature (about 236°K.). Above this temperature the function $\Sigma \frac{Q}{T_{max.}}$ was used to calculate the rest of the entropy in the interval ending at 241.00°K.; ΣQ is the total energy absorbed over the latter temperature interval, and $T_{max.}$ is the temperature of maximum heat capacity, in this interval (equal to about 240.1 ± 0.2°K.). The imperfect gas correction was made assuming a Berthelot equation of state and the estimated critical data.

TABLE IV

THE MOLAL ENTROPY OF 1,1,1-TRICHLOROETHANE FROM CALORIMETRIC DATA

0°C. = 273.16°K.; molecular weight = 133.415

	Entropy, cal./deg./mole
0–15°K. Debye extrapolation, $\Theta_D = 78.0°$	0.851
15–224.20°K. graphical (solid)	33.852
Eutectic at 206°K.	0.150
Transition, 1786/224.20	7.967
224.20–241.00°K., graphical (fusion range)	4.319
241.00–286.53°K., graphical (liquid)	5.828
Vaporization 7962/286.53	27.788
Entropy of real gas at 286.53°K. and 7.686 cm.	80.755 ± 0.16
Gas imperfection[a]	0.002
Correction to 1 atm.	− 4.553
Entropy of ideal gas at 286.53°K. and 1 atm.	76.22 ± 0.16
Entropy of ideal gas at 298.16°K. and 1 atm.	76.97 ± 0.16
Entropy of liquid at 298.16°K.	54.37 ± 0.12

[a] S (ideal) − S (real) = $\frac{27RT_c^3P}{32T^3P_c}$, P_c = 50 atm., T_c = 533°K.

The entropy was also calculated from the molecular data given in Table V.

The vibrational frequencies were taken to be harmonic. The fundamental frequencies, of which all are active in the Raman spectrum except the torsional one around the C–C axis, are: 345 (1), 523 (1), 977 (1), 1471 (1), 2939 (1), 241 (2), 340 (2), 713 (2), 1086 (2), 1450 (2) and 3000 (2). The numbers in the parentheses adjoining the frequencies are their degeneracies as assigned by us from rough polarization measurements. The frequency 340 (2) which overlaps 345 (1) is not certain. It corresponds to a bending vibration of the CH_3 and CCl_3 groups about the C–C bond. A more complete discussion of the spectrum will be given elsewhere. The moments of inertia for the rigid molecule were calculated from the following data of Beach and Stevenson[10]: C–Cl distance, 1.76Å.; C–C distance, 1.54Å.;

TABLE V

THE MOLAL ENTROPY OF GASEOUS 1,1,1-TRICHLOROETHANE AT 286.53°K. AND 1 ATM. FROM MOLECULAR DATA

	Entropy in cal./deg./mole
Translational	40.38
Rotational (free rotator)	28.85
Vibrational	8.24
Total for free rotator	77.47 ± 0.10
Calorimetric	76.22 ± 0.16
Difference	1.25 ± 0.16
Diff. calcd. for a potential of 2700 ± 350 cal./mole	1.26 ± 0.16

The Entropy from Molecular Data.—The calculated entropy for 1,1,1-trichloroethane from the molecular data is given in Table V.

An accurate value cannot be given for the mole percentage impurity present, mainly because a precise value of the freezing point and heat of fusion is not known. A rough estimate of an upper limit of 0.3 mole per cent. may be made from the data available. It may be remarked that this estimate is not unreasonable because large premelting effects are to be expected for small amounts of impurities present in substances having a low heat of fusion. The final entropy value is not affected to a significant extent by concentrations of impurity of this order of magnitude.

(9) W. Cawood and N. S. Patterson, *Trans. Faraday Soc.*, **29**, 522 (1933).

(10) J. Y. Beach and D. P. Stevenson, THIS JOURNAL, **61**, 2643–2651 (1939).

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C–H distance, 1.09Å.; C–C–H angle, 109°28′; and the Cl–C–C angle 110°. The symmetry number for the rigid molecule was taken as three.

The following natural constants, given by Birge,[11] were used in the calculations: 0°C. = 273.16°K., R = 1.9870 cal./deg./mole, r, the Boltzmann constant, = 1.3805×10^{-16} erg/deg., $N = 6.023 \times 10^{23}$ and $h = 6.624 \times 10^{-27}$ erg sec.

The difference between the calorimetric entropy value and the one calculated using molecular constants is 1.25 calories per mole, and this corresponds to a barrier of 2700 calories per mole. This value was calculated using the tables of Pitzer and Gwinn.[12] The reduced moment of inertia of the methyl group of the molecule was taken to be 5.26×10^{-40} c. g. s. units.

(11) R. T. Birge, *Rev. Modern Phys.*, **13**, 233 (1941).

(12) K. S. Pitzer and W. D. Gwinn, *J. Chem. Phys.*, **10**, 428 (1942).

We wish to thank Professor Alexander Goetz for supplying us with liquid hydrogen.

Summary

The heat capacity of 1,1,1-trichloroethane has been measured from 14°K. to room temperature. There is a transition point in the solid at 224.20°K. The heat of transition is 1786 ± 2 cal./mole. An approximate value for the melting point is 240.2 ± 0.5°K., and a rough value for the heat of fusion is 450 ± 300 cal./mole. The heat of vaporization is 7962 ± 12 cal./mole at 286.53°K. The entropy of the ideal gas at 286.53°K. and 1 atm. is 76.22 ± 0.16 cal./deg./mole, and 76.97 ± 0.16 cal./deg./mole at 298.16°K. and 1 atm. The entropy of the liquid at 298.16°K. is 54.37 ± 0.11 cal./deg./mole. A comparison of the statistical and calorimetric values of the entropy indicates a barrier of 2700 ± 350 cal./mole.

ITHACA, N. Y. RECEIVED JULY 21, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE]

The Ternary System: Dioxane–Benzene–Water

BY ROBERT J. BERNDT AND CECIL C. LYNCH

Several ternary liquid systems have been examined by Hand[1] for dineric distribution between conjugate phases. Bancroft and Hubbard[2] have recently presented a new method of determining dineric distribution in such systems and have examined two ternary systems in some detail.

The object of this work has been to study the ternary liquid system dioxane–benzene–water, in which the dioxane is the consulate liquid, for dineric distribution between the conjugate phases at 25°. Because of the extensive region of immiscibility in the system, we have employed both the method of Bancroft and an analytical method for determining the composition of conjugate phases.

Preparation of Materials

Dioxane.—Technical 1,4-dioxane from the Eastman Kodak Co. was purified by the method described by Eigenberger.[3] The product was kept over metallic sodium, from which it was distilled when needed; density d^{25}_4 1.0276, $n^{25}D$ 1.4197.

Benzene.—Thiophene-free benzene was dried with calcium oxide, from which it was fractionally distilled. It was kept in bottles protected from moisture with suitable drying tubes.

Freshly boiled redistilled water was used also in all mixtures.

Experimental Method

Mixtures were prepared in glass-stoppered flasks by direct weighing and were allowed to reach equilibrium in a water thermostat (25 ± 0.05°). The conjugate phases were sampled with pipets; for the lower layer, the tips of the pipets used were drawn off and sealed. These tips were broken off under the lower layer for sampling to avoid any contamination with the upper layer. Densities of all solutions were determined with 25-cc. or 10-cc. pycnometers to a precision of ± 0.0001 unit. All refractive indicex measurements were made with an Abbe refractometer to a precision ± 0.0002 unit.

The Binodal Curve.—The binodal curve for the 25° isotherm was determined by titration of binary mixtures of benzene and dioxane with water and of mixtures of dioxane and water with benzene to the first indication of immiscibility. In the overlapping portions from the two sets of titrations, these data were found to agree within ±0.2%. The data for the binodal curve are given in Table I, and the plot in Fig. 1.

TABLE I

DATA FOR THE BINODAL CURVE OF THE SYSTEM: DIOXANE–BENZENE–WATER AT 25°

% Dioxane	% Water	% Benzene	% Dioxane	% Water	% Benzene
10.24	89.66	0.10	9.97	0.14	89.89
20.38	79.49	.13	19.89	.26	79.85
30.10	69.73	.17	30.53	.58	68.89
39.76	59.98	.26	40.80	.84	58.36
50.21	49.10	.69	50.11	1.34	48.55
58.39	39.90	1.71	58.81	2.09	39.10
64.53	32.08	3.39	63.43	2.70	33.87
67.58	27.69	4.73	67.79	3.73	28.48
70.21	23.05	6.74	69.69	4.34	25.97
72.50	18.24	9.26	71.66	5.09	23.25
71.51	20.33	8.16	73.23	6.06	20.71
73.60	15.44	10.96	74.21	7.43	18.36
74.45	13.31	12.24	74.59	12.43	12.98
74.86	8.33	16.81	73.37	15.78	10.85
72.92	5.71	21.37			
75.01	10.24	14.75			

(1) Hand, *J. Phys. Chem.*, **34**, 1961 (1930).

(2) Bancroft and Hubbard, THIS JOURNAL, **64**, 347 (1942).

(3) Eigenberger, *J. prakt. Chem.*, **130**, 75 (1931).

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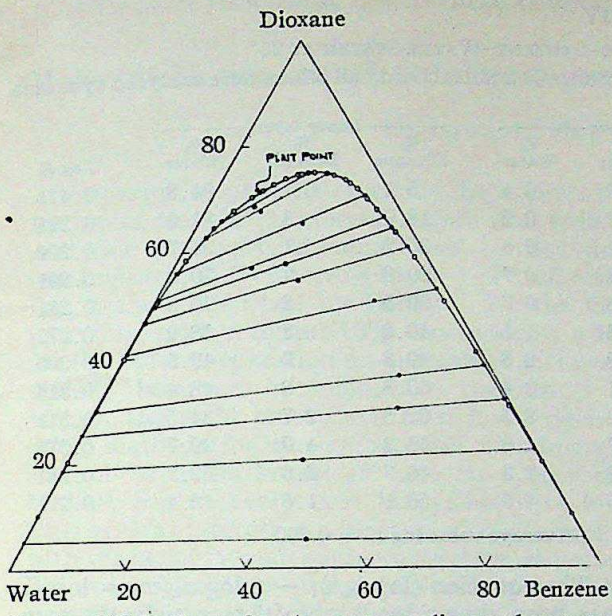

Fig. 1.—25° isotherm for the system: dioxane–benzene–water.

Analysis Data for the System.—Refractive indices and density data have been used for analytical purposes in the system. It was first necessary to consider refractive indices and densities for the binary systems. Hovorka, Shaefer and Dreisbach[4] have determined these data for the dioxane–water system, and Lynch[5] has extended the data on refractive index to lower concentrations for this system. Recently Teague and Felsing[6] have presented refractive index and density data for the dioxane–benzene system for a limited number of points. Accordingly, we have measured the refractive index and density of a number of benzene–dioxane mixtures. These data are included in Table II. All solutions were prepared by direct weighing in glass-stoppered flasks, and all measurements were made at 25°.

TABLE II

DENSITIES AND REFRACTIVE INDICES FOR THE BINARY SYSTEM DIOXANE–BENZENE AT 25°

% Dioxane	Density d^{25}_4	Refractive index, $n^{25}D$
0.00	0.8730	1.4978
10.83	.8877	1.4900
19.81	.9004	1.4837
29.83	.9147	1.4762
39.49	.9290	1.4685
50.19	.9452	1.4602
60.44	.9612	1.4530
69.19	.9752	1.4456
79.90	.9930	1.4370
84.20	1.0003	1.4324
90.92	1.0120	1.4270
100.00	1.0278	1.4197

(4) Hovorka, Schaefer and Dreisbach, THIS JOURNAL, **58**, 2264 (1936).
(5) Lynch, *J. Phys. Chem.*, **46**, 366 (1942).
(6) Teague and Felsing, THIS JOURNAL, **65**, 485 (1943).

For the ternary system all mixtures were prepared by direct weighing in glass-stoppered flasks, care being taken to keep in the miscible region, yet to cover the whole miscible area. The refractive index and density data at 25° for the ternary mixtures are given in Table III. From these

TABLE III

ANALYSIS DATA FOR THE SYSTEM DIOXANE–BENZENE–WATER AT 25°

% Dioxane	% Benzene	% Water	Density d^{25}_4	Refract. index $n^{25}D$
29.73	69.92	0.35	0.9151	1.4760
39.21	60.07	.73	.9297	1.4690
49.81	49.92	.77	.9458	1.4597
59.79	39.12	1.09	.9621	1.4511
68.37	30.45	1.18	.9761	1.4440
81.91	15.37	2.72	1.0019	1.4308
79.49	14.92	5.59	1.0041	1.4282
86.96	8.68	4.36	1.0145	1.4241
83.40	8.32	8.28	1.0168	1.4214
79.77	7.96	12.27	1.0189	1.4175
76.64	7.65	15.71	1.0204	1.4146
63.94	1.89	34.17	1.0332	1.3952
74.03	2.24	23.73	1.0320	1.4049
72.40	4.39	23.21	1.0277	1.4067
77.36	19.46	3.18	0.9953	1.4338
75.36	18.96	5.68	0.9972	1.4310
83.08	2.79	14.13	1.0289	1.4124
80.83	5.43	13.74	1.0239	1.4149
77.89	8.87	13.24	1.0174	1.4171
89.10	4.82	6.08	1.0220	1.4200
84.87	9.34	5.79	1.0138	1.4237
80.89	13.59	5.52	1.0064	1.4273
77.10	17.64	5.26	0.9993	1.4314
73.67	21.31	5.02	0.9928	1.4343

data the compositions of common refractive index and of common density were determined, and Fig. 2 shows the analysis diagram constructed therefrom.

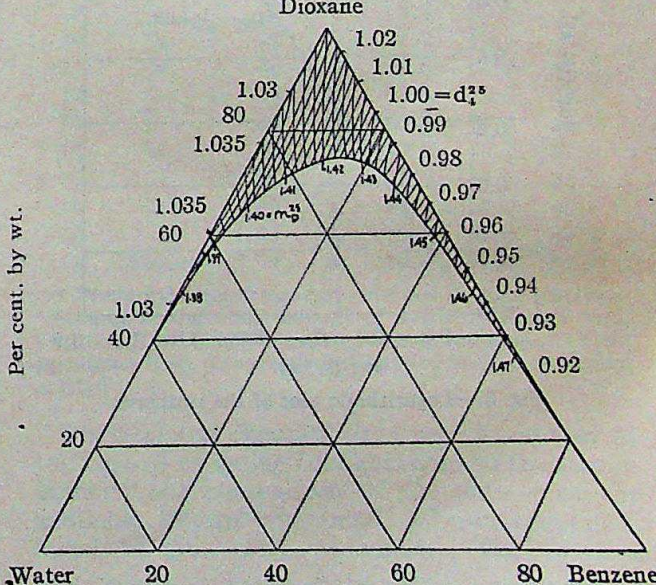

Fig. 2.—Analysis diagram for the system: dioxane–benzene–water at 25°.

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TABLE IV

DINERIC DISTRIBUTION IN THE DIOXANE–BENZENE–WATER SYSTEM AT 25°

Samples 7, 8, 9, 10 were analyzed by the titration method of Bancroft and Hubbard; all others were analyzed by means of the analysis diagram.

Sample number	Original mixture % Dioxane	Original mixture % Benzene	Original mixture % Water	Upper layer % Dioxane	Upper layer % Benzene	Upper layer % Water	Lower layer % Dioxane	Lower layer % Benzene	Lower layer % Water	Log K
1	5.13	47.69	47.18	5.2	94.7	0.1	5.1	0.1	94.8	0.415
2	20.47	39.52	40.01	22.5	77.3	0.2	18.9	.1	81.0	0.298
3	30.16	50.88	18.96	32.0	67.4	0.6	25.2	.1	74.7	0.299
4	36.16	47.93	15.91	38.5	60.8	0.7	29.8	.2	70.0	0.291
5	35.05	39.93	25.02	37.5	61.8	0.7	29.5	.2	70.3	0.281
6	50.53	37.06	12.41	53.0	45.5	1.5	40.8	.3	58.9	0.277
7	57.11	18.82	24.07	64.4	32.8	2.8	49.8	.7	49.5	0.290
8	55.23	14.39	30.37	66.5	30.1	3.4	50.8	.8	48.4	0.316
9	67.64	9.47	22.89	74.9	16.6	8.5	62.8	2.7	34.5	0.311
10	68.60	8.44	22.96	74.5	13.7	11.8	66.3	4.0	29.7	0.275
11	54.25	22.64	23.11	60.5	37.2	2.3	46.7	0.6	52.7	0.281
12	64.71	18.02	17.27	70.0	25.5	4.5	56.1	1.5	42.4	0.278

$\log K = \log (a_1/b_1) - 1.32 \log (a_2/w_2)$ Average value $\log K = 0.290$

Dineric Distribution for the System.—For determining the compositions of the conjugate phases, two methods were resorted to: (1) the titration method, which was given in detail by Bancroft and Hubbard[2] and (2) the use of the analysis diagram.

The distribution data for the system are given in Table IV, and the tie lines are plotted in Fig. 1.

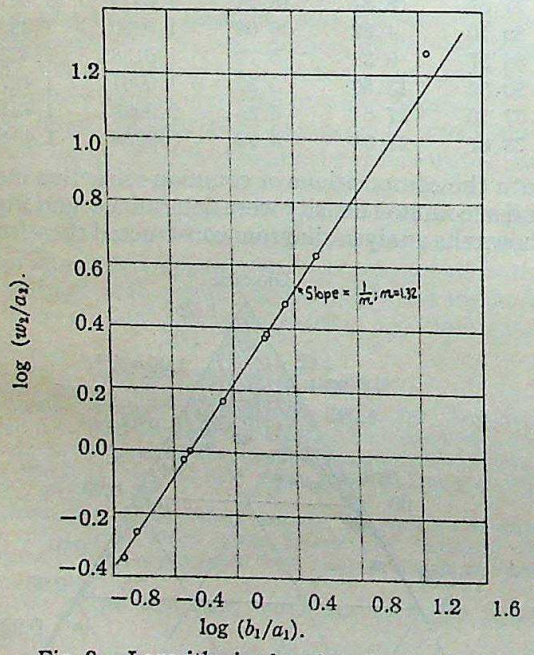

Fig. 3.—Logarithmic plot of the isotherm.

The equation ($\log a_1/b_1 - n \log a_2/w_2 = \log K$) has been shown by Bancroft[2] to satisfy the equilibrium distribution data for such a system. The value of n should be determined simply from the slope of the curve (straight line) in plotting ($\log b_1/a_1$) against ($\log w_2/a_2$), where a_1 and b_1 represent the percentage of dioxane and benzene, respectively, in the benzene-rich layer and a_2 and w_2, the percentage dioxane and water, respectively, in the water-rich layer. Such a plot of the above data is shown in Fig. 3, and the value of n obtained, 1.32. From the above relation employing this value of the slope, the distribution constants in Table IV were obtained. Except for the first value in the $\log K$ column, satisfactory distribution constants resulted. This first value is off, probably due to limitations in attaining equilibrium and in analysis. The plait point estimated from these data corresponds to 71% dioxane, 7.5% benzene, 21.7% water.

Summary

1. The 25° isotherm of the dioxane–benzene–water system has been presented.

2. Refractive index and density data at 25° for the dioxane–benzene and the ternary system dioxane–benzene–water has been given, as well as an analysis diagram for the miscible region of the ternary system.

3. Dineric distribution in the ternary system has been shown to satisfy the relation employed by Bancroft and Hubbard for several ternary liquid systems.

NEWARK, DELAWARE RECEIVED NOVEMBER 1, 1943

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[CONTRIBUTION FROM SHELL DEVELOPMENT COMPANY AND THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

Dehydrochlorination of 3-Chloro-2-propen-1-ol: Preparation of Propargyl Alcohol[1]

BY LEWIS F. HATCH AND ALLEN C. MOORE[2]

Propargyl alcohol has recently been prepared by interaction of paraformaldehyde and sodium acetylide in liquid ammonia[3] and by dehydrochlorination of 2-chloro-2-propen-1-ol[4] following the method described by Henry.[5] By the first procedure a yield of but 10% was reported while for the other preparation no percentage yield was stated; however, in analogy to the results of Henry, the yield must have been low. Several other methods for the preparation of propargyl alcohol[6] or of its homologs[7] also have been described, but in every case the yields were low. This evident interest in propargyl alcohol coupled with the lack of an adequate method for its preparation instigated the present investigation of the dehydrochlorination of *cis* and *trans* 3-chloro-2-propen-1-ol.

Of the possible starting materials, the isomeric *cis* and *trans* 3-chloro-2-propen-1-ols seemed the most promising for they should react in an analogous manner to the 2-bromo-2-propen-1-ol used by Henry to give propargyl alcohol. The isomeric chloroalcohols are easily prepared from the readily available corresponding dichlorides [*cis*- and *trans*-1,3-dichloropropene], by-products of the semi-commercial production of allyl chloride.[8] The 3-chloroalcohols have been reported,[9] but no note was taken of the presence of two isomeric forms, and the physical constants are unreliable.[10] As the geometric configuration of the isomers of both the 3-chloroalchohol and the dichloride has not as yet been definitely established, α- will be used to designate the lower boiling isomer and β- the higher boiling isomer in each case.

The β-isomer is less reactive than the α-, and, under the reaction conditions necessary for removal of hydrogen chloride, yields no propargyl alcohol. This is not surprising, since, under the conditions used (strong alkali at elevated temperatures), acetylenic alcohols are known to be decomposed.[11] The known decomposition products,[12] acetylene and sodium formate, were obtained from the reaction mixture.

When the sodium hydroxide concentration is greater than 10% there is also a certain amount of polymerization, yielding a polymer similar in properties to that obtained from acrolein under similar circumstances.[13] In view of the possible side reactions it would be anticipated that unreactive olefinic chloroalchols would give poor yields of acetylene derivatives. Since the α-3-chloroalcohol used in this work is more reactive than those hitherto employed, the reaction in this case proceeds satisfactorily and good yields are obtained.

TABLE I

DEHYDROCHLORINATION OF 3-CHLORO-2-PROPEN-1-OL

Run no.	Isomer	Moles of 3-chloro-alcohol	Time, hr.	NaOH, %	% Conversion from Cl^-	% Yield of propargyl alcohol
1	β	0.20	2	3.8	7.2	*a*
2	β	.25	2	12.0	12.8	*a*
3	β	.25	2	22.0	15.2	*a*
4	β	.25	2	29.3	20.2	*a*
5	β	.16	2	38.0	27.5	*a*
6	α	.20	0.5	9.0	36.0	*b*
7	α	.20	1	9.0	58.0	*b*
8	α	.20	3	9.0	72.5	*b*
9	α	.20	5	9.0	86.0	*b*
10	α	.20	2	3.2	52.5	*b*
11	α	.50	2	7.6	61.6	42.2
12	α	.50	2	12.6	70.6	65.1
13	α	.50	2	22.2	75.4	40.0
14	α	.50	2	29.2	79.2	37.8
15	α	.50	2	38.3	80.4	35.0
16	α	.50	3	12.4	76.0	65.8
17	α	1.00	3	12.5	81.0	69.3
18	Mixture	2.00	3	10.0	64.0	50.2[c]

[a] Propargyl alcohol was not obtained in these reactions. [b] Because of the small amount of α-3-chloroalcohol used, no attempt was made to isolate propargyl alcohol. [c] Yield calculated from 3-chloroalcohol applied instead of alcohol reacted.

Physical and chemical data were assembled in the hope of assigning configurations to the stereoisomers, but comparison of the data with the available known compound, 1-bromopropene-1, failed to give clear-cut results. The isomeric

(1) The process described in this paper for the production of propargyl alcohol is the subject of a patent application assigned to Shell Development Co., Emeryville, California.

(2) From the M.A. thesis of A. C. Moore, June, 1943. Present address: The Citadel, Charleston, S. C.

(3) Hennion and Murray, THIS JOURNAL, **64**, 1220 (1942).

(4) Pauling, Gordy and Saylor, *ibid.*, **64**, 1753 (1942).

(5) Henry, *Ber.*, **5**, 453, 569 (1872); **6**, 729 (1873).

(6) Paal and Heupel, *ibid.*, **24**, 3039 (1891).

(7) See Salkind and Teterin, *ibid.*, **66B**, 321 (1933); Guest, THIS JOURNAL, **47**, 860 (1925); Tchao yin Lai, *Bull. soc. chim.*, **53**, 682 (1933).

(8) Williams, *Trans. Am. Inst. Chem. Engrs.*, **37**, 157 (1941); *Chem. & Met. Eng.*, **47**, 834 (1940).

(9) van Romburgh, *Bull. soc. chim.*, [2] **36**, 555 (1881).

(10) van Romburgh[9] prepared the 3-chloro-2-propen-1-ol by hydrolyzing 1,3-dichloropropene. Apparently he used essentially pure high boiling (β) dichloride and carried out the hydrolysis under conditions (aqueous potassium hydroxide, refluxed for thirty hours) which would have dehydrochlorinated any low boiling (α) chloroalcohol present. He noted the formation of propargylic derivatives and obtained a chloroalcohol of b. p. 153°, d^{15} 1.162.

(11) Thompson and Margnetti, THIS JOURNAL, **64**, 573 (1942).

(12) Henry, *Ber.*, **8**, 398 (1875).

(13) Gilbert and Donleavy, THIS JOURNAL, **60**, 1911 (1938).

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pairs which have higher indices of refraction have lower densities (Table II). When the press of war commitments permits, further work will be done on the characterization of these compounds.

TABLE II

PHYSICAL PROPERTIES OF 3-CHLORO-2-PROPEN-1-OL, 1-BROMOPROPEN-1 AND PROPARGYL ALCOHOL

Constant	3-Chloro-2-propen-1-ol Alpha	3-Chloro-2-propen-1-ol Beta	1-Bromopropen-1[a] *cis*	1-Bromopropen-1[a] *trans*	Propargyl alcohol
B. p. °C.	146.3	153.6	57.8	63.25	112.9
B. p. Mm.	746	756			740
$d^{15.75}_4$			1.4338	1.4169	
d^{20}_4	1.1769	1.1729			0.9488
d^{25}_4	1.1720	1.1681			
d^{35}_4	1.1623	1.1582			
$n^{15.75}D$				1.4549	
$n^{16.2}D$			1.4564		
$n^{20}D$	1.4638	1.4664			1.4305
$n^{25}D$	1.4617	1.4641			
$n^{35}D$	1.4573	1.4600			
MR(calcd.)	21.98	21.98	23.35	23.35	15.58
MR(obsd.)	21.69	21.86	22.96	23.16	15.26

[a] From Freudenberg, "Stereochimie," Franz Deuticke, Wien, 1933, p. 751.

Acknowledgment

The portion of this research done at the University of Texas was financed in part by a grant from the University of Texas Research Institute, Project No. 76. The authors wish to express their appreciation.

Experimental

1,3-Dichloropropene.—In the semi-commercial distillation of crude allyl chloride, prepared by the chlorination of propylene, there remains an appreciable amount of higher boiling material which contains approximately 60% 1,3-dichloropropene and 30% 1,2-dichloropropane.[8] This crude material[13a] served as the source of 1,3-dichloropropene for this investigation. The unsaturated dichlorides were obtained by distillation through a 26 theoretical plate spiral column.[14] Fractions with a boiling range of 102.5–105.5° and 109.5–112.5° were taken and then refractionated to obtain constant boiling fractions at 104.3° and 112.0°. This careful separation was necessary because the isomeric dichlorides are more easily separated by fractionation than are the chloroalcohols.

α-1,3-Dichloropropene: 104.3°; d^{20}_4 1.224; $n^{20}D$ 1.4682; *MR* (calcd.) 25.32, (obsd.) 25.25.

β-1,3-Dichloropropene: 112.0°; d^{20}_4 1.217; $n^{20}D$ 1.4730; *MR* (calcd.) 25.32, (obsd.) 25.58.

3-Chloro-2-propen-1-ol.—Both α- and β-1,3-dichloropropene were hydrolyzed to the corresponding chloroalcohols by using a 10% excess of 10% sodium carbonate. The reaction mixture was refluxed two hours (reflux temperature: α-1,3-dichloropropene, 82.5–89°; β-1,3-dichloropropene, 86.0–93.5°), then extracted with diethyl ether, dried, and fractionated; yield, α = 81%; β = 76%. The physical data for the two chloroalcohols are given in Table II. Both isomers have a delayed vesicant action and care should be taken in handling them.

Anal. Calcd. for C_3H_5OCl: Cl, 38.32. Found: α-3-chloro-2-propen-1-ol, 38.22; β-3-chloro-2-propen-1-ol, 38.20.

Dehydrochlorination of β-3-Chloro-2-propen-1-ol.—The chloroalcohol was dehydrochlorinated by refluxing for two hours with a 10% excess of the desired concentration of sodium hydroxide. The reflux temperature varied from 102° for 3.8% sodium hydroxide to 117° for 38% sodium hydroxide. During this reflux period a gas was given off which did not condense at *ca.* −75°. The gas formed explosive salts of both copper and silver and was assumed to be acetylene. The extent of dehydrochlorination was determined by Cl^- titration (Volhard) and OH^- titration. In every case the moles of OH^- utilized by the reaction were greater than the moles of Cl^- produced, indicating a side reaction involving OH^-.

The remaining reaction mixture was made slightly acid with hydrochloric acid, filtered and extracted with diethyl ether. Only unreacted chloroalcohol was obtained. When the reaction mixture was acidified, a small amount of a light brown flocculent precipitate separated. This non-crystallizable solid was readily soluble in alkali and in concentrated sulfuric acid, ethyl alcohol and acetic acid but insoluble in benzene and only slightly soluble in water and diethyl ether. After the flocculent precipitate had been removed by filtration, the remaining solution was distilled to recover any unextracted propargyl alcohol as its water azeotrope (b. p. 97°). None was obtained. The presence of a small amount of formic acid, however, was indicated by the precipitation of manganese dioxide from dilute aqueous potassium permanganate and confirmed by crystals of sodium formate (melting at 253° (cor.)) which were obtained by evaporation of the basic solution.

The effect of sodium hydroxide concentration on the extent of dehydrochlorination is shown by runs 1–5 in Table I. Due to the unreactive nature of this isomer, no study was made of the effect of time on the extent of dehydrochlorination.

Dehydrochlorination of α-3-Chloro-2-propen-1-ol.—The method of dehydrochlorinating α-3-chloro-2-propen-1-ol was the same as that used for the β-isomer. Because the reactivity of α-3-chloro-2-propen-1-ol was considerably greater, not only was the effect of sodium hydroxide concentration studied (runs 10–15) but also the effect of time on the extent of dehydrochlorination was determined (runs 6–9). Data for these experiments are given in Table I.

The propargyl alcohol was recovered by distillation from the reaction mixture after acidification with hydrochloric acid. The water–alcohol azeotrope thus obtained contained in addition to propargyl alcohol any unreacted α-3-chloroalcohol. This azeotrope was saturated with potassium carbonate and extracted with diethyl ether; the ether extract was subsequently distilled through an efficient fractionating column to recover both propargyl alcohol and the unreacted α-3-chloro-2-propen-1-ol. The recovery of the propargyl alcohol from a dilute solution presents a difficult problem for there is only a 3° temperature differential between the boiling point of its water azeotrope and that of water. Continuous ether extraction is suggested as a useful alternative to the method used.

The yields of propargyl alcohol reported are calculated from the amount of 3-chloroalcohol converted (reacted) as indicated by chloride ion formation. The unconverted 3-chloroalcohol was in every case recovered nearly quantitatively and used in subsequent experiments for the production of propargyl alcohol.

Dehydrochlorination of a Mixture of α- and β-3-Chloro-2-propen-1-ol.[15]—An equimolar mixture of the two isomers of 3-chloro-2-propen-1-ol was dehydrochlorinated in a manner similar to that previously described. The only modification in technique was in the use of sodium chloride and isopropyl ether in recovering the alcohols from the water–alcohol azeotrope. The data for this experiment (run 18) are given in Table I. Because the unreacted 3-chloroalcohol consisted mainly of the unreactive β-isomer which could not be used in subsequent preparations of propargyl alcohol, the yield is calculated from the total chloroalcohol applied.

Summary

1. The two isomers of 3-chloro-2-propen-1-ol

(13a) Obtainable from Shell Development Co., Emeryville, California.

(14) Lecky and Ewell, *Ind. Eng. Chem., Anal. Ed.*, **12**, 544 (1940).

(15) This work was done by the senior author (L. F. H.) while in the employ of Shell Development Co., Emeryville, California.

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have been prepared and several physical constants have been determined.

2. The dehydrochlorination of the two isomers has been studied and the lower boiling isomer (α) is appreciably more reactive than the higher boiling isomer (β).

3. Propargyl alcohol has been prepared in good yields from the lower boiling isomer (α) and from a mixture of the two isomers.

4. It is impossible to assign definite geometrical structures to the two isomers from the data available.

AUSTIN, TEXAS RECEIVED AUGUST 9, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

The Preparation of Some Unsaturated Fatty Acid Chlorides[1]

BY THOMAS R. WOOD, F. L. JACKSON, A. R. BALDWIN AND H. E. LONGENECKER

A valuable approach to an understanding of the physical nature and physiological properties of natural fats is afforded by the synthesis of mixed triglycerides of known constitution.[2,3] As our attention turned to the important group of unsaturated triglycerides,[4,5,6] it became desirable to develop a satisfactory method for making unsaturated acyl chlorides of oleic, elaidic, linoleic and linolenic acids.

Attempts to prepare the unsaturated chlorides with thionyl chloride were unsatisfactory.[7] The use of oxalyl chloride had been suggested[8] for some saturated fatty acids and was found in this work to be distinctly preferable for the unsaturated acids.

The possibility of double bond rearrangement during the reaction and subsequent purification merits attention. We have considered the possible formation of conjugated systems, known to arise in polyene acids during alkali treatment or following oxidative changes.[9] No consideration has been given here to possible changes in geometric configuration during reaction. Evidence has been presented[10] for the existence of isomers of the *cis-trans* type in debromination linoleic and linolenic acids, such as were employed in the present study.

Conjugated diene, triene and tetraene linkages in preparations of linoleic and linolenic acids and their acid chlorides were estimated by comparison of the ultraviolet absorption of these compounds in appropriate spectral regions with that of pure 18-carbon conjugated polyene acids. We have employed standard absorption values compiled by Bradley and Richardson[11] for 9,11-(or 10,12)-linoleic, eleostearic and parinaric acids, whose molecular extinction coefficients (ϵ) are 33,600 (232 mμ), 46,700 (270 mμ), and 57,700 (320 mμ), respectively.

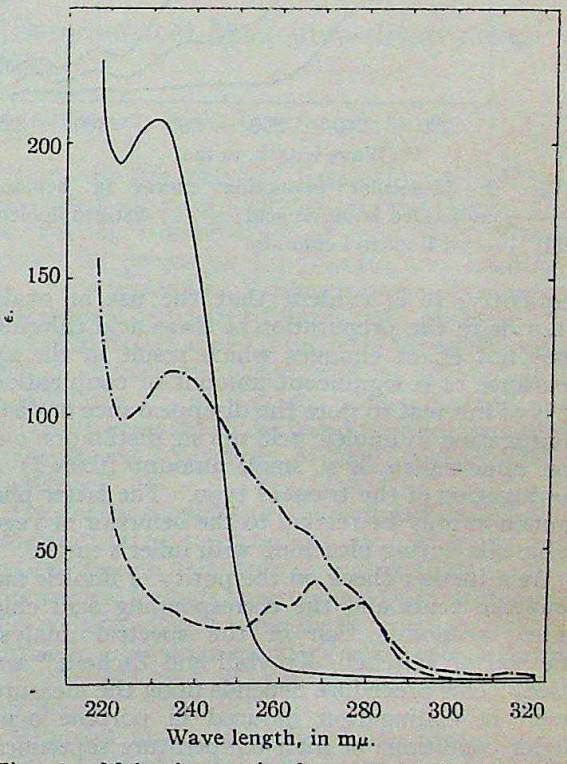

Fig. 1.—Molecular extinction curves in heptane: ———, undistilled linoleic acid; -------, distilled linoleic acid; ------, linoleyl chloride.

The ultraviolet absorption spectra of our linoleic acid and linoleyl chloride are plotted in Fig. 1, while Fig. 2 presents similar data for linolenic acid and linolenyl chloride. It is evident that conversion of the acids to the acid chlorides was in each instance accompanied by an increase in conjugation. In no case, however, was more than 1% of the total acid or acid chloride conjugated (Table II). Moreover, it has been our experience that any manipulation of these highly unsaturated compounds tends to introduce conjugation. Con-

(1) The authors are indebted to the Buhl Foundation for support of this investigation.

This paper was presented before the Division of Biological Chemistry of the American Chemical Society, Pittsburgh, September, 1943.

(2) Daubert and King, *Chem. Rev.*, **29**, 269 (1941).

(3) Daubert and Longenecker, *Oil and Soap*, in press.

(4) Jackson, Longenecker, Daubert and King, THIS JOURNAL, **66**, 289 (1944).

(5) Daubert, Fricke and Longenecker, *ibid.*, **65**, 2142 (1943).

(6) Daubert, Spiegl and Longenecker, *ibid.*, **65**, 2144 (1943).

(7) Jackson, F. L., Ph.D. Thesis, University of Pittsburgh, 1943.

(8) Adams and Ulich, THIS JOURNAL, **42**, 599 (1920).

(9) Mitchell and Kraybill, *ibid.*, **64**, 988 (1942).

(10) Mathews, Brode and Brown, *ibid.*, **63**, 1064 (1941).

(11) Bradley and Richardson, *Ind. Eng. Chem.*, **34**, 237 (1942).

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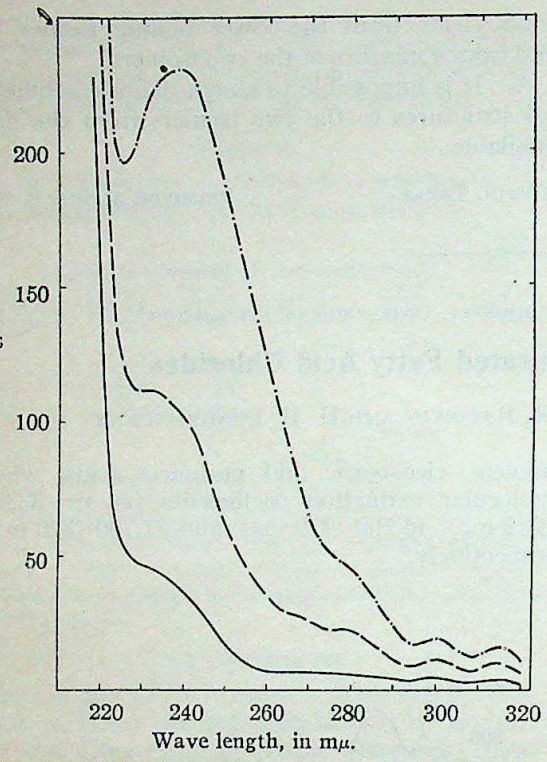

Fig. 2.—Molecular extinction curves in heptane: ———, undistilled linolenic acid; - - - - - -, distilled linolenic acid; ·····, linolenyl chloride.

sequently, it is evident that the use of oxalyl chloride in the preparation of these acid chlorides does not effect changes which result in the appearance of a significant amount of conjugation. It is of interest to note the disappearance of diene conjugation in linoleic acid during distillation and the appearance of a small amount (0.08%) of conjugation of the trienoid type. The latter phenomenon may be related to the behavior of vegetable oils during bleaching with fuller's earth.[9]

As a further check on the purity of linoleic and linolenic acids and the corresponding acid chlorides, a modification of the spectral analysis method of Mitchell, Kraybill and Zscheile[12] was used. This procedure depends upon the measurement of conjugation induced in polyene acids under conditions of high temperature saponification. Kass and Skell[13] postulated that this type of isomerization is effected by the removal of a proton from central active methylene groups in 1,4-diene systems with a final stabilization in conjugated linkages. In any case, it is unlikely that conjugation would be induced in 1,4- and 1,5-diene systems at equal rates. Since the molecular extinction coefficients at 232 and 270 mμ of the soaps derived from either acid and its corresponding acid chloride were identical within experimental error (Table II) it may be assumed that little or no "spreading" of the double bonds within the diene or triene systems takes place during the reaction of the acid with oxalyl chloride.

As previously indicated, migration of double bonds in the opposite direction with resultant conjugated configuration does not occur. Consideration of the remaining possibility of the formation of geometric isomers during acid chloride synthesis must await the preparation of linoleic and linolenic acids by the low-temperature crystallization technique.

(12) Mitchell, Kraybill and Zscheile, *Ind. Eng. Chem., Anal. Ed.*, **15**, 1 (1943).

(13) Kass and Skell, presented at the Detroit meeting of the American Chemical Society in April, 1943.

Experimental

Instrument and Methods.—All of the absorption data were obtained from measurements made with a Beckmann quartz spectrophotometer. Solutions of the acids and the acid chlorides were made in purified heptane. The absorption curves are plotted using the value of the molecular extinction coefficient on the ordinate and the wave length in mμ on the abscissa.

Molecular extinction coefficient (ϵ) = $\log_{10} I_0/I/cl$
I_0 = intensity of radiation transmitted by the solvent
I = intensity of radiation transmitted by the solution
c = concentration of solute in moles per liter
l = length in cm. of solution through which the light passes

Preparation of Highly Purified Fatty Acids.—Oleic acid was prepared by the crystallization technique of Brown and Shinowara,[14] and elaidic acid by the elaidinization of oleic acid according to the method of Lyutenberg.[15] Linoleic and linolenic acids were obtained by the debromination of tetrabromostearic acid (m. p. 115°, cor.) and hexabromostearic acid (m. p. 185°, cor.), respectively.

TABLE I

ANALYSES OF ACIDS

Acid	Iodine value (Wijs, 1 hr.) Calcd.	Found	$n^{40.0}D$	M. p.,[a] °C.
Oleic	89.9	89.7	1.4487	13.5
Elaidic	89.9	89.9	1.4468	44.5
Linoleic	181.0	182.0	1.4588	−6.5 to −6.0
Linolenic	273.5	273.1	1.4678	−15 to −14

[a] Filled capillaries were allowed to stand for twenty-four hours at −25° prior to observation of the melting point.

TABLE II

SPECTROPHOTOMETRIC ANALYSES OF LINOLEIC AND LINOLENIC ACIDS AND ACID CHLORIDES

	Conjugation,[a] % Diene	Triene	Tetraene	Molecular extinction coefficients of alkali-isomerized compounds (× 10^{-4}) at 232 mμ	at 270 mμ
Linoleic acid					
Undistilled	0.6	Trace	Trace	2 34	0.01
Distilled	< 0.08	0.08	< 0.003	2.35	0.01
Linoleyl chloride	.34	< .12	< .006	2.33	0.01
Linolenic acid					
Undistilled	< .13	< .015	.007		
Distilled	< .34	< .06	.018	1.55	1.29
Linolenyl chloride	.69	< .15	.029	1.54	1.25

[a] Calculated as per cent. of 18-carbon conjugated acid. Where no absorption peaks were observed, values are indicated as maximal.

(14) Brown and Shinowara, THIS JOURNAL, **59**, 6 (1937).

(15) Lyutenberg, *Fettchem. Umschau*, **42**, 89 (1935).

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The debrominations were carried out by the addition of zinc and hydrochloric acid to an ether solution of the bromides.[16] Analytical data for the above acids are presented in Table I.

Preparation of Fatty Acid Chlorides.—The acid chlorides of oleic, elaidic, linoleic and linolenic acids were prepared by the action of oxalyl chloride on the pure acids. As an example of the method, the preparation of linoleyl chloride is given.

Linoleic acid (16.5 g., 0.06 mole) was refluxed at 65 to 70° with 22.4 g. (0.18 mole) of oxalyl chloride (Eastman Kodak Company) for four hours in an all glass still. The excess oxalyl chloride was removed by warming the mixture to 100° *in vacuo*. The acid chloride was distilled under 2 to 3 mm. pressure. The yield was 14.5 g. (82% of the calculated amount) of water-white linoleyl chloride.

Anal. Calcd. for linoleyl chloride, $C_{18}H_{31}OCl$: Cl, 11.87. Found: Cl, 11.68, 11.77.

For the other acid chlorides:

Anal. Calcd. for oleyl chloride, $C_{18}H_{33}OCl$: Cl, 11.78. Found: Cl, 11.68, 11.68.

Anal. Calcd. for elaidyl chloride, $C_{18}H_{33}OCl$: Cl, 11.78. Found: Cl, 11.73, 11.83.

Anal. Calcd. for linolenyl chloride, $C_{18}H_{29}OCl$: Cl, 11.95. Found: Cl, 11.86, 12.08.

(16) Frankel and Brown, THIS JOURNAL, **65**, 415 (1943).

Summary

The preparation of oleyl, elaidyl, linoleyl, and linolenyl chlorides has been successfully accomplished through the use of oxalyl chloride.

Linoleic and linolenic acids and the corresponding chlorides were examined spectrophotometrically, and the results demonstrate that the reaction of the acids with oxalyl chloride was not accompanied by rearrangements of the double bonds to produce conjugated systems.

PITTSBURGH, PA. RECEIVED OCTOBER 29, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Unsaturated Synthetic Glycerides. IV. Symmetrical Monoöleo-disaturated Triglycerides[1]

BY F. L. JACKSON, B. F. DAUBERT, C. G. KING AND H. E. LONGENECKER

In other papers[2,3] of this series it was shown that methods available for the synthesis of unsymmetrical mixed triglycerides containing saturated acids were suitable, with little modification, for the preparation of 1-oleyl-2,3-disaturated triglycerides and 1-acyl-2,3-dioleins. This investigation likewise shows that methods suitable for the preparation of symmetrical mixed triglycerides containing saturated fatty acids can be adapted to the synthesis of those containing unsaturated acids. However, the reaction between the symmetrical diglyceride and the unsaturated acyl chloride cannot be completed under less rigorous conditions than refluxing for several hours on a steam-bath.[3] Amberger and Bromig[4] attempted to prepare 2-oleyl-1,3-distearin by treating 1,3-distearin with oleyl chloride in quinoline and pyridine solution at room temperature for several days. Their results were unsatisfactory as they succeeded only in isolating the original diglyceride. It has been our experience that good yields of unsaturated triglycerides may be obtained, in general, only when the acylation of the 1-mono- or 1,3-diglyceride with an unsaturated acyl chloride is carried out at 70 to 85° for three to six hours.

Although the methods of Fischer[5] and Verkade and associates[6,7,8] both were used in this work to prepare the symmetrical diglycerides which later were used as intermediates, it was found that the use of 1-monotrityl glycerol was unsatisfactory for preparing 1,3-dilaurin and 1,3-dicaprin. Poor yields of 1,3-dilaurin were obtained on hydrolysis of 1-trityl-2,3-dilauryl glycerol and successful isolation of 1,3-dicaprin was not accomplished. Hydrolytic cleavage of the low molecular weight fatty acids no doubt occurred simultaneously with removal of the trityl (triphenylmethyl) group during hydrolysis of the 1,2-diacyl-3-tritylglycerol.

The melting points of the symmetrical monoöleo-disaturated triglycerides are, with one exception, two to five degrees higher than the unsymmetrical isomers reported in a previous paper.[2] The melting points were determined on melted samples contained in capillary tubes cooled slowly to −20° and held at −20° for at least twenty-four hours.

Although measurable differences in refractive indices were obtained when compared with the unsymmetrical isomers, no definite conclusions can be drawn concerning this particular physical property.

Experimental

Preparation of Intermediates.—All saturated fatty acids and the corresponding acyl chlorides, oleic acid and oleyl chloride were prepared by the methods given in the first paper of this series.[2]

Two symmetrical diglycerides, 1,3-dipalmitin (m. p. 72.5°) and 1,3-dicaprin (m. p. 45.5°) were prepared using 1-iodohydrin (Alival) as the intermediate by the method described by Fischer.[5] 1-Monotritylglycerol, prepared as described by Verkade and Meerburg,[7] was used for the synthesis of 1,3-distearin (m. p. 79.5°), 1,3-dimyristin (m. p. 64.7°) and 1,3-dilaurin (m .p. 58°). The method is given in detail for 1,3-distearin.

(1) The authors are indebted to the Buhl Foundation for a grant in support of this investigation.

(2) Daubert, Fricke and Longenecker, THIS JOURNAL, **65**, 2142 (1943).

(3) Daubert, Spiegl and Longenecker, *ibid.*, **65**, 2144 (1943).

(4) Amberger and Bromig, *Biochem. Z.*, **130**, 252 (1922).

(5) Fischer, Bergmann and Barwind, *Ber.*, **53**, 1589 (1920).

(6) Verkade, van der Lee, de Quant and Zuydewijn, *Proc. Acad. Sci., Amsterdam*, **40**, 580 (1937).

(7) Verkade and Meerburg, *Rec. trav. chim.*, **54**, 716 (1935).

(8) Verkade and van der Lee, *ibid.*, **55**, 267 (1936).

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TABLE I

SYMMETRICAL MONOÖLEO-DISATURATED TRIGLYCERIDES AND THEIR HYDROGENATED PRODUCTS

Acyl radical	2-Oleyl-1,3-diacyl glycerides: Molecular weight Calcd.	Found	Iodine value Calcd.	Found	Melting point, °C.	$n^{45.0}D$	2-Stearyl-1,3-diacyl glycerides Melting point, °C. Reported	Found
Capryl	665	654 ± 1	38.2	38.0	5 to 6	1.45018[a]	44.5[a]	45.0
Lauryl	721	728 ± 1	35.2	35.1	14.5 to 15	1.45164	50.9[b]	51.5
Myristyl	777	792 ± 2	32.7	32.7	26 to 27	1.45244	55.5[a]	56.0
Palmityl	833	819 ± 2	30.5	30.6	35.5 to 36	1.45347	68.0[c]	68.0
Stearyl	889	890 ± 3	28.5	28.7	42.5 to 43	1.45417	71.5[d]	71.5

[a] Malkin and Meara, *J. Chem. Soc.*, 1141 (1939). [b] Averill, Roche and King, THIS JOURNAL, 51, 866 (1929). [c] Malkin and Meara, *J. Chem. Soc.*, 103 (1939). [d] Clarkson and Malkin, *ibid.*, 666 (1934). [e] Average $dn/dt = 0.00038$.

1-Monotrityl glycerol (8.0 g.) was dissolved in a mixture of 25 ml. of chloroform and 13 g. of pyridine. While cooling the solution in an ice-bath, 19 g. of stearyl chloride was added slowly. After standing for four days at room temperature, the mixture was dissolved in ether and the solution was washed successively with water, 0.5 *N* sulfuric acid, 5% potassium carbonate solution and again with water. After drying over anhydrous sodium sulfate and distilling the ether from the filtered liquid, a pale yellow, viscid liquid remained. The liquid solidified slowly on standing at room temperature. The product was dissolved in 400 ml. of petroleum ether and cooled to 0°. Dry hydrogen chloride was passed into the solution for thirty minutes, during which time the diglyceride separated as a white solid. The mixture was allowed to stand at room temperature for one hour. After the addition of sufficient ether to effect solution, it was washed successively with 5% potassium carbonate solution and water. The solution was dried over anhydrous sodium sulfate, filtered, and evaporated to dryness. The 1,3-distearin was crystallized repeatedly from 95% alcohol; yield, 12 g. (80%); m. p. 79.5°.

Preparation of 2-Oleyl-1,3-dilaurin.—Oleyl chloride (3.6 g.) was added slowly to a solution of 1,3-dilaurin (5 g. in 13 g. of chloroform and 5 g. of quinoline) in a glass-stoppered flask. After refluxing for three hours on a steam-bath, the reaction mixture was allowed to stand overnight. It was then dissolved in petroleum ether and washed successively with 0.5 *N* sulfuric acid, 10% potassium carbonate solution and water. After drying over anhydrous sodium sulfate, the solution was filtered and evaporated to dryness under reduced pressure. The yellow liquid remaining was dissolved in ethyl ether and refluxed with activated charcoal for twenty minutes. After filtration the ether was removed from the filtrate and the colorless liquid remaining was redissolved in petroleum ether. Several crops of crystals were obtained as the solution was progressively cooled to −30°. The iodine values of the successive crops of crystals were 34.8, 35.0 and 35.2, respectively (calcd. for 2-oleyl-1,3-dilaurin, 35.2). The iodine value of the residue recovered from the mother liquor was 42.9. The two fractions having iodine values of 35.0 and 35.2 were combined and recrystallized several times from petroleum ether; yield, 6 g. (75%).

Anal. Calcd. for $C_{45}H_{84}O_6$: C, 74.95; H, 11.74. Found: C, 74.81, 74.78; H, 11.69, 11.60.

The physical and chemical constants for 2-oleyl-1,3-distearin, 2-oleyl-1,3-dipalmitin, 2-oleyl-1,3-dimyristin, and 2-oleyl-1,3-dicaprin, prepared in a similar manner, are given in Table I.

Proof of Structure.—Hydrogenation of the symmetrical monoöleo-disaturated triglycerides to the corresponding saturated analogs gave added support to the symmetrical structure (Table I). The hydrogenation procedure was similar to that described previously.[2,3]

Summary

2-Oleyl-1,3-dicaprin, -dilaurin, -dimyristin, -dipalmitin and -distearin have been prepared in high purity, their structure demonstrated by hydrogenation, and their melting points and refractive indices measured. These properties both increase numerically with increasing length of the carbon chain of the saturated fatty acids.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Unsaturated Synthetic Glycerides. V. Unsymmetrical Monoelaidyl-Disaturated and Monosaturated-Dielaidyl Triglycerides[1]

BY B. F. DAUBERT

The evident need of obtaining physical and chemical data on synthetic mixed triglycerides containing unsaturated acids for the purpose of characterizing more adequately those glycerides present as components in natural fats has been discussed recently in previous communications of this series.[2,3]

Elaidic acid, the *trans* isomer of oleic acid, does not occur free or combined in glycerides of natural fats so far as the author is aware. Notwithstanding this fact, however, the physical and chemical properties of this group of glycerides are of considerable interest for the purpose of comparison with the corresponding synthetic oleyl- and stearyl-glycerides.

It is well known that the melting point of a fat may be increased considerably through the process of elaidinization. The melting point data for the synthetic glycerides reported in this paper give ample verification to this observation.

Therefore, physical and chemical data are reported for a series of unsymmetrical monoelaidyl-

(1) The author is indebted to the Buhl Foundation for a grant in support of this investigation.

(2) Daubert, Fricke and Longenecker, THIS JOURNAL, 65, 2142 (1943).

(3) Daubert and Longenecker, *Oil and Soap*, in press.

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TABLE I

Acyl radical	Molecular weight[a] Calcd.	Found	Iodine value[b] Calcd.	Found	M. p.,[c] °C.	$n^{45.9}D$	M. p. of 1-stearyl-2,3 diacyl glycerol, °C.
			1-Elaidyl-2,3-diacyl Glycerols				
Myristyl	777.24	772 ± 8	32.7	32.8	39.5	1.45136	56.0
Lauryl	721.13	719 ± 6	35.2	35.0	27.0	1.45023	45.5
Capryl	665.03	658 ± 6	38.1	37.8	15.0	1.44895	41.0
Caprylyl	608.91	601 ± 9	41.7	41.4	3.0	1.44786	32.0[d]
			1-Acyl-2,3-dielaidins				
							1-Acyl-2,3-distearin
Myristyl	831.31	821 ± 8	61.1	60.8	40.0	1.45619	62.5
Lauryl	803.25	796 ± 6	63.2	63.0	35.5	1.45507	54.0
Capryl	775.20	770 ± 3	65.5	65.1	25.0	1.45391	49.0

[a] Molecular weights determined by the method of Menzies and Wright,[10] as modified by Hanson and Bowman.[11] [b] Iodine values (Wijs) are averages of triplicates differing by not more than 0.1 unit. [c] Melting points were determined by the capillary tube method. Fused samples were cooled to −20° and held at −20° for at least twenty-four hours. [d] 1-Stearyl-2,3-dicaprylin was also prepared from 1-monostearin and caprylyl chloride; m. p. 31.5°; molecular weight, 603 ± 6 (calcd. 610.93); *anal.* calcd. for $C_{37}H_{70}O_6$: C, 72.73; H, 11.55. Found: C, 72.56, 72.62; H, 11.36. 11.42.

disaturated and monosaturated-dielaidyl triglycerides.

Experimental

All saturated fatty acids used in this investigation were prepared as described in the first paper of this series.[2]

Elaidic acid was prepared by the method of Lyutenberg[4] using a highly purified oleic acid. Final crystallization of the acid from ethyl ether yielded a product melting at 44.5°. Saponification equivalent, 282.1 (calcd. 282.2); iodine value (Wijs), 89.8 (calcd. 89.9); refractive index at 50.0°, 1.44682.

Preparation of Elaidyl Chloride.—In a previous communication[5] from this Laboratory it was indicated that oxalyl chloride serves as a satisfactory acylating agent for elaidic acid.

Elaidic acid (38 g.) in a round-bottom flask was treated with oxalyl chloride (38 g.) and the mixture warmed at a bath temperature of 70–80°. After one-half hour the vigorous reaction ceased, but the reaction mixture was refluxed for an additional three hours at 70–80°. Excess oxalyl chloride was removed by distillation at a bath temperature of 100°. The elaidyl chloride was then rapidly distilled at 168–170° under reduced pressure (1 mm.). The distillation yielded 27 g. (91%) of a water-white product.

Anal. Calcd. for $C_{18}H_{33}OCl$: Cl, 11.78. Found: Cl, 11.68, 11.68.

All saturated fatty acid chlorides were prepared with thionyl chloride after the method described by McMasters and Ahmann.[6]

Preparation of 1-Monoelaidin.—Elaidyl chloride (21 g.) was added slowly to a mixture of acetone-glycerol[7] (8 g.), quinoline (15 ml.) and chloroform (20 ml.). The mixture after standing at room temperature twenty-four hours was dissolved in ethyl ether (300 ml.) and the solution washed successively with cold 0.5 *N* sulfuric acid, 5% potassium carbonate solution and distilled water. After drying the ether solution over anhydrous sodium sulfate, it was reduced, *in vacuo*, to a volume of 50 ml. Concentrated hydrochloric acid (100 ml.) was added with constant stirring to the solution, cooled in an ice-bath. After standing one-half hour, ice-water (400 ml.) was added and the flocculent white precipitate which separated was washed repeatedly with ice water until free of mineral acid. The product, after solution in ethyl ether, was dried over anhydrous sodium sulfate. On cooling the filtered liquid to 5° for twenty-four hours crystallization occurred. A constant melting point of 58.5° was obtained after crystallization from a 1:1 mixture of ether and petroleum ether. Molecular weight, 354 ± 2 (calcd. 356.23); iodine value, 71.0 (calcd. 71.2).

The 1-monoglyceride of elaidic acid was also prepared by a slight modification of the method of Malkin and Shurbagy.[7]

Dry hydrogen chloride was passed into a mixture of elaidic acid (7 g.) and acetone-glycerol (15 g.) until the mixture liquefied (about 20 minutes). The mixture was diluted to a total volume of 50 ml. with ethyl ether and treated with concentrated hydrochloric acid (50 ml.). The precipitated product was crystallized from a 1:1 mixture of ethyl ether and petroleum ether as described under the preceding method; m. p. 58.5°. Mixed with the 1-monoelaidin prepared above, no melting point depression was observed.

For further identification each compound prepared by the two independent methods was hydrogenated to 1-monostearin, m. p. 81.5°. Mixed melting points with a 1-monostearin prepared from acetone-glycerol and stearyl chloride[8] showed no depression. Preliminary X-ray investigations show the 1-monoelaidin to have a diffraction pattern typical of all 1-monoglycerides examined to date.[9]

Preparation of 1-Elaidyl-2,3-dimyristin.—1-Monoelaidin (2 g.) was dissolved in a mixture of quinoline (10 ml.) and chloroform (10 ml.) and to this solution myristyl chloride (2.8 g.) was added slowly. The mixture was refluxed on a steam-bath for four hours. After the addition of ethyl ether (200 ml.), the solution was washed successively with cold 0.5 *N* sulfuric acid, 5% potassium carbonate solution, distilled water and dried over anhydrous sodium sulfate. The solution was filtered and the ether removed by distillation under reduced pressure. Fractional crystallizations from mixtures of ether and petroleum ether, and ether and 95% alcohol, yielded a product melting at 39.5°.

Anal. Calcd. for $C_{49}H_{92}O_6$: C, 75.72; H, 11.93. Found: C, 75.49, 75.61; H, 11.84, 11.79.

Other analytical constants together with the melting points of the saturated analogs obtained by a hydrogenation procedure described in a previous paper,[2] for this compound and 1-elaidyl-2,3-dilaurin, 1-elaidyl-2,3-dicaprin, 1-elaidyl-2,3-dicaprylin are listed in Table I.

Preparation of 1-Myristyl-2,3-dielaidin.—To a solution of 1-monomyristin (3.5 g.) in a mixture of quinoline (5 ml.) and chloroform (10 ml.), elaidyl chloride (8.5 g.) was added slowly. The mixture, after refluxing on a steam-bath for four hours, was dissolved in petroleum ether (200 ml.) and the solution washed successively with 0.5 *N* sulfuric acid, 5% potassium carbonate solution and distilled water. The solution was then dried over anhydrous

(4) Lyutenberg, *Fettchem. Umschau.*, **42**, 89 (1935).
(5) Wood, Jackson, Baldwin and Longenecker, THIS JOURNAL, **66**, 287 (1944).
(6) McMasters and Ahmann, *ibid.*, **50**, 147 (1928).
(7) Malkin and Shurbagy, *J. Chem. Soc.*, 1628 (1936).
(8) Fischer, *Ber.*, **53**, 1621 (1920).
(9) Unpublished results.
(10) Menzies and Wright, THIS JOURNAL, **43**, 2309, 2314 (1921).
(11) Hanson and Bowman, *Ind. Eng. Chem., Anal. Ed.*, **11**, 440 (1939).

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sodium sulfate and filtered. Crystallization occurred on cooling the solution to −20° overnight. Repeated fractional crystallizations from petroleum ether and finally 95% alcohol gave a product melting at 40.0°.

Other analytical constants and melting points of the saturated analogs obtained by hydrogenation for this compound and for 1-lauryl-2,3-dielaidin, and 1-capryl-2,3-dielaidin are also given in Table I.

Discussion

Bömer and Kappeller[12] reported a melting point of 44.8° for the 1-monoelaidin they prepared from elaidyl chloride and acetone-glycerol. Unfortunately, these investigators did not report the method by which they determined the melting point nor did they report other physical and chemical constants for the compound. Preliminary warming and cooling curves have established the existence of at least three forms for 1-monoelaidin. Form I melts at 58.5°, Form II at 44.0° and Form III at 17.6°. The melting point reported by Bömer is in good agreement with the melting point of Form II. This suggests, perhaps, that the melting point (44.8°) of the 1-monoelaidin prepared by these investigators was not that of the stable phase.

The mixed triglycerides, 1-elaidyl-2,3-distearin (m. p. 61.0°), and 1-elaidyl-2,3-dipalmitin (m. p. 51.0°) prepared from 1-monoelaidin were in good agreement with those previously reported by Bömer and Kappeller, as also were 1-stearyl-2,3-dielaidin (m. p. 49.5°) and 1-palmityl-2,3-dielaidin (m. p. 46.0°).

It will be observed from the data in Table I that the melting points of the 1-elaidyl-2,3-disaturated triglycerides are, on the average, approximately 20° lower than their fully saturated analogs, and, on the average, approximately 15° higher than the same triglycerides containing an oleyl in place of the elaidyl group. Data for the latter have been reported in a previous paper.[2] Thus, the melting point relationships show the mixed triglycerides containing one elaidyl group to be intermediate between those containing one oleyl group and one stearyl group, respectively, the other saturated acids in the molecule, of course, being the same.

The above relationship also holds true for the series of unsymmetrical monosaturated-dielaidins, except that the magnitude of difference in average melting point is larger between those glycerides containing two elaidyl and those containing two oleyl groups. The average difference in melting point is about 30°.

It may also be observed, in comparing the melting point data of the two series of triglycerides (Table I) that the double bond in the single elaidyl group has the greater influence on the melting point, particularly in lower members of the series. The converse seems to be true for the monosaturated-dielaidins, *i.e.*, the chain length of the elaidyl groups has the greater influence on the melting point.

The refractive indices of the new monoelaidyl-disaturated triglycerides and the monosaturated-dielaidins are measurably lower than the corresponding synthetic mixed triglycerides containing oleic acid. The change in refractive index with change in temperature ($dn/dt = 0.00038$) is approximately the same as that reported previously for other series.

Molecular weights and iodine values were used as criteria for purity in preference to combustion data. The carbon and hydrogen values, however, were determined for one compound as proof against errors or confusion.

Summary

Physical and chemical data are reported for seven new unsaturated synthetic glycerides, 1-elaidyl-2,3-dimyristin, 1-elaidyl-2,3-dilaurin, 1-elaidyl-2,3-dicaprin, 1-elaidyl-2,3-dicaprylin, 1-myristyl-2,3-dielaidin, 1-lauryl-2,3-dielaidin and 1-capryl-2,3-dielaidin.

Data are also reported for 1-stearyl-2,3-dicaprylin.

PITTSBURGH, PA. RECEIVED NOVEMBER 13, 1943

(12) Bömer and Kappeller, *Fette und Seifen*, **44**, 340 (1937).

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[CONTRIBUTION FROM THE U. S. DEPARTMENT OF INTERIOR, BUREAU OF MINES, PACIFIC EXPERIMENT STATION, UNIV. OF CALIFORNIA]

Specific Heats at Low Temperatures of Calcium Sulfite, Sodium Sulfite, and Manganese Dithionate Dihydrate[1]

BY K. K. KELLEY[2] AND G. E. MOORE[3]

As part of its program of supplying fundamental thermochemical data for substances of metallurgical interest, the Bureau of Mines has reported previously on the low-temperature specific heats and entropies of manganese[4] and eleven of its inorganic compounds.[4,5] The present paper adds another compound to this list, the dithionate-dihydrate, and also presents similar data for calcium and sodium sulfites, as these substances are of interest in connection with certain hydrometallurgical methods of extracting manganese.

This work represents the first measurements of low-temperature specific heats of any members of the two classes of substances concerned—sulfites and dithionates—and is of some interest from this viewpoint alone.

Materials

Calcium sulfite was prepared from C. P. calcium carbonate, low in alkali. The fine carbonate was suspended in a flask of water, previously boiled to remove air, and allowed to react with a rapid stream of sulfur dioxide at 80° in a system protected from contact with air. The reaction was continued until virtually all the carbonate was decomposed, as shown by intermittent tests. (The carbonate test consisted of removing a sample from the flask, acidifying with strong acid, and leading the evolved gas slowly through a concentrated iodine–potassium iodide solution to remove sulfur dioxide and then through barium hydroxide solution to detect carbon dioxide.) When the reaction was considered complete, the temperature was raised and the flask boiled dry while the sulfur dioxide stream was continued. At this point the product gave no test for sulfate. It was transferred to a high-vacuum system and heated five hours at 155°, after which a direct test for water gave 7.1%. (Röhrig's[6] claim that calcium sulfite may be dehydrated to hemihydrate at 80° and to the anhydrous salt at 100° is incorrect.) Heating was continued several hours longer at temperatures up to 245°, with but little additional removal of water. At about 275° water removal again commenced, and the temperature was raised slowly to 310° and held for two hours until evolution of water stopped. At this point 0.5% water remained in the material, and it was still free of sulfate. Seven hours of heating and pumping at 390–400° was finally required before the water content was reduced to a negligible quantity. During the latter process some sulfate was formed and some sulfite decomposed. Analyses were made for CaO, $SO_4^=$, CO_2, and H_2O. The results corresponded to 98.75% calcium sulfite, 0.9% calcium sulfate, 0.24% calcium oxide, 0.07% calcium carbonate, and 0.02% water, and it was felt that this product was about as good as could be obtained in any reasonable time. A 117.96-g. sample was used in the measurements.

Reagent-grade anhydrous sodium sulfite was used without further purification. Analyses gave 98.8% sodium sulfite and 0.90% sodium sulfate. It required 158.82 g. to fill the calorimeter.

Manganese dithionate is difficult to prepare in pure form, and after some preliminary experiments the following procedure was adopted. A suspension of reagent-grade manganese dioxide in a flask of water was cooled with ice–salt mixture and sulfur dioxide passed from a cylinder until reaction was complete. The sulfur dioxide flow was maintained slow enough to prevent the temperature in the flask from rising above 7°. The solution, containing mainly manganese dithionate but also some manganous sulfate, was filtered, diluted with water and treated with enough barium hydroxide solution to precipitate the sulfate and all the manganese. After filtering, the solution contained mainly barium dithionate, of which a fraction was crystallized out after low-temperature evaporation. The crystalline barium dithionate then was filtered off, redissolved in water, and titrated with reagent-grade manganous sulfate to precipitate barium sulfate and leave manganese dithionate in solution. This final solution was evaporated slowly under vacuum at 35° until a satisfactory yield of hydrated crystalline manganese dithionate was obtained. It was originally intended to dry these crystals to anhydrous form, but this was found to be impossible without considerable sacrifice of purity, because of the instability of manganese dithionate with respect to manganous sulfate and sulfur dioxide. Prolonged drying, for several weeks, at 35° in a warmed desiccator, first over concentrated sulfuric acid and then over phosphorus pentoxide, and finally under 10^{-4} mm. pressure at 45° for several hours, resulted in a sample of manganese dithionate-dihydrate that had decomposed only slightly. Under these conditions, dehydration ceased at the dihydrate point. Experiments on further dehydration at higher temperatures (up to 100°) resulted in too much decomposition. The product used in the measurements was analyzed and found to contain 99.0% $MnS_2O_6 \cdot 2H_2O$, 0.58% BaS_2O_6, and 0.42% $MnSO_4$. In computing the analytical results it was assumed that all $SO_4^=$ was present as manganous sulfate from decomposition of manganese dithionate, as the latter is much less stable than barium dithionate. The odor of sulfur dioxide was detectable over the preparation after standing in a sealed container, but the decomposition at room temperature is quite slow. This was shown by analyses for sulfate made before and after the specific heat measurements, which indicated no significant change. The specific heat measurements were made using a 123.18-g. sample.[7]

Measurements

The method and apparatus[8] used previously again were employed. The results of the specific heat measurements are listed in Table I and shown plotted against temperature in Fig. 1. The defined calorie (1 calorie = 4.1833 int. joules) is used throughout, and the molecular weight values in the headings of Table I are in accord with the 1941 international atomic weights. The calcium sulfite data have been corrected for the impurities previously listed, assuming the specific heats to be additive. The cor-

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(2) Acting Supervising Engineer, Pacific Experiment Station, Bureau of Mines.

(3) Formerly Physical Chemist, Pacific Experiment Station, Bureau of Mines.

(4) Kelley, THIS JOURNAL, 61, 203 (1939).

(5) (a) Millar, *ibid.*, 50, 1875 (1928); (b) Anderson, *ibid.*, 53, 476 (1931); (c) Anderson, *ibid.*, 56, 849 (1934); (d) Kelley, *ibid.*, 63, 2750 (1941); (e) Moore and Kelley, *ibid.*, 64, 2949 (1942); (f) Kelley and Moore, *ibid.*, 65, 782 (1943); (g) Kelley and Moore, *ibid.*, 65, 1264 (1943); (h) Kelley, Bureau of Mines Bulletin 434, 1941, 115 pp.

(6) Röhrig, *J. prakt. Chem.*, 37, 232 (1888).

(7) The authors wish to acknowledge the assistance of Mr. A. R. Fox, formerly Assistant Chemist, Bureau of Mines, who carried the preparation of this product up to the final dehydration stage.

(8) Kelley, THIS JOURNAL, 63, 1137 (1941).

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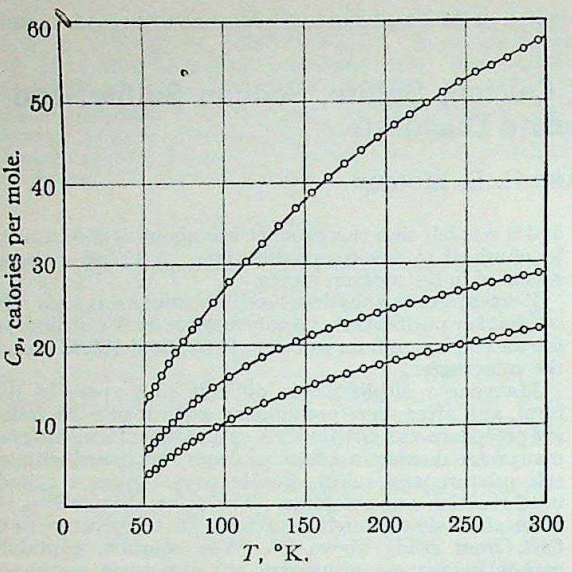

Fig. 1.—Specific heats of $CaSO_3$, Na_2SO_3, and $MnS_2O_6 \cdot 2H_2O$: upper curve, $MnS_2O_6 \cdot 2H_2O$; middle curve, Na_2SO_3; lower curve, $CaSO_3$.

rection amounted to 0.00 to 0.14%, depending on the temperature. Likewise, the sodium sulfite results were corrected for the 0.9% sodium sulfate content. In this instance, the correction varied from 0.07 to 0.16%. The impurity correction of the manganese dithionate-dihydrate data was the largest, on the average, of the three substances under consideration, 0.04 to 0.39%, depending on the temperature.

The two sulfites were measured in our best calorimeter, while the dithionate was measured in an older one that had been in use previously. This was considered advisable because of the possibility of the decomposition pressure of the dithionate reaching a value that would burst the container. This appears theoretically possible, according to available thermochemical data, but it did not occur because of the slowness of decomposition. It is believed that the measurements of calcium and sodium sulfites are accurate on the average to within 0.3% and those of the manganese dithionate-dihydrate to within 0.5%, the difference being attributable to the use of the older calorimeter for the last substance. The average deviation of the results from a smooth curve is considerably smaller than the error claimed, being less than 0.1%.

As is seen from Fig. 1, no abnormal behavior was noted for these compounds, and the course of their specific heat curves needs no discussion. There are no previous data with which to compare any of the present measurements.

TABLE I

SPECIFIC HEAT OF $CaSO_3$ (MOLE WT. = 120.14 G.)

T, °K.	C_p, cal./mole	T, °K.	C_p, cal./mole	T, °K.	C_p, cal./mole
53.2	4.180	114.9	11.96	215.8	18.56
57.1	4.753	124.5	12.85	225.6	19.06
61.7	5.473	135.3	13.75	236.1	19.47
66.7	6.246	145.2	14.47	245.9	19.94
71.4	6.933	155.9	15.22	255.9	20.34
76.0	7.567	165.7	15.88	266.2	20.80
80.4	8.164	175.4	16.43	276.3	21.25
85.2	8.767	185.9	17.05	286.0	21.56
95.2	9.953	195.7	17.60	295.3	21.82
104.3	10.93	206.0	18.09		

SPECIFIC HEAT OF Na_2SO_3 (MOLE WT. = 126.05 G.)

53.2	7.292	113.1	17.40	214.3	25.05
56.5	7.991	123.3	18.54	224.1	25.53
59.9	8.746	133.6	19.55	234.7	26.04
63.8	9.592	144.1	20.48	244.6	26.53
67.7	10.44	154.0	21.26	255.1	27.03
72.2	11.35	164.4	22.06	265.7	27.48
80.4	12.81	174.1	22.67	275.9	27.92
84.0	13.41	184.7	23.36	285.8	28.28
92.8	14.80	194.4	23.97	295.1	28.62
103.0	16.18	204.5	24.54		

SPECIFIC HEAT OF $MnS_2O_6 \cdot 2H_2O$ (MOLE WT. = 251.08 G.)

53.1	13.81	113.4	30.31	215.0	48.30
56.8	14.96	123.6	32.56	225.5	49.71
60.9	16.26	133.9	34.74	235.4	51.03
65.4	17.79	144.3	36.90	245.3	52.22
69.7	19.15	154.3	38.80	255.8	53.47
74.4	20.52	164.7	40.67	265.7	54.23
80.0	21.98	174.5	42.35	275.6	55.20
83.8	22.94	184.8	43.99	285.7	56.30
93.0	25.30	195.0	45.58	294.9	57.30
103.0	27.82	205.2	47.05		

Entropies at 298.16°K.

The entropies at 298.16°K. were calculated in the usual manner. Between 50.12° and 298.16°K., graphical integrations were made under the C_p against log T curves, $\int_{50.12}^{298.16} C_p \, d \ln T$. The entropy increments lying below 50.12°K. were obtained by extrapolation. This was accomplished by fitting the experimental data over the entire experimental range by the following series of Debye and Einstein functions

$$CaSO_3: \; C_p = D\left(\frac{201}{T}\right) + 2E\left(\frac{322}{T}\right) + E\left(\frac{720}{T}\right) + E\left(\frac{1316}{T}\right)$$

$$Na_2SO_3: \; C_p = D\left(\frac{175}{T}\right) + 3E\left(\frac{256}{T}\right) + 2E\left(\frac{860}{T}\right)$$

$$MnS_2O_6 \cdot 2H_2O: \; C_p = D\left(\frac{91.7}{T}\right) + 4E\left(\frac{197}{T}\right) + 4E\left(\frac{501}{T}\right) + 2E\left(\frac{857}{T}\right) + 2E\left(\frac{1205}{T}\right)$$

Only the first two functions are of significance in each instance in computing the extrapolated portion of the entropy. The results are listed in Table II.

TABLE II

ENTROPIES AT 298.16°K. (CAL./DEG. MOLE)

	$CaSO_3$	Na_2SO_3	$MnS_2O_6 \cdot 2H_2O$
0–50.12°K. (extrap.)	1.68	2.65	7.15
50.12°–298.16°K. (graph.)	22.55	32.23	59.51
$S°_{298.16}$	24.2 ± 0.3	34.9 ± 0.4	66.7 ± 1.0

The entropy of calcium sulfite is 1.3 to 1.6 unit less than that of calcium sulfate,[9] depending on the variety of calcium sulfate, and the entropy of sodium sulfite is 0.8 unit less than that of

(9) Kelley, Southard, and Anderson, Bureau of Mines Tech. Paper 625, 1941, 78 pp.

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sodium sulfate.[10] Thus, in these two instances, the effect on the entropy of removing one oxygen atom from a sulfate group to form a sulfite group is a decrease of about 1 unit. A difference of this order of magnitude reasonably may be expected between sulfates and sulfites of other metals, and this offers a means of estimating the entropy of the sulfite when that of the sulfate is known or *vice versa*.

The entropy of manganese dithionate-dihydrate may be subject to some correction because of unextracted magnetic entropy; but sufficient information on this point is not available at present, and it is not taken account of in the error assigned to the entropy value in Table II. In view of recent observations[11] on the approximate constancy of the entropy of water of crystallization, one would estimate the entropy of anhydrous manganese dithionate to be about 45 units at 298.16°K. and that of the hexahydrate to be about 110 units.

(10) Pitzer and Coulter, THIS JOURNAL, **60**, 1310 (1938).

(11) Kelley and Moore, *ibid.*, **65**, 2340 (1943).

Summary

Low-temperature specific heat measurements, throughout the temperature range 51 to 298°K., have been made of calcium sulfite, sodium sulfite, and manganese dithionate-dihydrate.

The respective entropies at 298.16°K. are 24.2 ± 0.3, 34.9 ± 0.4, and 66.7 ± 1.0.

It is suggested that the difference in entropy between a sulfate and a sulfite group in a solid compound is about 1 unit at 298.16°K.

BERKELEY, CALIF. RECEIVED OCTOBER 25, 1943

[CONTRIBUTION FROM STEELE CHEMICAL LABORATORY, DARTMOUTH COLLEGE]

The Crystal Structure of Potassium Silver Carbonate, $KAgCO_3$[1]

BY JERRY DONOHUE[2] AND LINDSAY HELMHOLZ

Introduction.—The determination of the structure of potassium silver carbonate, which is colorless, was undertaken in conjunction with that of silver carbonate,[3] which is yellow, for the purpose of establishing the character of the silver-oxygen bond in those crystals, and discussing the difference in color in terms of the rule suggested by Pitzer and Hildebrand,[4] which states that the color of a compound formed from colorless ions is related to the amount of "covalent character" in the bond between these ions. Since the electronic structure of the carbonate group can readily be interpreted in terms of single bond double bond resonance, any effect of silver to oxygen covalent bond formation on the normal ionic configuration could be discussed in a relatively straightforward manner. Unfortunately an accurate structure of silver carbonate, in which appreciable covalent bond formation is suggested both by approximate distances and the rule of Pitzer and Hildebrand, is not yet available.

Experimental.—Potassium silver carbonate was prepared by the method of de Schulten.[5] Silver nitrate solution (0.25 *m*) was added dropwise to 50% potassium carbonate saturated with potassium bicarbonate. The yellow precipitate first formed turned white on standing. Complete solution takes place on heating. Slow cooling of this hot solution in a Dewar flask gives needle-like crystals, elongated in the *c* direction. The crystals prepared in this manner had all the properties described by de Schulten. Goniometric examination showed the crystals to be possibly orthorhombic, there being well-developed (100) and (110) faces ($a:b = 3.54:1$). Laue photographs showed the Laue symmetry D_{2h}-mmm, this establishing the orthorhombic symmetry.

Oscillation photographs were taken with the *c* axis vertical, using CuKα radiation. One oscillation photograph using Mo Kα radiation was taken for the purpose of obtaining more layer lines. The dimensions of the unit cell, as determined by indexing those photographs, were found to be $a_0 = 20.23$ Å., $b_0 = 5.75$ Å., $c_0 = 5.95$ Å. (all ±0.5%) ($a:b:c = 3.521:1:1.036$). Indexing of symmetric and asymmetric Laue photographs ($\lambda_{min.} = 0.24$ Å.) showed no first order reflections requiring a larger unit cell.

The number of molecules in the unit cell (using de Schulten's density value of 3.77 g./cc.) is calculated to be 7.66. Assumption of eight molecules in the unit cell gives a calculated density of 3.94 g./cc. de Schulten's value is low probably due to the fact that potassium carbonate clings tenaciously to the surface of the crystals as prepared. Attempts to measure the density also gave low values.

The intensities of the reflections on the oscillation photographs were estimated by means of the multiple film technique,[6] and by taking pictures of different exposure times over the same range. It was found necessary to correct the intensities for absorption; the correction factor was derived by integrating the expression for the path of beam through the crystal (assumed to be bathed by the beam) in accordance with the relation $I = I_0K|F|^2 e^{-\mu P} dp$ where I = the corrected intensity, I_0 = the incident intensity, K = the product of the Lorentz, polarization and temperature factors, F = the structure factor, μ = the absorption coefficient, and P = the path length of the beam through the crystal. The path length is expressed as function of: A, the width of the crystal; α, the angle through which the crystal has been rotated; and φ, the azimuthal scattering angle. Two cases are considered: (1) the incident and the emergent rays pass through the same crystal face, and (2) these two rays pass through different crystal faces. For case (1), the simplified expression is $I = I_0K|F|^2 \frac{A \sin\alpha}{\mu c}$, where $c = 1 + \frac{\sin\alpha}{\sin(\alpha - \varphi)}$. For case (2), the simplified expression is $I = I_0K|F|^2 \left(\frac{\sin(2\alpha - \varphi)}{\mu^2}\right)$. In

(1) Abstracted from a thesis submitted by Jerry Donohue to Dartmouth College in partial fulfillment of the requirements for the degree of Master of Arts.

(2) Present address: Gates and Crellin Laboratories of Chemistry, California Institute of Technology, Pasadena, California.

(3) John E. Eldridge, Thesis, 1943, Dartmouth College.

(4) K. S. Pitzer and J. H. Hildebrand, THIS JOURNAL, **63**, 2478 (1941).

(5) A. de Schulten, *Compt. rend.*, **105**, 811 (1887).

(6) J. J. de Lange, J. M. Robertson and I. Woodward, *Proc. Roy. Soc.* (London), **A171**, 398 (1939).

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simplifying the integrated expressions, certain terms were found to be negligible because of the large value of μ (575).

The validity of the correction factors was checked by calculating the F values of certain reflections which appear when the crystal has been rotated through different angles, and hence appear on different films with different intensities. Some of these comparisons are shown in Table I.

TABLE I

(*hkl*)	Observed intensity	α	F, corrected
(132)	2.50	30°	20
	1.40	41°	18
(532)	4.15	12°	32
	1.50	63°	25
(752)	2.50	33°	17
	1.45	77°	16

Determination of the Structure.—The following regular absences, observed on the oscillation photographs: (hkl) with $h + k + l \neq 2n$, (hkO) with $h \neq 2n$ and $k \neq 2n$, $(h0l)$ with $h \neq 2n$ and $l \neq 2n$, and $(0kl)$ with $k \neq 2n$ and $l \neq 2n$, establish the space group uniquely as $D_{2h}^{27} - Ibca$.[7] The sets of positions for the space group $D_{2h}^{27} - Ibca$ are[7]

$(0\ 0\ 0;\ \tfrac{1}{2}\ \tfrac{1}{2}\ \tfrac{1}{2}) +$

8:	(a)	0	0	0;	0	$\frac{1}{2}$	$\frac{1}{2}$;	$\frac{1}{2}$	0	$\frac{1}{2}$;	$\frac{1}{2}$	$\frac{1}{2}$	0
	(b)	$\frac{1}{4}$	$\frac{1}{4}$	$\frac{1}{4}$;	$\frac{1}{4}$	$\frac{3}{4}$	$\frac{3}{4}$;	$\frac{3}{4}$	$\frac{1}{4}$	$\frac{3}{4}$;	$\frac{3}{4}$	$\frac{3}{4}$	$\frac{1}{4}$
	(c)	x	0	$\frac{1}{4}$;	$\bar{x}$	0	$\frac{3}{4}$;	x	$\frac{1}{2}$	$\frac{3}{4}$;	$\bar{x}$	$\frac{1}{2}$	$\frac{1}{4}$
	(d)	$\frac{1}{4}$	y	0;	$\frac{3}{4}$	$\bar{y}$	0;	$\frac{3}{4}$	y	$\frac{1}{2}$;	$\frac{1}{4}$	$\bar{y}$	$\frac{1}{2}$
	(e)	0	$\frac{1}{4}$	z;	0	$\frac{3}{4}$	$\bar{z}$;	$\frac{1}{2}$	$\frac{3}{4}$	z;	$\frac{1}{2}$	$\frac{1}{4}$	$\bar{z}$
16:	(f)	x	y	z;	x	$\bar{y}$	$\frac{1}{2}$	z;	$\frac{1}{2} - x, y, \bar{z}$;		$\bar{x}, \frac{1}{2} - y, z$;		
		$\bar{x}$	$\bar{y}$	$\bar{z}$;	$\bar{x}, y, \frac{1}{2} + z$;				$\frac{1}{2} + x, \bar{y}, z$;		$x, \frac{1}{2} + y, \bar{z}$.		

Into a unit cell of such a spatial symmetry must be placed 8 silver atoms, 8 potassium atoms, 8 carbon atoms, and 24 oxygen atoms.

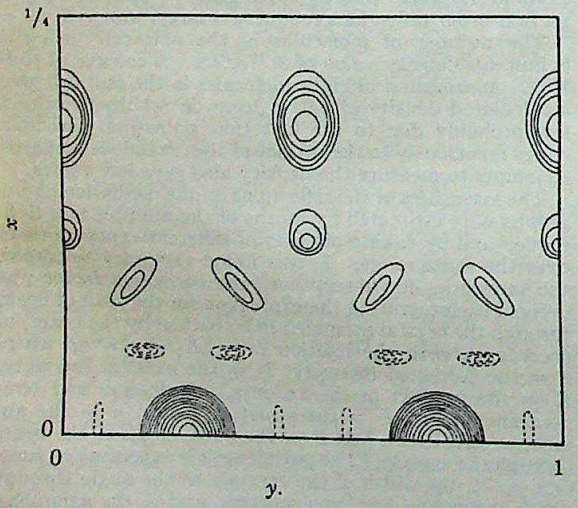

Fig. 1.—(x, y). Projection of electron density of 1/4 of the unit cell on (001). Contours are drawn at 12.5, 25, 37.5, 50, and at 100 to 800 in 100 unit intervals, in terms of an arbitrary scale.

The silver atoms must be assigned to the position 8(e) to account for the fact that reflections for which $l \neq 2n$ are exceedingly weak compared to those for which $l = 2n$. Positions 8(a) and 8(b) are excluded by the presence of strong reflections with h or k odd. With the silver atoms assigned to the positions 8(e), the signs of all the F_{hk0}'s can be determined. A Fourier projection on the xy plane made by using the 42 available $(hk0)$ reflections is shown in Fig. 1. The peaks at $x = 0, y = \frac{1}{4}$ and $x = 0, y = \frac{3}{4}$ are clearly those of the silver atoms. The next largest peak at $x \approx 0.185, y = \frac{1}{2}$ is due to the potassium atom superimposed on one oxygen atom of the carbonate group. The remainder of the carbonate group is also clearly shown. The peaks drawn in with dotted contours are believed to be spurious. No reasonable interpretation could be given to any of these spurious peaks. The Fourier projection places the potassium atoms, the carbon atoms, and eight oxygen atoms in the positions 8(c); the remaining sixteen oxygen atoms must fall into the general positions 16(f). There are thus in all seven parameters to be determined.

As a start in the parameter determination, the carbonate group was assumed to have the same configuration and dimensions as in calcite.[8] The intensities of the $(h00)$ reflections can thus be considered to be functions of two variables: the x parameter for the potassium atom, and the x parameter for the carbonate group. Using the eleven available $(h00)$ reflections, limits for these parameters were obtained by calculating and comparing F values in the usual way. Atomic scattering factors taken from the tables of Pauling and Sherman,[9] and a temperature factor with $\beta = 1.5$ were used in these calculations.

Using these x parameters, the z parameters for the silver atoms and the oxygen atoms in the general positions (O_{II}) can now be obtained in the same way from F values of (hkl) reflections. If $z_{O_{II}} = z_{Ag} + 0.250$ the silver atom is bisphenoidally surrounded by four oxygen atoms. Any other arrangement is chemically unreasonable, unless the silver atom is two coördinated, and this structure leads to improbable interatomic distances. The F values of the reflections of the type $h \neq 2n, k \neq 2n, l = 2$ were found to be very sensitive to small changes in the silver parameter, since its value is very close to $\frac{1}{8}$. The y parameter of O_{II} can now be calculated, because of the assumption made concerning the configuration and dimensions of the carbonate group. A check on the parameters of O_{II} is found in the F values for reflections of the type $h \neq 2n, k = 2n, l \neq 2n$, since none of the other atoms in the cell contribute to these reflections.

The final parameter values are

K	$x =$	-0.182		
C	$x =$	.122		
O	$x =$	.187		
Ag	$z =$	.128		
O_{II}	$x =$	.089	$y = 0.146$	$z = 0.378$

We believe it unlikely that any of the potassium

(7) "International Tables for the Determination of Crystal Structures," Vol. I.

(8) N. Elliott, THIS JOURNAL, 59, 1380 (1937).

(9) L. Pauling and J. Sherman, *Z. Krist.*, 81, 1 (1932).

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TABLE II

VALUES OF $F_{(hkl)}$

hkl	$F_{obs.}$	$\lvert F\rvert_{calcd.}$	hkl	$F_{obs.}$	$\lvert F\rvert_{calcd.}$	hkl	$F_{obs.}$	$\lvert F\rvert_{calcd.}$
200	[a]		121	10	4	022	19	17
400	28	24	321	13	8	222	14	11
600	30	41	521	abs.	2	422	7	5
800	20	16	721	10	6	622	14	10
10.0.0	38	44	921	9	5	822	20	15
12.0.0	31	34	11.2.1	abs.	1	10.2.2	abs.	5
14.0.0	17	12	13.2.1	abs.	3	12.2.2	abs.	1
16.0.0	29	26	231	12	7	14.2.2	10	10
18.0.0	21	14	431	11	10	16.2.2	7	8
20.0.0	18	14	631	abs.	3	18.2.2	abs.	2
22.0.0	27	28	831	abs.	1	20.2.2	6	5
24.0.0	14	12	10.3.1	17	9	22.2.2	5	6
020	16	14	12.3.1	8	6	132	19	22
220	44	48	14.3.1	abs.	4	333	23	24
420	32	36	16.3.1	abs.	2	532	28	26
620	21	15	18.3.1	abs.	2	732	24	24
820	35	39	20.3.1	4	5	932	22	20
10.2.0	20	20	141	abs.	2	11.3.2	19	18
12.2.0	25	22	341	abs.	3	13.3.2	20	19
14.2.0	27	30	541	abs.	1	15.3.2	23	18
16.2.0	14	11	741	abs.	3	17.3.2	17	18
18.2.0	22	19	941	abs.	3	19.3.2	14	16
20.2.0	21	22	11.4.1	abs.	0	042	16	13
22.2.0	12	9	251	4	2	242	7	6
24.2.0	14	18	451	4	5	442	abs.	2
040	34	30	651	4	4	642	10	8
240	17	13	851	abs.	2	842	0	9
440	29	22	10.5.1	10	6	10.4.2	5	5
640	31	34	12.5.1	8	4	12.4.2	abs.	2
840	19	13	14.5.1	abs.	0	14.4.2	9	8
10.4.0	36	21	16.5.1	5	3	16.4.2	9	8
12.4.0	25	17	18.5.1	5	3	18.4.2	abs.	0
14.4.0	24	10	202	[a]		20.4.2	abs.	4
16.4.0	29	26	402	abs.	4	152	16	21
18.4.0	17	16	602	12	14	352	19	17
20.4.0	8	8	802	12	11	552	16	14
060	abs.	5	10.0.2	9	8	752	16	15
260	25	20	12.0.2	9	2	952	14	18
460	23	19	14.0.2	7	9	11.5.2	12	19
660	13	12	16.0.2	12	10	13.5.2	15	16
860	23	22	18.0.2	abs.	1	15.5.2	12	13
10.6.0	15	10	20.0.2	abs.	4	062	7	8
12.6.0	18	11	22.0.2	7	7	262	8	5
14.6.0	20	20	112	25	25	462	abs.	2
211	abs.	3	312	36	33	662	4	5
411	12	12	512	27	37	862	5	8
611	12	9	712	26	32	10.6.2	abs.	3
811	14	8	912	24	24	12.6.2	abs.	0
10.1.1	11	7	11.1.2	20	18			
12.1.1	5	3	13.1.2	18	19			
14.1.1	abs.	1	15.1.2	17	22			
16.1.1	6	4	17.1.2	16	21			
18.1.1	7	5	19.1.2	15	18			
20.1.1	abs.	1	21.1.2	11	14			
22.1.1	abs.	0	23.1.2	9	12			
24.1.1	5	3						

[a] Not observed because of experimental arrangement.

or silver parameters are in error by as much as ±0.002, since variation of this magnitude leads to serious discrepancies between observed and calculated F values. The oxygen and carbon parameters may be in error by more than this amount if there is a distortion from the assumed configuration of the carbonate group. However, a big distortion is rather unlikely.

Calculated and observed F values are shown in Table II.

Discussion

A projection of a portion of the unit cell on (100) is shown in Fig. 2. The silver atoms are surrounded by four oxygen atoms at 2.42 ± 0.05 Å. The potassium atom has nine close oxygen neighbors, one at 2.65 ± 0.08 Å., and four each at 2.88 Å. and 3.00 Å. all ±0.05 Å. The shortest potassium to oxygen distance is the only coördination the potassium atom has in that direction.

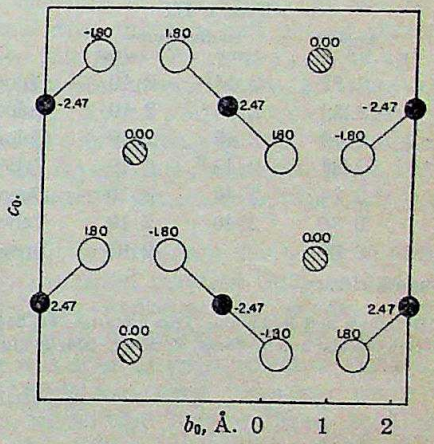

Fig. 2.—Projection of a portion of the unit cell on (100). Numbers give heights of atoms in Å. above plane of diagram ($x = 1/2$). Black circles represent carbon atoms, open circles, oxygen atoms and shaded circles, silver atoms. In this projection, the positions of the potassium atoms coincide with those of the carbon atoms.

The oxygen atoms in the positions 8(c) are octahedrally coördinated; in addition to being bonded to the carbon atom in the carbonate group, they are surrounded by five potassium atoms (one at 2.65 Å., two each at 2.88 Å. and 3.00 Å.) in such a way as to form a deformed octahedron. The oxygen atoms in the general positions have a more nearly triangular coördination, being close to two silver atoms (at 2.42 Å.), in addition to the carbonate group bond. Their next nearest neighbor is a potassium atom, at 2.88 Å.

Although we have made an assumption concerning the internal structure of the carbonate group, we feel that any significant deviation from the normal configuration would have been detected. Since the X-ray data indicate that such deviation is unlikely, it is probable that the carbonate group has its usual structure[8] in this crystal.

It is seen that the carbonate groups are tipped about 42° out of a plane parallel to (001). The bind-

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ing between the silver atoms and the oxygen atoms is staggered in such a way that there are strong forces in both the *b* and *c* directions. This is in agreement with the observed growth of the crystals.

A preliminary report on the structure of silver carbonate[3] follows: Laue and rotation pictures showed the crystals to be monoclinic with $a_0 = 4.83$ Å., $b_0 = 9.52$ Å., $c_0 = 3.23$ Å., $\beta = 92.7°$, $z = 2$ (calcd. 1.99). The probable space group is C_2^2-$P2_1$. Patterson and Fourier analysis of (*hk*0) data gives positions for the silver atoms and probable positions for the carbonate groups. The silver atoms are surrounded by deformed tetrahedra of oxygen atoms at about 2.3 Å. The binding is somewhat similar to that in potassium silver carbonate, there being a staggered arrangement of bonds between the silver and oxygen atoms.

The table given by Helmholz and Levine[10] can now be extended:

TABLE III

Compound	Ag–O,[a] Å.	Radius Sums Ionic	Radius Sums Covalent	Color
$AgClO_3$[11]	2.51	2.46	2.19	Colorless
Ag_2SO_4	2.50	2.46	2.19	Colorless
$KAgCO_3$	2.42	2.46	2.19	Colorless
Ag_3PO_4	2.34	2.46	2.19	Yellow
Ag_3ASO_4	2.34	2.46	2.19	Deep red
Ag_2CO_3	2.30	2.46	2.19	Yellow
Ag_2O	2.06		2.02	Brown-black

[a] Average distance.

(10) L. Helmholz and R. Levine, THIS JOURNAL, **64**, 354 (1942).
(11) I. Naray-Szabo and J. Pocza, *Z. Krist.*, **104**, 28 (1942).

The correlation between the color and the bond distance is in reasonable accord with the rule of Pitzer and Hildebrand.[4] In view of the nature of the absorption process,[12] it seems probable that the *change* in absorption when, for example, silver is substituted for sodium in salts of these acids, rather than the color of the silver salt itself, should serve as a criterion for the amount of covalent character, in crystals of the type considered here. The apparent discrepancies in Table III of potassium silver carbonate and silver arsenate can be explained on this basis, and would lead, in the case of silver arsenate, to the reasonable conclusion that the tendency of the arsenate group to share electrons is greater than that of the phosphate group.

Summary

The crystal structure of potassium silver carbonate has been determined. The crystal is orthorhombic holohedral, with $a_0 = 20.23$ Å., $b_0 = 5.75$ Å., $c_0 = 5.95$ Å. The space group is D_{2h}^{27}-*Ibca*. The Ag-O bond distance was found to be 2.42 Å., and this is discussed in relation to other silver salts, including silver carbonate, for which a preliminary structure is given. The application of the rule of Pitzer and Hildebrand to the probable nature of this bond is also discussed.

(12) G. K. Rollefson and M. Burton, "Photochemistry and the Mechanism of Chemical Reactions," Prentice Hall, New York, N. Y., 1939, Chapter VI.

PASADENA, CALIF. RECEIVED OCTOBER 11, 1943

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF MISSOURI]

Normal and Pseudo Structures of 8-Benzoyl-1-naphthoic Acid and Derivatives[1,2]

BY H. E. FRENCH AND J. E. KIRCHER

An earlier paper from this Laboratory[3] gave evidence for both the symmetrical and the unsymmetrical forms for 1,8-naphthalyl dichloride. This work has now been extended to the 8-benzoyl-1-naphthoic acid and certain of its derivatives.

8-Benzoyl-1-naphthoic Acid.—This acid was prepared by the method of Mason.[4] Upon crystallization from ethanol, 70% acetic acid, or chloroform, we obtained a product melting at 110°, as reported by Mason. From xylene, cyclohexane or toluene, the substance melted at 129–130°, checking the melting point reported by Knapp.[5] A sample of the 110° melting material heated to 90° for four hours under a watch glass was found to melt at 154°. From all of these samples, material of melting point 110° or 129–130° could be obtained by crystallization from the proper solvent.

Absorption curves were plotted for the acids melting at 110° and 129°, in chloroform solution, and for the 129° variety after refluxing in cyclohexane solution for twenty-four hours. The curves were all of the same form, with maximum and minimum points in the same regions. These maximum and minimum points are given in Table I. These curves for the acid are similar to the curve for diphenylnaphthalide, and bear no resemblance to the curve for dibenzoylnaphthalene which shows only one minimum and one maximum. Data for these curves are also given in Table I.[6]

Diphenylnaphthalide, ditolylnaphthalide and naphthalic anhydride, all of which have a ring structure across the 1,8 positions, were found to

(1) This paper is a summary of part of the thesis material submitted by Dr. Kircher to the graduate faculty of the University of Missouri.
(2) The material in this paper was presented at the meeting of the American Chemical Society at Detroit, Mich., in April, 1943.
(3) French and Kircher, THIS JOURNAL, **63**, 3270 (1941).
(4) Mason, *J. Chem. Soc.*, **125**, 2116, 2119 (1924).
(5) Knapp, *Monatsh.*, **67**, 332 (1936).
(6) The spectroscopic data were determined by Dr. Victor Ells, University Spectroscopist for the University of Missouri.

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TABLE I

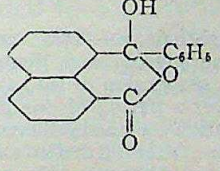
MAXIMUM AND MINIMUM POINTS FOR 8-BENZOYL-1-NAPHTHOIC ACID AND DERIVATIVES

Compound	Min., Å.	Max.	Min.	Max.	Min.	Max.
110° acid in chloroform	2710			3115	3252	3289
129° acid in chloroform	2718			3120	3246	3297
129° acid in cyclohexane, reflux 24 hr.	2661			3081	3221	3252
Acid chloride	2730	2961	3000	3074	3214	3251
Diphenyl-naphthalide	2675			3092	3215	3275
Pseudo ester	2655			3085	3200	3259
Normal ester	2700	2946				
Diethyl naphthalate	2665	2950				
1,8-Dibenzoyl-naphthalene	2754	2910				

Absorption spectra measurements were made in cyclohexane solution unless otherwise noted.

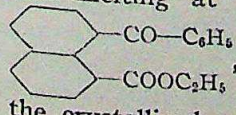
show a blue fluorescence under ultraviolet light, while the ethyl ester of 8-benzoyl-1-naphthoic acid and 1,8-diethylnaphthalate, which do not possess this closed structure, appear gray-white under the ultraviolet lamp. The samples of 8-benzoyl-1-naphthoic acid of various melting points all showed the blue fluorescence, as did 8-toluyl-1-naphthoic acid.

It is concluded from the evidence of absorption spectra and ultraviolet fluorescence that the acid in solution is very largely, if not completely, in the form of the cyclic compound of the structure

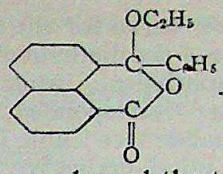


Ethyl Derivatives of 8-Benzoyl-1-naphthoic Acid.—Mason[4] prepared the acid chloride by the action of thionyl chloride on the acid of melting point 110°. The chloride was crystallized from benzene, and melted at 125–127°, and gave with ethyl alcohol an ethyl derivative melting at 166°. We repeated these reactions and obtained results which corresponded to those of Mason.

We also obtained an ethyl derivative by the action of the silver salt of the acid on ethyl iodide. This ethyl derivative melted at 134°. A mixture of the two ethyl derivatives gave a melting point depression of 15°. Without question the derivative melting at 134° was the normal ester,



, and the product obtained from the crystallized acid chloride and ethyl alcohol possessed some other structure, probably that of



the pseudo ester . Analyses for carbon and hydrogen showed the two compounds to be isomeric.

The normal ester, melting at 134°, gave the gray-white fluorescence of the open compounds, under the ultraviolet light, while the pseudo ester, melting at 166°, showed the blue fluorescence characteristic of the closed structure across the 1,8 positions.

Experiment with a known mixture showed that nearly quantitative separation of the two isomers could be accomplished by chromatographic adsorption on alumina from a benzene–petroleum ether solution. The crude product from the reaction of ethyl alcohol on the recrystallized chloride was dissolved in the benzene–petroleum ether mixture and passed through the column of alumina. As in the case of the known mixture, the isomer melting at 134° was adsorbed in the first layer, and fluoresced gray-violet, while the isomer melting at 166° was adsorbed in the second layer, and fluoresced light blue. In these experiments the high melting ester predominated.

In certain experiments the chloride was prepared by the usual reaction but, instead of crystallizing from benzene, the excess of thionyl chloride was distilled off and the brown oil remaining was treated with absolute alcohol. The reaction here was very vigorous, quite unlike those in which the recrystallized acid chloride were used. When chromatographed, the same two ethyl derivatives were obtained, but with the low melting form predominating. The acid chloride used in these experiments was prepared in some cases from acid melting at 110° and in other cases from acid melting at 130°. The results, however, corresponded throughout as shown in the following table.

TABLE II

ETHYL DERIVATIVES OF 8-BENZOYL-1-NAPHTHOIC ACID

M. p., °C., acid	Reagent for chloride	M. p., °C., chloride	% ratio of isomers m. p. 166°/m. p. 134°
110	$SOCl_2$	oil	15/85
110	$SOCl_2$	oil	5/95
110	$SOCl_2$	125	87/13
130	$SOCl_2$	oil	23/77
130	PCl_3	oil	33/67
130	$SOCl_2$	125	96/4

The recrystallized acid chloride with benzene and aluminum chloride gave diphenylnaphthalide in yields of from 25 to 50% of theoretical. No dibenzoylnaphthalene could be isolated from any of these reactions. When the acid chloride was used in the form of an oil, only hydrogen chloride and tars were obtained.

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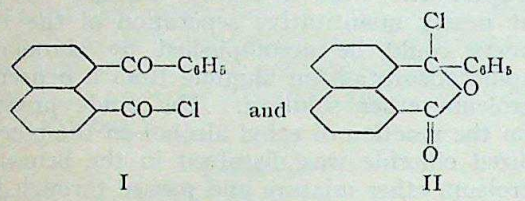
The absorption curve for the true ester corresponded to those of the diethylnaphthalate and the 1,8-dibenzoylnaphthalene, while the curve for the pseudo ester corresponded to that for the diphenylnaphthalide (see Table I). It is evident, then, that the ethyl derivative melting at 134° is the true ester and the one melting at 166° is the pseudo ester.

8-Benzoyl-1-naphthoyl Chloride.—As shown in Table II, the ratio of pseudo ester to the true ester in the reaction between the acid chloride and ethyl alcohol, can be practically inverted at will. There seems to be no doubt as to the existence of two chlorides represented by the formulas



I II

As pointed out in an earlier section of this paper, these chlorides differ in physical properties, one being an oil and the other a crystalline solid, as well as in the rates with which they react with ethyl alcohol. The recrystallized compound, no doubt represented by Formula II, yields diphenylnaphthalide in the Friedel–Crafts reaction, while the isomeric compound yields only tars and hydrogen chloride under the same conditions. The absorption curve for the chloride recrystallized from benzene was plotted and the maximum and minimum points are given in Table I. These points occur in the regions which characterize both the closed structures, such as diphenylnaphthalide, and the open structures, such as diethylnaphthalate. Results from the Friedel–Crafts reaction suggest the presence of the closed structure chiefly.

Experimental

The 8-benzoyl-1-naphthoic acid and its chloride were prepared by the method of Mason.[4] The diphenylnaphthalide was prepared as previously described.[3]

8-Benzoyl-1-ethyl Naphthoate.—Five grams of benzoylnaphthoic acid was dissolved in an excess of ammonium hydroxide after which the excess of ammonia was removed by boiling. To the neutral solution was added a slight excess of silver nitrate solution, and the white silver salt was filtered and dried.

The silver salt was placed in a 250-cc. conical three-neck flask equipped with reflux condenser and stirrer, and 17 cc. of ethyl iodide was added slowly. A vigorous reaction took place with the precipitation of silver iodide. After the reaction had subsided, the mixture was refluxed for thirty minutes. The silver iodide was repeatedly extracted with 20 cc. portions of boiling ethyl alcohol. On concentration of the solution the ester crystallized as white needles, m. p. 134°; yield, nearly quantitative.

Anal. Calcd. for $C_{20}H_{16}O_3$: C, 78.94; H, 5.26. Found: C, 78.43; H, 5.49.

8-Benzoyl-1-ethyl Naphthoate from the Acid Chloride.—Four grams of benzoylnaphthoic acid was treated with 4 cc. of thionyl chloride. After the initial vigorous reaction, the mixture was heated over a water-bath for thirty minutes, when the excess of thionyl chloride was distilled off, leaving an oily residue. To the residue 100 cc. of absolute alcohol was slowly added, whereupon a vigorous reaction took place. The solution was refluxed for an hour and then concentrated to 50 cc., and the white crystalline product filtered off. This solid material was then dissolved in benzene and chromatographed on alumina, after the addition of enough petroleum ether (b. p. 70–80°) to make the solution nearly saturated. The first major layer fluoresced gray-violet with only a small band showing a blue fluorescence. The gray-violet band was treated with alcohol and the material which crystallized melted at 128–130°. Repeated crystallizations from alcohol brought the melting point up to 134°; average yield 60%. *Anal.* Calcd. for $C_{20}H_{16}O_3$: C, 78.94; H, 5.26. Found: C, 79.22; H, 5.50. From the small layer showing blue fluorescence, the 3-phenyl-3-ethoxynaphthalide was obtained in about a 10% yield on extraction with alcohol.

3-Phenyl-3-ethoxynaphthalide.—The chloride of benzoylnaphthoic acid was prepared and crystallized from benzene as directed by Mason. The chloride was then treated with absolute ethyl alcohol, approximately 10 cc. per gram of chloride being used. There was practically no evolution of heat. The mixture was refluxed for approximately an hour. The chloride went into solution with some difficulty. Upon cooling the pseudo ester crystallized in colorless crystals melting at 166°. The average yield from several runs was about 60%. *Anal.* Calcd. for $C_{20}H_{16}O_3$: C, 78.94; H, 5.26. Found: C, 78.91; H, 5.43. In addition to the pseudo ester small amounts of the normal ester, melting at 134°, were also obtained.

1,8-Diethyl Naphthalate.—The silver salt of naphthalic acid was prepared by adding a slight excess of silver nitrate in aqueous solution to a solution of the sodium salt of the acid. A considerable excess of ethyl iodide was added as described in the preparation of 8-benzoyl-1-ethyl naphthoate. After the initial reaction had subsided the mixture was refluxed for one hour. The precipitated silver iodide was heated with ethyl alcohol and filtered, then washed repeatedly with 20 cc. portions of alcohol. The combined alcoholic solutions were concentrated and diluted with water. Upon cooling, the ester crystallized as white crystals, m. p. 54°.

1,8-Dibenzoylnaphthalene.—Two grams of 9,10-diphenylacenaphthene glycol[7] was dissolved in 50 cc. of dry benzene and a suspension of lead tetraacetate in benzene was added over a period of one hour, at room temperature. The solution was then refluxed for thirty minutes on the water-bath. After filtration the benzene was removed under reduced pressure. The solid material thus obtained was crystallized from dilute ethyl alcohol. The pure product melted at 186°.

Summary

1. 8-Benzoyl-1-naphthoic acids having melting points of 110, 129, and 154° have been obtained as allotropic forms. They are readily interconverted. The evidence points to the pseudo acid structure for the compound in solution.

2. The normal and pseudo ethyl derivatives of the acid as well as two forms for the acid chloride have been prepared.

COLUMBIA, MO. RECEIVED SEPTEMBER 10, 1943

(7) Bachmann, THIS JOURNAL, 58, 1118 (1936).

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS, AND THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

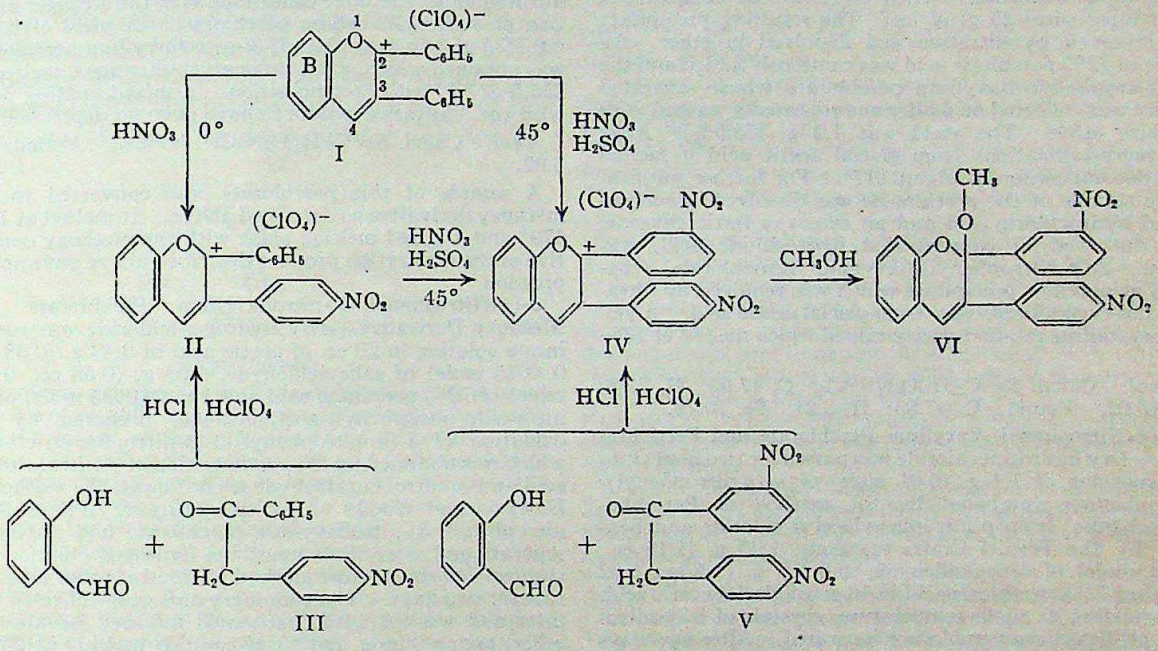
Benzopyrylium Salts. IV. Nitration of 2,3-Diphenyl-benzopyrylium Perchlorate

BY R. L. SHRINER AND ROBERT BRUCE MOFFETT

One of the most interesting reactions of flavylium salts is their behavior on nitration. Le Fevrè[1] showed that nitration of flavylium perchlorate produced the 3′-nitro derivative. In the present investigation the nitration reactions have been extended to a study of 2,3-diphenyl-benzopyrylium perchlorate (I) in order to establish the orientation of the substituents and relative ease of substitution in the two phenyl groups.

Treatment of 2,3-diphenyl-benzopyrylium perchlorate (I) with fuming nitric acid at 0° produced a 53% yield of the mono-nitro derivative (II). The latter was best purified and characterized by conversion to its ferrichloride. The structure of II was established by synthesis from salicylaldehyde and α-(*p*-nitrophenyl)-acetophenone (III). The perchlorates and ferrichlorides of the two samples of compound II were identical.

When the original perchlorate (I) was treated with concentrated nitric and sulfuric acids at 45° a 93% yield of a dinitro derivative was obtained. Exactly the same product could be obtained by nitration of the mono-nitro derivative (II). The structure of this dinitrodiphenyl-benzopyrylium perchlorate was shown to be that represented by formula (IV) by synthesis from salicylaldehyde and α-(*p*-nitrophenyl)-*m*-nitro-acetophenone (V). The three samples of compound IV were shown to be identical by analyses, mixed melting points and conversion to the same methoxy derivative (VI).



The above experiments show that under mild conditions of nitration a nitro group is introduced into the *para* position of the phenyl group in position 3 of the flavylium salt (I) and that under more drastic conditions an additional nitro-group is introduced in the meta position of the phenyl group in position 2.

The position taken by a group entering the benzene ring is fundamentally dependent on the charge of the atom already attached to the ring.[2] If the charge is zero or negative the entering group goes into the ortho or para position whereas a considerable positive charge sends the entering group to the meta position. The results of the present nitration experiments are in agreement with the carbonium structure for these salts[3] which in the present case is represented by formula I. Using the approximation method of Latimer and Porter[2a] the charge on carbon atom 2 is about +1.2 whereas the charge on carbon atom 3 is about 0.

It is remarkable that no nitration products were obtained with substituents in Ring B of formula I. Examination of the reaction mixtures showed that no additional nitro derivatives were produced in these experiments with 2,3-diphenyl-

(1) Le Fevrè, *J. Chem. Soc.*, 2771 (1929); Le Fevrè and Le Fevrè, *ibid.*, 1988 (1932); Le Fevrè, Le Fevrè and Pearson, *ibid.*, 37 (1934).

(2) (a) Latimer and Porter, THIS JOURNAL, **52**, 206 (1930); (b) Price, *Chem. Rev.*, **29**, 32 (1941).

(3) Shriner and Moffett, THIS JOURNAL, **63**, 1694 (1941).

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benzopyrylium perchlorate. The nitration of other benzopyrylium salts is being studied in an effort to locate such substitutents since it is important in connection with other possible resonance structures of I.

Experimental

Nitration of 3-Phenylflavylium Perchlorate at 0°.—To 10 cc. of yellow, fuming nitric acid cooled in an ice–salt bath was added slowly with shaking 2 g. of 3-phenylflavylium perchlorate. When solution was complete, it was poured onto 25 g. of ice. The resulting precipitate was removed by filtration and dissolved in ether. An excess of 72% perchloric acid was cautiously added and the 3-(*p*-nitrophenyl)-flavylium perchlorate which separated at once was collected on a filter and repeatedly washed with absolute ether. The yield was 1.2 g. (53.5%). After two recrystallizations from glacial acetic acid it melted with decomposition at about 217°. For further purification a sample of the perchlorate was dissolved in concentrated hydrochloric acid and an excess of ferric chloride, also dissolved in concentrated hydrochloric acid, was added. 3-(*p*-Nitrophenyl)-flavylium ferrichloride separated as a yellow precipitate which was removed by filtration and crystallized twice from glacial acetic acid. A yellow crystalline product was obtained which melted at 136–137°.

Anal. Calcd. for $C_{21}H_{14}O_3NFeCl_4$: C, 47.95; H, 2.68; Fe, 10.62. Found: C, 47.89; H, 3.21; Fe, 10.78.

3-(*p*-Nitrophenyl)-flavylium Perchlorate and Ferrichloride.—Dry hydrogen chloride was passed for two hours into a suspension of 1.4 g. (0.01 mole) of α-(*p*-nitrophenyl)-acetophenone (prepared by the method of Petrenko-Kritschenko[4] from *p*-nitrophenylacetyl chloride and benzene by the Friedel–Crafts reaction), 1.35 g. (1.15 cc., 0.011 mole) of salicylaldehyde, and 2.7 g. (1.5 cc., 0.02 mole) of 72% perchloric acid in 40 cc. of glacial acetic acid. On standing at room temperature, crystals of 3-(*p*-nitrophenyl)-flavylium perchlorate separated. After two days the crystals were collected on a filter, washed with absolute ether, and recrystallized from glacial acetic acid yielding 4.0 g. (93.5%) of yellow crystals, which after a second recrystallization melted at 235–237° with decomposition.

Anal. Calcd. for $C_{21}H_{14}O_7NCl$: N, 3.28. Found: N, 3.28.

A sample of this perchlorate was converted to the ferrichloride as described above yielding yellow crystals of 3-(*p*-nitrophenyl)-flavylium ferrichloride which melted at 137–138°. When mixed with the ferrichloride from the nitration product no depression of the melting point occurred.

Anal. Calcd. for $C_{21}H_{14}O_3NFeCl_4$: C, 47.95; H, 2.68; Fe, 10.62. Found: C, 47.77; H, 2.90; Fe, 10.66.

Nitration of 3-Phenylflavylium Perchlorate at 45°.—Ten grams of 3-phenylflavylium perchlorate was dissolved in 40 cc. of concentrated sulfuric acid, cooled in an ice–salt bath, and 40 cc. of cold concentrated nitric acid was slowly added with shaking and cooling. This solution was warmed for five minutes at 45° and then poured onto ice. The resulting precipitate was removed by filtration, dissolved in ether, and an excess of 72% perchloric acid was cautiously added. The 3-(*p*-nitrophenyl)-3′-nitroflavylium perchlorate which separated was collected on a filter and repeatedly washed with absolute ether. The yield was 11.5 g. (93%) of a light yellow crystalline powder which melted at about 145–150° with decomposition. Repeated recrystallization either from glacial acetic acid containing a little perchloric acid, or from a mixture of acetic acid and nitromethane, yielded a product which melted at 258–258.5° with decomposition.

(4) Petrenko-Kritschenko, *Ber.*, **25**, 2239 (1892).

Anal. Calcd. for $C_{21}H_{13}O_9N_2Cl$: N, 5.93. Found: N, 5.90.

A sample of this perchlorate was dissolved in methanol by refluxing. When cooled, pale yellow crystals of the methoxy derivative separated, which after recrystallization from methanol with the aid of norite yielded pale yellow crystalline plates melting at 177.5–178.5°.

Anal. Calcd. for $C_{22}H_{16}O_6N_2$: N, 6.93. Found: N, 7.08.

Nitration of 3-(*p*-Nitrophenyl)-flavylium Perchlorate.—Two grams of 3-(*p*-nitrophenyl)-flavylium perchlorate was nitrated under the same conditions as in the stronger nitration of 3-phenylflavylium perchlorate. A yield of 2.1 g. (90.7%) of 3-(*p*-nitrophenyl)-3′-nitroflavylium perchlorate was obtained which, after three crystallizations, melted at 255.5–257.5° with decomposition. A mixed melting point with the dinitration product above gave no depression.

Anal. Calcd. for $C_{21}H_{13}O_9N_2Cl$: N, 5.93. Found: N, 5.92.

A sample of this perchlorate was converted to the methoxy derivative as described above. It melted at 178–179° and a mixed melting point with the methoxy derivative of the dinitration product described above gave no depression.

3-(*p*-Nitrophenyl)-3′-nitroflavylium Perchlorate and Methoxy Derivative.—Dry hydrogen chloride was passed into a solution in 20 cc. of acetic acid of 0.43 g. (0.38 cc., 0.0035 mole) of salicylaldehyde, 0.96 g. (0.58 cc., 0.007 mole) of 72% perchloric acid and 1 g. (0.0035 mole) of *m*-nitro-α-(*p*-nitrophenyl)-acetophenone, prepared by the oxidation of 1-(*m*-nitrophenyl)-2-(*p*-nitrophenyl)-ethanol which was obtained by the condensation of *p*-nitro-α-toluic acid and *m*-nitrobenzaldehyde according to the method of Harrison and Wood.[5] After two hours, crystals of 3-(*p*-nitrophenyl)-3′-nitroflavylium perchlorate had started to separate and after three hours the hydrogen chloride was stopped and the mixture allowed to stand at room temperature for two days. The yellow crystals were collected on a filter and washed with acetic acid followed by absolute ether, giving 0.99 g. (60%) of crystals melting at 254.5–255.5° with decomposition. After recrystallization from glacial acetic acid containing a little perchloric acid the compound melted at 257–258.5° with decomposition. Mixed melting points with both the perchlorates from the stronger nitration of 3-phenylflavylium perchlorate and from the nitration of 3-(*p*-nitrophenyl)-flavylium perchlorate gave no depressions.

Anal. Calcd. for $C_{21}H_{13}O_9N_1Cl$: N, 5.93. Found: N, 6.02.

A sample of this perchlorate was converted to the methoxy derivative as described above. It melted at 178–179° and mixed melting points with both the methoxy derivative from the stronger nitration of 3-phenylflavylium perchlorate and the methoxy derivative from the nitration of 3-(*p*-nitrophenyl)-flavylium perchlorate gave no depression.

Anal. Calcd. for $C_{22}H_{16}O_6N_2$: N, 6.93. Found: N, 6.85.

Summary

Mild conditions of nitration introduced a nitro-group in the para position of the phenyl group in position 3 of 2,3-diphenylbenzopyrylium perchlorate. More vigorous nitration conditions introduced an additional nitro-group in the meta position of the phenyl group in position 2. The structures of the nitration products were established by syntheses.

BLOOMINGTON, INDIANA RECEIVED DECEMBER 2, 1943

(5) Harrison and Wood, *J. Chem. Soc.*, 577 (1926).

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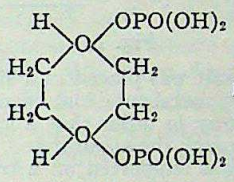
NOTES

Dioxane Diphosphate

By Erich Baer

Dioxane readily forms coördination compounds with several types of organic and inorganic substances. The oxonium salts of sulfuric acid[1] and perchloric acid[2] for example are well known. A phosphate, however, has not been described.[3] In the following the preparation and some of the properties of dioxane diphosphate[4] (I) are reported.



I

Experimental

The dioxane diphosphate (I) is easily obtained in good yields from an 88% aqueous solution of orthophosphoric acid by any one of the following three procedures. (a) Dioxane (one mole) and phosphoric acid (two moles) are mixed and crystallization is induced. The temperature of the mixture rises immediately to approximately 60°. To increase the yield of dioxane diphosphate the mixture is cooled. (b) Dioxane and phosphoric acid in separate containers are kept in a vessel under reduced pressure and at room temperature. The evaporating dioxane is absorbed by phosphoric acid and dioxane diphosphate precipitates. Any excess of absorbed dioxane, which decreases the yield of diphosphate,[5] can be readily removed *in vacuo*. (c) A dry current of air saturated with dioxane at 85° is bubbled through phosphoric acid kept at 100 to 120° until an excess of dioxane has passed into the reaction mixture. The product on cooling thickens to a crystalline sludge.

To isolate the very hygroscopic dioxane diphosphate from the crude reaction mixture obtained by any one of the above methods, the mother liquor is removed either by spreading the thick paste on porous clay plates in a desiccator or by filtering with suction using the rubber sheet technique.[6] The product is dried in a high vacuum over sodium hydroxide. The oxonium salt crystallizes in prisms and is obtained in yields as high as 84%; m. p. 83–87°[7] (sintering at 78°). A recrystallization from ether (10 g. of substance in 20 cc. of dry ether at −60°) does not change this melting point. The diphosphate is readily soluble at 25° in several solvents: water (giving a strongly acid solution), ethyl alcohol, *n*-butyl alcohol, cyclohexanol, benzyl alcohol, acetone, cyclohexanone, acetic acid, ether, dioxane, glycol dimethyl ether, ethyl acetate, trimethyl phosphate, and very slightly soluble or insoluble in benzene, cyclohexane, petrol ether, chloroform and bromoform. Dioxane diphosphate is unstable in water. Its aqueous solution gives all the usual reactions of phosphoric acid and loses dioxane on concentration. The dissociation of the molecular compound in organic solvents has not yet been investigated. *Anal.* Calcd. $C_4H_{14}O_{10}P_2$ (284): C, 16.9; H, 4.93; P, 21.82. Found: C, 16.9; H, 4.84; P, 21.80.

Dioxane diphosphate when kept dry is stable at room temperature. It remains apparently unchanged when heated for a short time in a glass vessel to 150°. Above 175° the substance rapidly turns dark brown and gives off fumes which when condensed form a colorless liquid. This distillate consisting mainly of dioxane [b. p. (756 mm.) 100°, $n^{25}D$ 1.4190] also contains an appreciable amount of acetaldehyde[8] [2,4-dinitrophenylhydrazone m. p. 147°,[9] from chloroform]. If a dry mixture of one mole of dioxane diphosphate with either 2.2 moles of Na_2HPO_4[10] or 1.1 mole of K_3PO_4[10] or 1.1 mole of anhydrous Na_3PO_4[10] is heated in an oil-bath to approximately 120 to 130° dioxane distils over in almost the theoretical yield. After redistilling the dioxane over metallic sodium, its refractive index and boiling point are $n^{25}D$ 1.4190, b. p. (751 mm.) 99.5–100.5°. The readily obtainable molecular compound should prove to be a valuable intermediate for the purification of dioxane.

Dioxane diphosphate, which is soluble in many organic liquids, may perhaps be used as a substitute for crystalline phosphoric acid, when a dry solution of phosphoric acid in an organic solvent is required.

(1) A. Faworski, *J. Russ. Phys.-Chem. Soc.*, **38**, 741 (1906).

(2) C. Smeets, *Natuurw. Tijdschr.*, **19**, 12 (1937).

(3) In spite of an intensive search of the literature no record of the substance could be found. A coördination compound of dioxane with a substituted phosphoric acid, the dioxanate of dimeric glyceraldehyde-1-bromide-3-phosphate has been used successfully where other methods failed to obtain this phosphate in an analytically pure state (Baer and Fischer, *J. Biol. Chem.*, **150**, 226 (1943).

(4) Patent applied for.

(5) Dioxane diphosphate is readily soluble in dioxane.

(6) L. F. Fieser, "Experiments in Organic Chemistry," 2d. ed., 1941, p. 321.

(7) The melting point was taken in a sealed tube. According to Kelley and McCusker (This Journal, **65**, 1307 (1943)) an unsharp melting point seems to be normal for a molecular compound containing a volatile component.

(8) The distillation of dioxane with a small amount of sulfuric acid yields dioxane containing acetaldehyde (Faworski, *loc. cit.*).

(9) Purgotti, reports a m. p. of 147° for acetaldehyde 2,4-dinitrophenylhydrazone, *Gazz. chim. ital.*, **24**, I, 565 (1894).

(10) A slight excess over the amount which is needed to convert all phosphoric acid into NaH_2PO_4 or KH_2PO_4.

Banting Institute
Department of Chemistry
University of Toronto
Toronto, Canada

Received October 11, 1943

The Preparation of Certain Phenolic Esters[1]

By Erwin Baumgarten, Howard G. Walker and Charles R. Hauser

Phenolic esters have been prepared from the sodium salt of the phenol in aqueous solution and the acid anhydride,[2] from the phenol and anhydride in the presence of the sodium salt of the acid from which the anhydride is derived,[3] and from the phenol and acid chloride in the presence of pyridine with[4] or without[5] an inert solvent. For the preparation of the rather large quantities of certain phenolic esters required in another investigation, the method involving the acylation of the phenol with the acid chloride in pyridine

(1) This work was supported by a grant from the Duke University Research Council.

(2) Chattaway, *J. Chem. Soc.*, 2495 (1931); Abramovitch and Hauser, This Journal, **64**, 2271 (1942).

(3) Hazlet and Kornberg, *ibid.*, **61**, 3037 (1939).

(4) Hazlet, Hensley and Jass, *ibid.*, **64**, 2449 (1942).

(5) Einhorn and Hollandt, *Ann.*, **301**, 95 (1898); Reichstein, *Helv. chim. Acta*, **9**, 800 (1926).

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has been found very satisfactory. By this method three new phenolic esters have been prepared on a one to three mole scale.

Ethyl 4-Phenylphenyl Carbonate.—To a solution of 510 g. (3 moles) of 4-phenylphenol in 720 ml. of pyridine (dried over potassium hydroxide pellets) in a 2-liter reaction flask, carrying a reflux condenser, dropping funnel and mercury-sealed "Hershberg" stirrer, there was added, with stirring at 0°, over a period of 30 minutes, 365 g. (3.4 moles) of ethyl chlorocarbonate. A bulky precipitate formed. Stirring was continued for thirty minutes after addition was complete. The reaction mixture was stirred to a paste with 500 ml. of water and filtered under suction; the precipitate was washed with three 200-ml. portions of ice-water prior to fusion *in vacuo*. The fused material was recrystallized from 800 ml. of 95% ethanol. There was obtained 430 g. (60%) of ethyl 4-phenylphenyl carbonate, m. p. 73.2–74.3°. A sample, recrystallized repeatedly from methanol, melted at 73.9–75.0°.

Anal.[6] Calcd. for $C_{15}H_{14}O_3$: C, 74.36; H, 5.82. Found: C, 73.90; H, 5.88.

4-Phenylphenyl Isobutyrate.—The acylation of 255 g. (1.5 moles) of 4-phenylphenol in 360 ml. of pyridine by means of 180 g. (1.7 moles) of isobutyryl chloride as described for ethyl 4-phenylphenyl carbonate gave 294 g. (82%) of 4-phenylphenyl isobutyrate, m. p. 73.2–74.8°. A sample, recrystallized repeatedly from methanol, melted at 74.2–74.8°.

Anal.[6] Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.53; H, 6.80.

Phenyl Isobutyrate.—A solution of 94 g. (1 mole) of phenol in 240 ml. of pyridine was acylated by means of 128 g. (1.2 moles) of isobutyryl chloride essentially as described above. After reaction was complete, the mixture was diluted with water and ether to produce two clear phases. The aqueous phase was extracted with ether and the combined ether phases were dried over anhydrous sodium sulfate followed by "Drierite." After removal of the solvent at atmospheric pressure, the residue was distilled through an eight-inch Vigreux column. Fractions boiling at 60–110° (55 g.) and 110–112° (131 g.) were obtained. The lower boiling fraction was distilled up to 105° at 25 mm. and the residue combined with the fraction boiling at 110–112°. Distillation of the mixture gave 4 g. of a fore-run, b. p. 105–111° at 25.5 mm., and 144 g. (87%) of phenyl isobutyrate, b. p. 111–112.2° at 25.5 mm. A mid-fraction (b. p. 112° at 25.5 mm., const.) was analyzed.

Anal.[6] Calcd. for $C_{10}H_{12}O_2$: C, 73.15; H, 7.37. Found: C, 72.84; H, 7.32.

(6) Analysis by T. S. Ma, University of Chicago, Chicago, Illinois.

DEPARTMENT OF CHEMISTRY
DUKE UNIVERSITY
DURHAM, NORTH CAROLINA
RECEIVED DECEMBER 6, 1943

The Preparation of 1- and 2-Phenylpyrrole

BY F. F. BLICKE AND J. L. POWERS

Recently we have been able to synthesize relatively large quantities of 1- and 2-phenylpyrrole by means of the procedures reported below.[1]

The apparatus used for the preparation of 1-phenylpyrrole consisted of two round, cast-iron shells with flanges which were clamped together by means of eight short bolts fitted with wing nuts (only two bolts are shown in the drawing); several "cranite" asbestos gaskets placed between the shells prevented leakage.[2] Each of the shells was sixteen inches in diameter and three inches high at the point at which the pipe was attached. Two iron pipes, one inch in diameter, were screwed into the shells as shown in the diagram. The upper, outlet pipe was attached by rubber tubing to a Pyrex glass tube (combustion type) about six feet long which served as a condenser. At the beginning of the process it was found necessary to cool the condenser with wet cloths, but during the end of the operation it was essential, in some instances, to warm the glass tube with a flame to prevent the condensed material from clogging the tube.

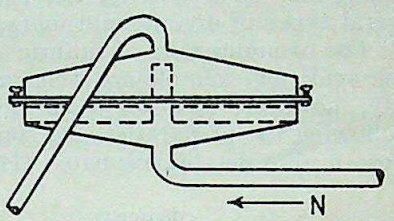

Fig. 1.

The mucic acid salt was placed in a shallow galvanized iron tray. A short, metal tube had been inserted through the center of the tray in order that a stream of nitrogen could be passed through the apparatus.

The apparatus was supported on a tripod, and heated from below with eight Meker burners. Since it was found that rubber tubing attached to the burners melted in a short time, due to the intense heat, it was necessary to unscrew the side arms from the burners and replace them with threaded iron pipes about eighteen inches long.

The upper shell of the apparatus was covered with several removable layers of heavy asbestos, and the whole apparatus was surrounded with a large sheet of the same material.

1-Phenylpyrrole.—In order to prepare the required aniline salt of mucic acid, an intimate mixture of 1116 g. of aniline and 1260 g. of mucic acid was placed in a large evaporating dish, 60 cc. of water added, and the mixture stirred and heated on a steam-bath until it became solid. The material was then pulverized and air-dried.

The salt (396 g.) was placed in the apparatus and the distillate was collected in a 2-liter, round-bottomed flask which contained 110 cc. of concd. hydrochloric acid and 400 cc. of water. The aniline dissolved and the insoluble pyrrole was obtained as a brown, crystalline material. After one-half hour the reaction was complete. The crude material was subjected to steam distillation. The phenylpyrrole separated in the distillate in the form of colorless crystals while a tarry residue remained in the distillation flask. The average yield was 60 g. (42%). The product melted at 58°,[3] and boiled at 230–234°.

2-Phenylpyrrole.—A five-foot length of Pyrex combustion tubing was bent, twenty inches from one end, at a 75° angle, and placed in a combustion furnace. To facilitate the flow of the product through the tube, one end of the furnace was raised about two inches above the level of the laboratory table. Fifty grams of 1-phenylpyrrole were put into a 125-cc. distillation flask in which the usual side arm had been replaced by another 10 cm. long and 9 mm. in thickness, sealed close to the bulb and fitted to the tube by a cork. The tube was heated to a dull red heat, and the pyrrole was distilled through the tube at such a rate that about thirty minutes were required to empty the distillation flask. Since the rearrangement was not complete, the product was distilled through the hot tube two more times.

The material was fractionated, and the recovered 1-phenylpyrrole was subjected to the rearrangement process. From 200 g. of 1-phenylpyrrole there was produced 127 g. (63%) of 2-phenylpyrrole; b. p. 272–278°.[4] A completely colorless product could be obtained only by distillation under reduced pressure; b. p. 151–154° (5 mm.).

(1) Other methods described during the last few years are those of Allen, Gilbert and Young (*J. Org. Chem.*, **2**, 230 (1937)) and of Adkins and Coonradt (THIS JOURNAL, **63**, 1566 (1941)).

(2) When new gaskets are used, the bolts must be tightened again after the apparatus has become hot.

(3) Köttnitz (*J. prakt. Chem.*, [2] **6**, 148 (1873)) found 62°.

(4) Piutti and Testoni (*Gazz. chim. ital.*, **28**, 1905 (1895)) found 271–272°.

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But even this material soon turned pink when exposed to air. However, after several recrystallizations of the vacuum-distilled product from 70% alcohol the pyrrole was obtained in a form which remained colorless; m. p. 128–129°.[5]

(5) The melting point has been reported to be 129° (ref. 4).

COLLEGE OF PHARMACY
UNIVERSITY OF MICHIGAN
ANN ARBOR, MICHIGAN RECEIVED SEPTEMBER 30, 1943

Reactions of *t*-Butyl Cinnamate and *t*-Butyl Benzoate with Phenylmagnesium Bromide[1]

BY FRED FROSTICK, ERWIN BAUMGARTEN AND CHARLES R. HAUSER

Kohler and Heritage[2] showed that methyl cinnamate undergoes both 1,2- and 1,4-addition with phenylmagnesium bromide yielding a mixture of products. We have found that *t*-butyl cinnamate (in which the carbonyl group is relatively hindered) undergoes apparently only 1,4-addition yielding *t*-butyl β,β-diphenylpropionate.

$$C_6H_5CH{=}CHCOOC(CH_3)_3 \xrightarrow{C_6H_5MgBr} (C_6H_5)_2CHCH_2COOC(CH_3)_3$$

To a stirred solution of phenylmagnesium bromide, prepared from 5.6 g. (0.23 mole) of magnesium and 46.1 g. (0.23 mole) of bromobenzene in 100 ml. of dry ether, was added during twenty minutes 23.5 g. (0.115 mole) of *t*-butyl cinnamate.[3] The reaction mixture refluxed gently and a precipitate formed. After refluxing for three hours, the mixture was poured into an ice-cold saturated ammonium chloride solution. The ether layer was shaken with cold 10% sulfuric acid, and then with cold 5% potassium hydroxide solution. After drying with anhydrous sodium sulfate followed by "Drierite," the solvent was distilled, finally using the water aspirator. The solid residue (29.5 g.) was recrystallized from petroleum ether (b. p. 30–60°), yielding 15 g. (44%) of essentially pure *t*-butyl β,β-diphenylpropionate. Four recrystallizations yielded a product melting at 55.5–55.6°.

Anal.[4] Calcd. for $C_{19}H_{22}O_2$: C, 80.85; H, 7.86. Found: C, 80.93; H, 7.60.

The product was further identified by hydrolysis in the presence of concentrated hydrochloric acid to β,β-diphenylpropionic acid, which, after recrystallization from acetone–water mixture, melted at 152–154° (reported, 155°).[5]

Analogous to methyl or ethyl benzoate, *t*-butyl benzoate has been found to undergo the "normal" carbonyl addition reaction with phenylmagnesium bromide, yielding triphenylcarbinol. Some benzoic acid (which might have resulted from hydrolysis of the ester) was also isolated. Neither isobutene nor *t*-butylbenzene was found; these products would have resulted had the elimination or substitution reaction occurred.

To a stirred solution of phenylmagnesium bromide (prepared from 0.5 mole each of magnesium and bromobenzene in 150 ml. of ether), contained in a reaction flask equipped with a U-tube immersed in a dry ice-bath, was added during one-half hour 0.3 mole of *t*-butyl benzoate[6] in 100 ml. of ether. After standing overnight the reaction mixture was refluxed for five hours. The liquid condensed in the U-tube did not absorb an appreciable amount of bromine in carbon tetrachloride solution, indicating that no significant amount of isobutene was formed. After decomposition of the reaction mixture with ammonium chloride, the ether solution was shaken with bicarbonate (from which was isolated a 10% yield of benzoic acid), dried and the solvent distilled. The residue was subjected to steam distillation until oily material (containing diphenyl but apparently no *t*-butylbenzene) ceased to pass over, and then recrystallized from alcohol, yielding triphenylcarbinol (41%), m. p. 159–162°.

In a similar experiment, carried out with *t*-butyl benzoate and methylmagnesium iodide, no isobutene appeared to be formed.

(1) This work was supported by a grant from the Duke University Research Council.

(2) Kohler and Heritage, *Am. Chem. J.*, **33**, 21 (1905); see also Allen and Blatt in "Organic Chemistry," Gilman, Editor-in-Chief, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 681.

(3) Abramovitch, Shivers, Hudson and Hauser, THIS JOURNAL, **65**, 986 (1943).

(4) Analysis by T. S. Ma, University of Chicago, Chicago, Illinois.

(5) Bacon, *Am. Chem. J.*, **33**, 84 (1905).

(6) Norris and Rigby, THIS JOURNAL, **54**, 2097 (1932).

DEPARTMENT OF CHEMISTRY
DUKE UNIVERSITY
DURHAM, NORTH CAROLINA RECEIVED DECEMBER 6, 1943

Nature of Carotenes in Alfalfa

BY A. R. KEMMERER AND G. S. FRAPS

According to Beadle and Zscheile,[1] spinach and some other plants contain appreciable amounts of "neo-β-carotene," stereoisomer of β-carotene, which can be produced by heating β-carotene in petroleum ether. This pigment is the same as that termed pseudo-α-carotene by Gillam and El Ridi,[2] and neo-β-carotene B, by Polgár and Zechmeister.[3] Kemmerer and Fraps,[4] by chromatographic analysis with calcium hydroxide, found, besides β-carotene and this "neo-β-carotene" in plants, another pigment which they termed "carotenoid X." "Carotenoid X" did not possess vitamin A potency, while "neo-β-carotene" had one-half the potency of β-carotene. Polgár and Zechmeister,[4] by various treatments of β-carotene, secured about twelve neo-β-carotenes including neo-β-carotenes B and U. Since the identification of the carotenes in plants is of both practical and scientific importance, both the "neo-β-carotene" and "carotenoid X" in alfalfa were studied.

Neo-β-carotene B was prepared by refluxing a solution of 20 mg. of crystalline carotene in 100 ml. of hexane for one hour.[4] The solution was chromatographed on calcium hydroxide and the neo-β-carotene B was separated and extracted. Then it was purified by another chromatographic treatment. This pigment is just below the β-carotene band in the chromatogram. Neo-β-carotene U was prepared by dissolving about 10 mg. of crystalline carotene in petroleum naphtha (Skellysolve F), adding a small crystal of iodine, and allowing the solution to stand an hour.[4] The neo-β-carotene U was separated and purified by absorption on calcium hydroxide. The neo-β-carotene U is just above the β-carotene in the chromatogram.

"Carotenoid X" and "neo-β-carotene" were prepared from alfalfa leaf meal by extraction with alcholic potassium hydroxide and petroleum naphtha (Skellysolve F) and chromatographic separation on calcium hydroxide.[3]

(1) B. W. Beadle and F. P. Zscheile, *J. Biol. Chem.*, **144**, 21 (1942).

(2) A. E. Gillam and M. S. El Ridi, *Biochem. J.*, **30**, 1735 (1936).

(3) A. Polgár and L. Zechmeister, THIS JOURNAL, **64**, 1856 (1942).

(4) A. R. Kemmerer and G. S. Fraps, *Ind. Eng. Chem., Anal. Ed.*, **15**, 714 (1943).

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Solutions of neo-β-carotene U and "carotenoid X" were mixed and subjected to chromatographic analysis on calcium hydroxide. There was no separation of bands, showing that the two pigments were identical. By a similar experiment neo-β-carotene B and "neo-β-carotene" from alfalfa were found to be identical.

Direct comparisons of the absorption of light by the preparations were made by means of a quartz spectrograph. In petroleum naphtha (Skellysolve F) solutions, photographed at different settings of the photometer, "carotenoid X" and neo-β-carotene U both had absorption maxima at 468 and 443 mμ; "neo-β-carotene" from alfalfa and neo-β-carotene B likewise had the same absorption curve with maxima at 473 and 446 mμ.

The pigments were also compared by dissolving approximately equal quantities in hexane, treating with iodine and analyzing the product by chromatographic separation on calcium hydroxide. The colorimetric ratio of the pigments formed from neo-β-carotene U was, unknown pigment: neo-β-carotene U: β-carotene: neo-β-carotene B: neo-β-carotene E = 2:22:42:29:5 and from "carotenoid X" of alfalfa = 3:23:46:24:4. For neo-β-carotene B the ratio was, 2:25:45:28:0 and for neo-β-carotene from alfalfa 1:22:43:34:0. The ratios of stereoisomers produced by this treatment were nearly the same in the two comparisons, another evidence of the identity of the carotenes compared from alfalfa. The same carotenes have been found in the chromatographic analysis of other plants (spinach, collards, grasses, etc.).

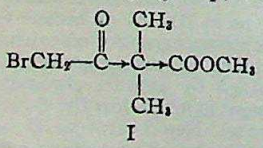
DIVISION OF CHEMISTRY
TEXAS AGRICULTURAL EXPERIMENT STATION
COLLEGE STATION, TEXAS RECEIVED NOVEMBER 22, 1943

The Action of Sodium Cyanide on Methyl γ-Bromo-α,α-dimethylacetoacetate

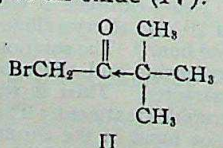
BY C. F. KOELSCH

The reaction of sodium cyanide with an α-halogenated ketone usually leads to the formation of a β-ketonitrile; for example, bromopinacolone yields pivaloylacetonitrile.[1] A few α-haloketones, however, furnish α,β-oxidonitriles; for example, desyl chloride yields α,β-epoxy-α,β-diphenylpropionitrile.[2]

On the basis of the polarizations indicated in formulas I and II, it was anticipated that methyl γ-bromo-α,α-dimethylacetoacetate (I) might not parallel bromopinacolone (II) in its behavior toward sodium cyanide, but might suffer attack at its carbonyl group, leading to an oxide (IV).

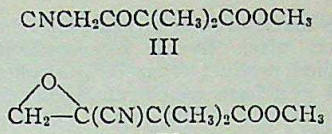


I



II

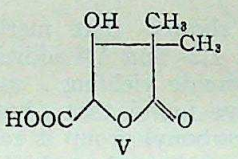
The reaction had been studied long ago[3,4,5] and the product had been assigned structure III. But a survey of the old data indicated that the properties of the product were more in accord with structure IV.



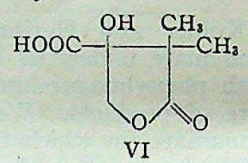
III

IV

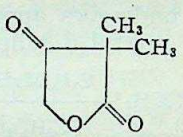
In the present work it was demonstrated that IV is correct. This was done by showing that the hydrolysis product of the nitrile, previously considered to be formed through hydration of the enol of III and formulated as V, actually is VI. The hydrolysis product was identical with the acid obtained by adding hydrogen cyanide to VII and hydrolyzing the resulting cyanohydrin, procedures which can lead only to VI.



V



VI



VII

2,4-Diketo-3,3-dimethyltetrahydrofuran[6] (VII), b. p. 200–210° (740 mm.) or 103–107° (16 mm.), was obtained in 86% yield when 25 g. of methyl γ-acetoxy-β-keto-α,α-dimethylbutyrate[7] was boiled for two hours with 5 g. of 10 molar alcoholic hydrogen chloride (contrary to the statement of Conrad and Gast,[6] the acetoxy ester was unchanged after it had been kept for three months; it also was unaffected when it was heated with potassium carbonate). When 1.3 g. of VII was shaken for fifteen minutes with a solution of 0.6 g. of sodium cyanide and 0.8 ml. of hydrochloric acid in 4 ml. of water, it furnished an oily cyanohydrin. This was removed with ether and boiled for one hour with 6 ml. of 20% hydrochloric acid; when the solution was cooled, it deposited 0.5 g. of VI, colorless prisms from water, m. p. 213–217° alone or mixed with the compound obtained from I by the procedure of Lawrence.[3] When it was boiled with methanol and sulfuric acid, VI gave a methyl ester that melted at 104–105° alone or mixed with Lawrence's ester.

Recognition of the correct structure (IV) for the nitrile previously considered to be III necessitates changes in the structures of substances derived from this compound. Simple esters, etc., need not be specifically mentioned here, but the following revisions must be pointed out. "3-Acetoxy-4,4-dimethyl-5-ketotetrahydro-furoic acid"[4] is actually 3-acetoxy-4,4-dimethyl-5-ketotetrahydrofuran-3-carboxylic acid; "4,4-dimethyl-5-ketotetrahydrofuroic acid"[4,5] is actually 4,4-dimethyl - 5 - ketotetrahydrofuran - 3 - carboxylic acid; "ethyl α′-chloro-β-hydroxy-α,α-dimethylglutarate"[3] is actually ethyl α-chloromethyl-α-hydroxy-β,β-dimethylsuccinate; "α,α-dimethyl glutaconic acid"[5] is actually[8] α,α-dimethylitaconic acid. Some doubt now attaches to the structures formerly assigned[3] to homologs of III and V, *viz.*, ethyl γ-cyano-β-keto-α-ethyl-α-

(1) Widman and Wahlberg, *Ber.*, **44**, 2065 (1911).

(2) Kohler and Brown, THIS JOURNAL, **55**, 4299 (1933). Other examples may be found in the work of Justoni [*Gazz. chim. ital.*, **71**, 41 (1941), *Chem. Abs.*, **36**, 1016 (1942)] and of Delbaere [*Bull. soc. chim. Belg.*, **51**, 1 (1942), *Chem. Abs.*, **37**, 5018 (1943)].

(3) Lawrence, *J. Chem. Soc.*, **75**, 417 (1899).

(4) Conrad and Gast, *Ber.*, **32**, 137 (1899).

(5) Conrad, *ibid.*, **33**, 1920 (1900).

(6) Conrad and Gast, *ibid.*, **31**, 2728 (1898).

(7) Conrad and Kreichgauer, *ibid.*, **30**, 857 (1897).

(8) Perkin, *J. Chem. Soc.*, **81**, 249 (1902).

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methyl-(and α,α-diethyl)-butyrate, and 3-hydroxy-4-ethyl-4-methyl- (and 4,4-diethyl)-5-keto-tetrahydrofuroic acid, but circumstances will not permit a continuation of the present study to include these substances.

SCHOOL OF CHEMISTRY
UNIVERSITY OF MINNESOTA
MINNEAPOLIS, MINNESOTA RECEIVED NOVEMBER 5, 1943

Observations on the Rare Earths. L.[1] The Separation of Erbium from Yttrium by Fractional Precipitation of the Ferrocyanides[2]

BY THERALD MOELLER AND H. E. KREMERS

Yttrium and erbium oxide mixtures which accumulate during bromate fractionations of the yttrium earths are usually further separated by basicity methods, although the very favorable solubility difference between the ferrocyanides of these elements[3,4] renders ferrocyanide fractionation more rapid. In spite of the gelatinous nature of the precipitates, comparatively pure yttrium material has been prepared by this procedure,[5,6,7,8] and Prandtl,[9] using large quantities of nitric acid to promote crystallinity, has obtained erbium oxide of high purity. The lack of specificity in Prandtl's directions suggested a further study of the problem, and the resulting modified procedure gives consistently reproducible results, is rapid, and is free from undesirable oxidation of the ferrocyanide.

Experimental

Ferrocyanide Precipitation.—Erbium–yttrium chloride solutions were prepared in 3 *N* hydrochloric acid to contain 2% rare earth oxide and 10% ammonium chloride. To these solutions at room temperature, sufficient 20% potassium ferrocyanide solution (calculated as the trihydrate) to precipitate about one-half the rare earth material was added slowly with constant stirring. Experimentally, about 15 ml. precipitated the equivalent of 1 g. of rare earth oxide from material analyzing 85–100% Er_2O_3 and 20 ml. for lower erbium concentrations. Slow precipitation began only after complete addition of the ferrocyanide. After several hours, the precipitates were removed by suction filtration on qualitative paper.

Recovery of Rare Earth Materials.—Part of the iron was removed from the precipitates by boiling the solids with 50% sodium hydroxide, diluting, and filtering. After ignition of these hydroxides, the remainder of the iron was removed by oxalate precipitation of the rare earths from chloride solutions. The ferrocyanide mother liquors gave iron-free oxides after two precipitations with oxalic acid.

Fractionation of Erbium–Yttrium Mixtures.—Erbium–yttrium mixtures showing no absorption lines for holmium or thulium were fractionated by the above procedure. Each fractionation was followed by means of spectrophotometric analyses (based upon the 489 and 653 mμ erbium absorption bands)[10] of oxides recovered from both precipitates and mother liquors. Oxides of approximately the same composition were combined and refractionated.

The fractionation of 43 g. of a mixture (ER-18) containing 57% Er_2O_3 gave 4.8 g. of 89% Er_2O_3, 2.1 g. of 86% Er_2O_3, 5.9 g. of 80% Er_2O_3, 6.8 g. of 62% Er_2O_3, 6.7 g. of 38% Er_2O_3, and 15 g. of an oxide mixture low in erbium after twenty-eight fractional precipitations (five series with five or six fractions in each).

A series of fractions (ER-34) obtained from a urea separation[11] and a previous ferrocyanide fractionation and consisting of (1) 6.9 g. of 87% Er_2O_3, (2) 5.9 g. of 80% Er_2O_3, (3) 13.8 g. of 59% Er_2O_3, (4) 20.3 g. of 27% Er_2O_3, and (5) 45 g. of 17% Er_2O_3 yielded ultimately 3.14 g. of 98.5% Er_2O_3 (two precipitations of fraction (1)); 1.3 g. of 94% Er_2O_3, 2.35 g. of 93% Er_2O_3 and 2.8 g. of 80% Er_2O_3 (four precipitations of fractions (2), (3), and (4), respectively); and 5.6 g. of 48% Er_2O_3 (three precipitations of fraction (5)). In addition, 5.0 g. of 65% Er_2O_3, 17.6 g. of 44% Er_2O_3, and 9.5 g. of 27% Er_2O_3 were recovered from the final mother liquors.

Success of the ferrocyanide procedure is dependent upon the complete removal of iron, since even traces of iron yield gelatinous blue precipitates which nullify the effects of crystallinity in the rare earth ferrocyanides. Although some unavoidable loss is inherent in the oxalate precipitations, the speed and efficiency of the method recommend it.

Acknowledgment.—The authors wish to express their appreciation to Dr. C. J. Rodden of the National Bureau of Standards for the analysis of an erbium oxide sample used in the calibration of our spectrophotometer.

(1) For the preceding communication in this series see Kleinberg, Taebel and Audrieth, *Ind. Eng. Chem., Anal. Ed.*, **11**, 368 (1939).

(2) Presented before the Division of Physical and Inorganic Chemistry at the 106th meeting of the American Chemical Society at Pittsburgh, Pa., September 6, 1943.

(3) Rowland, *Chem. News*, **70**, 68 (1894).

(4) Prandtl and Mohr, *Z. anorg. allgem. Chem.*, **236**, 243 (1938).

(5) Bettendorf, *Ann.*, **352**, 88 (1907).

(6) Meyer and Wuorinen, *Z. anorg. Chem.*, **80**, 7 (1913).

(7) Prandtl, *Z. anorg. allgem. Chem.*, **143**, 277 (1925).

(8) Canneri, *Atti accad. Lincei*, **8**, 164 (1928).

(9) Prandtl, *Z. anorg. allgem. Chem.*, **198**, 157 (1931).

(10) Rodden, *J. Research Natl. Bur. Standards*, **28**, 265 (1942).

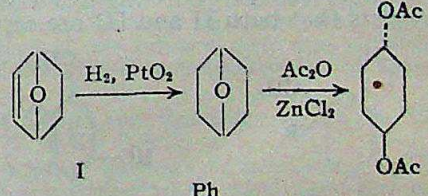
(11) Fogg and Hess, THIS JOURNAL, **58**, 1751 (1936).

NOYES CHEMICAL LABORATORY
UNIVERSITY OF ILLINOIS
URBANA, ILLINOIS RECEIVED SEPTEMBER 20, 1943

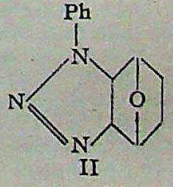
3,6-Epoxycyclohexene from Furan and Ethylene[1]

BY WALTER NUDENBERG AND LEWIS W. BUTZ

3,6-Epoxycyclohexene (I) has now been prepared by the procedure and with the apparatus previously employed in similar preparations.[2] It has been characterized as indicated below.



I



II

Into a mixture of 30–35 g. of furan and a few crystals of hydroquinone ethylene was introduced in two or three portions with intermittent shaking up to an initial pressure of 1100–1200 lb. per sq. in. at room temperature. The bomb was heated to 155° and kept at 150–155°, the pressure dropping and ultimately becoming constant after six-

(1) Not subject to copyright. This work was supported by an allotment from the Special Research Fund (Bankhead–Jones Act of June 29, 1935).

(2) Joshel and Butz, THIS JOURNAL, **63**, 3350 (1941).

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teen hours. After cooling the bomb, the gas was allowed to escape through a trap cooled by solid carbon dioxide, and the deposited furan was returned to the reaction mixture. The whole was distilled in three fractions: the first, of unreacted furan, 14–16 g.; the second, b. p. 40–118°, chiefly furan, 1.5 g., the third, a colorless liquid, b. p. 118–122°, 1.2–1.5 g. This last was 3,6-epoxycyclohexene, b. p. 118–119°, $n^{20}D$ 1.4629; yield, 5–8% on the furan consumed.

The triazoline derivative, formula II,[3] was prepared by mixing a few drops of phenyl azide with a similar quantity of epoxycyclohexene and allowing the resulting yellow solution to crystallize in the ice box overnight. Repeated crystallization from ethyl acetate gave fine white needles, m. p. 166–167° (cor.) (after drying over phosphorus pentoxide).

Anal.[4] Calcd. for $C_{12}H_{13}ON_3$: C, 67.0; H, 6.1; N, 19.5. Found: C, 67.1; H, 6.1; N, 19.5.

The epoxycyclohexene (4.5 g.) in 12 ml. of methanol was hydrogenated using 50 mg. of Adams catalyst. Distillation of the residue remaining after removal of the catalyst and methanol gave a fraction b. p. 110–120°. This material was refluxed, without further purification, with acetic anhydride and several crystals of zinc chloride for two hours. The excess acetic anhydride was distilled off and the remaining brown oil poured into hot water. Crystallization did not occur. The oil was extracted with ether, the solution dried and the ether evaporated. The residual oil on standing deposited crystals, m. p. 102–103.6°, from aqueous ethanol. A mixture with authentic ester,[5] m. p. 102–104°, also melted at 102–103.6°.

(3) Alder and Stein, *Ann.*, **501**, 1 (1935).

(4) Analysis by Dr. T. S. Ma, University of Chicago.

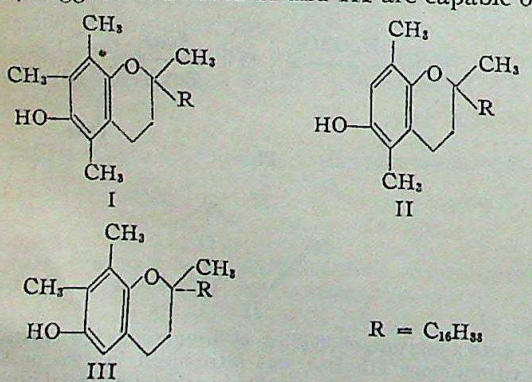
(5) Baeyer, *Ann.*, **278**, 93 (1894). The *trans*-quinitol diacetate was kindly furnished by Mr. A. M. Gaddis, who prepared it from hydroquinone.

BUREAU OF ANIMAL INDUSTRY
AGRICULTURAL RESEARCH ADMINISTRATION
UNITED STATES DEPARTMENT OF AGRICULTURE
BELTSVILLE, MARYLAND RECEIVED OCTOBER 2, 1943

Coupling of Gamma Tocopherol and Failure of β-Tocopherol to Couple with Diazonium Salts

BY MARY LOUISE QUAIFE

Inspection of the structural formulas of α-tocopherol (I), β-tocopherol (II), and γ-tocopherol (III) suggests that both II and III are capable of



coupling with diazonium salts.[1] We have found that γ-tocopherol couples readily, but the beta isomer, surprisingly, does not. Consequently, III can be determined in the presence of I and II. This note describes the reaction upon which the procedure is based and also experiments showing the failure of β-tocopherol to couple.

γ-Tocopherol is determined by photometric estimation of the red dye produced by its reaction with diazotized *p*-nitroaniline in aqueous alcohol solution at *p*H of about 6. The dye, extracted with Skellysolve H, gives a stable color with absorption maxima at 530 mμ and 380 mμ. Over the range of quantity of γ-tocopherol employed in the analysis (0.2 to 0.5 mg.) absorption at either wave length is proportional to concentration. It is measured at 520 mμ for convenience. The method has been applied to estimation of γ-tocopherol content of tocopherol concentrates with results as shown in Table I. Total tocopherols were determined by the method of Emmerie and Engel.[2]

TABLE I

γ-TOCOPHEROL CONTENT OF VEGOL (CONCENTRATE OF NATURAL MIXED TOCOPHEROLS) FRACTIONS (DUPLICATE ANALYSES)

Sample	γ-Tocopherol, %	% total tocopherols	Ratio of γ- to total tocopherol; % γ-
Vegol (C)	2.8	4.3	65
	3.1	4.5	69
Vegol (I)	16.3	26.3	62
	17.8	26.7	67
Vegol (II)	21.4	42.0	51
	19.7	42.3	47
Vegol (III)	9.0	40.2	22
	9.5	40.2	24

When the procedure was applied to natural β-tocopherol, it required 12 mg. to give absorption at 520 mμ, equivalent to that given by only 0.05 mg. of γ-tocopherol. Since in this case the *p*H was about 6, the ability of β-tocopherol to couple with benzenediazonium chloride was tested over a *p*H range of 4.5 to 11. The test procedure was similar to that used in the analytical method except for increased amounts of β-tocopherol. Control series were run using equal amounts of γ-tocopherol as well as aqueous alcohol blanks. The resultant Skellysolve extracts of the reaction mixtures of the tocopherols (0.4 mg./cc.) and of the blank had colors as shown in Table II.

TABLE II

COLORS OF COUPLING PRODUCTS OF TOCOPHEROLS AND BENZENEDIAZONIUM CHLORIDE

*p*H	Blank	β-Tocopherol	γ-Tocopherol
4.5	Colorless	Colorless	Colorless
9.0	Light yellow	Light yellow	Deep orange
11.0	Light yellow	Light yellow	Deep orange

Absorption spectra over the range of 310 to 620 mμ of the reaction products at *p*H 9 show no difference in absorption between the Skellysolve extracts of the β-tocopherol reaction mixture and the blank. The γ-tocopherol azo dye formed at *p*H 9 had a density of 1.7 at 475 mμ, the peak of absorption.

(1) Scudi and Buhs, *J. Biol. Chem.*, **146**, 6 (1942).

(2) Emmerie and Engel, *Rec. trav. chim.*, **57**, 1351 (1938).

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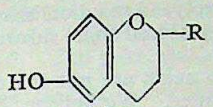
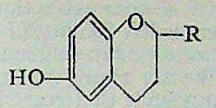
This difference in coupling ability of γ- and β-tocopherols suggests possible fixation of the bond structure in the benzenoid nucleus of the tocopherols according to IV instead of V. The sub-



IV



V

stituted tetralins, which have a ring system similar to that of the tocopherols, are considered to have a double bond between the rings. The observed difference in the tocopherol isomers may also be related to the Mills–Nixon effect.[3,4]

The advice of Dr. C. F. H. Allen is gratefully acknowledged.

(3) Mills and Nixon, *J. Chem. Soc.*, 2510 (1930).

(4) Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, 2nd Ed., Vol. I, p. 136.

COMMUNICATION NO. 56
FROM THE LABORATORIES OF
DISTILLATION PRODUCTS, INC.
ROCHESTER, NEW YORK RECEIVED DECEMBER 7, 1943

The Alkylation of Isopropylmalonic Ester Using Sodium Triphenylmethide[1]

BY J. C. SHIVERS, B. E. HUDSON, JR., AND CHARLES R. HAUSER

The difficulty of alkylation of secondary alkyl malonic esters, for example, isopropylmalonic ester, by the ordinary procedure using sodium ethoxide[2] in alcoholic solution has been ascribed to the incomplete formation of the sodio derivative.[3]

$$RCH(CO_2C_2H_5)_2 + NaOC_2H_5 \rightleftarrows [RC(CO_2C_2H_5)_2]Na + C_2H_5OH$$

Wallingford and co-workers[3b] found that, by substituting an alkyl carbonate for alcohol as a reaction medium and distilling all alcohol produced from the reaction with sodium ethoxide, certain secondary alkyl malonic esters could be alkylated. We have found that alkylation of isopropylmalonic ester may be achieved by using the stronger base, sodium triphenylmethide, in an inert solvent. The yields of alkylation product with ethyl iodide and isopropyl iodide were 73 and 23%, respectively.

$$(CH_3)_2CHCH(CO_2C_2H_5)_2 + NaC(C_6H_5)_3 \longrightarrow Na[(CH_3)_2CHC(CO_2C_2H_5)_2] + HC(C_6H_5)_3$$

$$RI + Na[(CH_3)_2CHC(CO_2C_2H_5)_2] \longrightarrow (CH_3)_2CHC(CO_2C_2H_5)_2 + NaI$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad R$$

Crossley and Le Sueur[2b] found that ethylisopropylmalonic ester (R = ethyl, prepared by isopropylating ethylmalonic ester using sodium ethoxide) undergoes alkaline hydrolysis to form partly ethylisopropylmalonic acid and partly ethylisopropylmalonic acid ester, which on decarboxylation gives ethyl ethylisopropylacetate. We have found that di-isopropylmalonic ester (R = isopropyl) undergoes alkaline hydrolysis only with difficulty yielding di-isopropylmalonic acid ester, which undergoes decarboxylation with difficulty.

Experimental

Diethyl isopropylmalonate (b. p. 217–218°)[4] was prepared in 56% yield essentially according to the directions given in "Organic Syntheses"[5] for the preparation of diethyl *n*-butyl malonate.

Diethyl Ethylisopropylmalonate.—To sodio-isopropylmalonic ester, prepared from 42.0 g. (0.205 mole) of the ester and 0.205 mole of an ether solution of sodium triphenylmethide,[6] was added 32 g. (0.205 mole) of ethyl iodide. After standing for seven days, the ether solution (above the thin layer of sodium iodide crystals) was transferred by means of nitrogen pressure to a flask and the solvent distilled through a column up to 40°. More ethyl iodide (11.6 g.) in 100 cc. of dry benzene was added to the residue and the mixture was refluxed eighteen hours. On working up the mixture there was obtained 35 g. (73%) of diethyl ethylisopropylmalonate, b. p. 118–120° (15 mm.) (234–236° at atm. pres.).[2b]

Refluxing diethyl ethylisopropylmalonate ten hours with 95% alcoholic potassium hydroxide and decarboxylation of the resulting malonic acid gave a 48% yield of ethylisopropylacetic acid, b. p. 104–105° (15 mm.). Neutral equivalent, calculated for $C_7H_{14}O_2$: 130.18. Found: 131.28. With aniline the acid gave the anilide, melting at 118–119°. (*Anal.*[7] Calcd. for $C_{13}H_{19}ON$: N, 6.83. Found: N, 6.53). No attempt was made to isolate ethyl ethylisopropylacetate obtained by Crossley and Le Sueur.[2b]

Diethyl Di-isopropylmalonate.—Sodio-isopropylmalonic ester was prepared by the decolorization of 0.1 mole of sodium triphenylmethide solution with 20.2 g. (0.1 mole) of isopropyl malonic ester, and practically all of the ether was distilled from the mixture in an atmosphere of nitrogen. To the residue was added 10 cc. of dry benzene followed by 21.2 g. (0.125 mole) of isopropyl iodide in 40 cc. of benzene. After standing overnight, the mixture was refluxed twenty-four hours, additional (4.3 g.) isopropyl iodide was added, and the mixture refluxed for twenty-four hours longer. On working up the mixture there was obtained 5.6 g. (23%) of diethyl di-isopropylmalonate, b. p. 122–124° (15 mm.).

Anal.[7] Calcd. for $C_{13}H_{24}O_4$: C, 63.90; H, 9.90. Found: C, 63.52; H, 9.79.

Long refluxing (eighteen to twenty-four hours) of diethyl di-isopropylmalonate with alcoholic potassium hydroxide yielded unchanged ester and ethyl hydrogen di-isopropylmalonate, m. p. 71–72°. Neutral equivalent, calculated for $C_{11}H_{20}O_4$: 216.3. Found: 213.6. The mono acid-ester on heating slowly decarboxylated to form a neutral material, b. p. 71–72° (15 mm.), which was apparently ethyl di-isopropylacetate (*Anal.* Calcd. for $C_{10}H_{20}O_2$: C, 69.72; H, 11.70. Found: C, 68.71; H, 11.31).[7]

(1) Paper XXII on "Condensations."

(2) (a) Fischer and Dilthey, *Ann.*, **335**, 337 (1904); (b) Crossley and Le Sueur, *J. Chem. Soc.*, **77**, 83 (1900).

(3) (a) See Shonle, Kelch and Swanson, THIS JOURNAL, **52**, 2440 (1930); (b) Wallingford, Thorpe and Homeyer, *ibid.*, **64**, 580 (1942).

(4) Conrad and Bischoff, *Ann.*, **204**, 144 (1880), report a boiling point of 213–214°.

(5) Adams and Kamm, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 245.

(6) Renfrow and Hauser, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 607.

(7) Microanalyses by Dr. T. S. Ma, University of Chicago.

DEPARTMENT OF CHEMISTRY
DUKE UNIVERSITY
DURHAM, NORTH CAROLINA RECEIVED NOVEMBER 8, 1943

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Color Reactions for Certain Amino Acids

BY HENRY TAUBER

We have observed that certain amino acids are converted to chromogens when heated. Alcoholic extracts containing these chromogens become more deeply colored when alkali is added, but on subsequent acidification become colorless or much lighter in color.

The procedure has been as follows. Ten mg. of the amino acid in a dry Pyrex test-tube is heated over a burner until the first color change occurs, which may be to yellow or brown depending on the amino acid. Overheating should be avoided since it destroys the chromogens. After cooling, 3 cc. of ethyl alcohol is added and the solution boiled for thirty seconds and the resulting solution divided equally among three small test-tubes. To the first is added 0.2 cc. of 0.1 *N* sodium hydroxide, to the second 0.2 cc. of 0.1 *N* sulfuric acid, and to the third 0.2 cc. of water.

Twenty-one biologically important amino acids have been found to behave as follows: three (*dl*-alanine, *dl*-valine and *dl*-iso-leucine) when heated sublime completely, leaving no pigment or residue. Twelve (*l*-cystine, *l*-cysteine, glycine, *l*-hydroxyproline, *dl*-methionine, glutamic acid, *dl*-aspartic acid, *dl*-serine, *l*-proline, *d*-arginine-monohydrochloride, *dl*-lysine, and *d*-lysine) change to yellow, brown or black decomposition products without chromogenic properties. Six (phenylalanine, *l*-tyrosine, *l*-leucine, *l*-histidine, *l*-tryptophan and *dl*-threonine) form chromogens which react as follows when subjected to the above tests: *l*-tyrosine, *l*-tryptophan and *dl*-threonine turn reddish brown on heating, exhibit a light brown or reddish color in alcoholic solution, become more deeply colored on the addition of alkali and turn a light brown or, in the case of *l*-tyrosine, a yellow color on acidification. *l*-Histidine-monohydrochloride becomes light brown on heating, light yellow in alcoholic solution, deep yellow on the addition of alkali and almost colorless on acidification. *dl*-β or *l*-β-phenylalanine and *l*-leucine on heating partially sublime, turn yellow and give a yellow or light yellow color in alcoholic solution. This color turns to a deep yellow on addition of alkali and becomes almost colorless on subsequent acidification. In the case of the β-phenylalanines the alkaline alcoholic solution exhibits a greenish-yellow fluorescence which is particulary strong in ultraviolet light, without the addition of alkali.

This fluorescent pigment from phenylalanine has been isolated in a more concentrated form as follows. One gram of phenylalanine is heated in a large Pyrex test-tube and stirred with a thermometer until the temperature of the material reaches 250°. After cooling, the crystalline reaction mixture is extracted four times with 15-cc. portions of acetone. The deep yellow, fluorescent solution is concentrated to 10 cc., filtered and evaporated to dryness in vacuum. Ninety-five mg. of reddish-brown hygroscopic material is obtained. Dilute alcoholic solutions of this pigment show intense fluorescence in ultraviolet light but not in daylight. On the addition of alkali, however, deep greenish-yellow fluorescence is shown in daylight. In acetone the fluorescence is much stronger than in alcoholic solution. The pigment gives a much more intense xanthoproteic reaction (deep orange-red) than phenylalanine. After acetone extraction of the pyrolyzed reaction mixture there is left 550 mg. of white material and some substance is lost owing to sublimation.

We are aware that these amino acids are not the only compounds that react in this manner. We believe, however, that these observations are interesting enough to warrant recording. Especially remarkable is the strongly fluorescent compound that forms on the pyrolysis of phenylalanine.

AGRICULTURAL RESEARCH ADMINISTRATION
U. S. DEPARTMENT OF AGRICULTURE
WASHINGTON, D. C. RECEIVED SEPTEMBER 28, 1943

Substituted α-Amyl-cinnamylaldehydes

BY A. WEIZMANN

α-Amyl-cinnamylaldehyde is, because of its jasmin-like odor, manufactured industrially from heptanal and benzaldehyde.[1] It seemed possible that the same synthesis with substituted benzaldehydes, which by themselves exhibit pleasant odors, would give especially valuable products. This was, however, not the case. 4-Methoxy-, 3,4-methylene-dioxy- and 3,4-dimethoxy-α-amyl-cinnamylaldehydes have been synthesized and studied; the first of them has been described briefly before.[2] The substituted benzaldehydes proved less reactive than benzaldehyde itself in this condensation, as in other similar cases.[3] In all these experiments, a mixture of pyridine and piperidine proved a more convenient catalyst, than the commonly used potassium hydroxide. Vanillin did not react at all with oenanthal under these conditions.

Experimental

4-Methoxy-α-amyl-cinnamylaldehyde.—A mixture of heptanal (12 g.), anisaldehyde (14 g), pyridine (100 cc.) and piperidine (10 cc.) was heated on the water-bath for eight hours, poured out into ice-cold dilute sulfuric acid and extracted with ether. The product was twice distilled at 0.3 mm.; b. p. 145°; yield, 10 g.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.6; H, 8.6. Found: C, 77.6; H, 9.0.

The semicarbazone separated from a mixture of the aldehyde (1.5 g.), semicarbazide hydrochloride (0.75 g.) and potassium acetate (0.6 g.) in aqueous alcohol at room temperature. It formed needles, m. p. 143–145°, when crystallized from propyl alcohol. Calcd. for $O_{16}H_{23}O_2N_3$: N, 14.5. Found: N, 14.3.

3,4-Dimethoxy-α-amyl-cinnamylaldehyde.—Veratraldehyde (13 g.) and heptanal (9.5 g.) were condensed by heating for eight hours in presence of pyridine (50 cc.) and piperidine (5 cc.). The condensation product had b. p. 165° (0.6 mm.).

Anal. Calcd. for $C_{16}H_{22}O_3$: C, 73.3; H, 8.4. Found: C, 73.4; H, 8.7.

The semicarbazone, prepared as above, was recrystallized from propyl alcohol and formed needles, m. p. 175°.

Anal. Calcd. for $C_{17}H_{25}O_3N_3$: C, 64.0; H, 7.8; N, 12.7. Found: C, 64.4; H, 8.4; N, 13.0.

(1) Rutowski and Korolew, *J. prakt. Chem.*, [2] **119**, 272 (1928).
(2) I. G. Farbenindustrie A. G., French Patent 628,739 (1927).
(3) Weizmann, *Org. Chem.*, **66**, 233 (1937).

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3,4-Methylenedioxy-α-amyl-cinnamylaldehyde was prepared analogously from heptanal (11.4 g.) and piperonal (15 g.). The fraction 150–160° (0.8 mm.) of the condensation product was purified *via* the semicarbazone as above. From butyl alcohol long needles, m. p. 155°, were obtained.

Anal. Calcd. for $C_{16}H_{21}O_3N_3$: N, 13.9. Found: N, 14.0. The pure aldehyde had b. p. 158–159° (0.9 mm.).

THE DANIEL SIEFF RESEARCH INSTITUTE
REHOVOTH, PALESTINE RECEIVED NOVEMBER 26, 1943

NEW COMPOUNDS

Some Aryl and Aralkyl Ureas

In connection with a study of the hypnotic properties of aryl ureas carried out by a pharmacological group in these Laboratories, a number of halogenated unsymmetrical aryl alkyl ureas have been prepared. Data on these and on some related unhalogenated ureas and symmetrically substituted ureas are presented in Table I.

Preparation of Secondary Amines.—The 3-chloro and bromo anisyl methyl and homo anisyl methyl amines (leading to ureas XVI–XIX) were prepared by halogenation of N-methyl anisyl and N-methyl homo anisyl amines in hydrochloric acid solution (XXIV in hydrobromic acid).

Whereas non-halogenated aromatic secondary amines are readily prepared by alkylation with alkyl halides, isolation of the secondary amine as the nitrosamine followed by reduction with stannous chloride, the alkyl bromides and iodides are unsuitable for reaction with halogenated aromatic amines,[1] the halogen being removed or displaced with resulting complications. By use of alkyl sulfates and alkyl toluene-sulfonates the desired alkyl groups can be introduced satisfactorily.

Ethylation was accomplished by stirring the primary amine with ethyl sulfate and water on the steam-bath until the layers had disappeared after which the conventional nitrosamine procedure was followed.

The secondary propyl and butyl amines corresponding to ureas IV and VI were obtained by warming 1 mol of alkyl toluene sulfonate with 2 mols of primary amine for three hours at 110–120°. The partially cooled melts were sludged with benzene and the bulk of the primary amines separated as salts of *p*-toluenesulfonic acid. Addition to the filtrate of alcoholic hydrogen chloride equivalent to about half of the remaining base precipitated virtually all of the remaining primary amines, after which the hydrochlorides of the secondary amines could be separated without trouble. In some runs sulfonamide formation was encountered.

Preparation of Ureas.—The symmetrically substituted ureas XX and XXI were prepared from ethyl isocyanate and the appropriate aromatic bases.

TABLE I

SECONDARY ARYL AND ARALKYL UREAS $R_1R_2NCONH_2$

	R_1	R_2	M. p., °C.[a]	Appearance	Cryst. solvent[b]	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
I	C_6H_5	CH_2CH_2OH	110		Æ	$C_9H_{12}O_2N_2$	59.97	6.71	59.68	7.05
II[c]	2-Me-4-Cl-C_6H_3	C_2H_5	93	Stout prisms	Æ-H	$C_{10}H_{13}ON_2Cl$	56.46	6.16	56.59	6.19
III[d]	2-Me-4-Br-C_6H_3	C_2H_5	88.5–89	Rect. prisms	E-H	$C_{10}H_{13}ON_2Br$	46.70	5.10	47.00	5.35
IV	The same	*n*-C_3H_7	94.5–95.5	Prisms	H	$C_{11}H_{15}ON_2Br$	48.70	5.58	48.76	5.78
V[e]	2-Me-5-Cl-C_6H_2	C_2H_5	166–167	Felted needles	A-Aq	$C_{10}H_{13}ON_2Cl$	56.46	6.16	56.52	6.37
VI[f]	The same	*n*-C_4H_9	79.5–80	Prisms	H	$C_{12}H_{17}ON_2Cl$	59.86	7.12	59.84	7.44
VII[g]	4-Me-2-Br-C_6H_3	C_2H_5	116	Tiny prisms	E	$C_{10}H_{13}ON_2Br$	46.70	5.10	46.82	5.21
VIII[h]	2-Et-4-Br-C_6H_3	C_2H_5	95	Small stout prisms	E-H	$C_{11}H_{15}ON_2Br$	48.70	5.58	48.45	5.86
IX[i]	4-Et-C_6H_4	C_2H_5	122–124	Stout prisms	Æ-H	$C_{11}H_{16}ON_2$	68.70	8.39	68.99	8.62
X[j]	4-Et-2-Br-C_6H_3	C_2H_5	114	Stout prisms	E-H	$C_{11}H_{15}ON_2Br$	48.70	5.58	48.65	5.76
XI	2,4-$Me_2C_6H_3$	C_6H_5	73–74	Prisms	H	$C_{11}H_{16}ON_2$	68.70	8.39	68.75	8.50
XII	$C_6H_5CH_2$	CH_3	135	Needle prisms	Æ	$C_9H_{12}ON_2$	65.82	7.37	65.99	7.32
XIII	The same	*n*-C_4H_9	61–62	Needles	H	$C_{12}H_{18}ON_2$	69.84	8.80	69.80	8.72
XIV[k]	2-EtO-5-Br-C_6H_3	C_2H_5	124–124.5	Needles	Æ-H	$C_{11}H_{15}O_2N_2Br$	45.98	5.27	46.24	5.50
XV	4-MeO-C_6H_4-CH_2	CH_3	140–141	Flattened needles	A-Aq	$C_{10}H_{14}O_2N_2$	61.82	7.27	62.12	7.46
XVI	4-MeO-3-Cl-$C_6H_3CH_2$	CH_3	169–169.5	Leaflets	A	$C_{10}H_{13}O_2N_2Cl$	52.49	5.73	52.52	5.64
XVII	4-MeO-3-Br-$C_6H_3CH_2$	CH_3	178	Leaflets	A	$C_{10}H_{13}O_2N_2Br$	43.95	4.80	44.22	5.10
XVIII	4-MeO-3-Cl-$C_6H_3CH_2CH_2$	CH_3	117.5–118	Prisms	Æ	$C_{11}H_{15}O_2N_2Cl$	54.41	6.23	54.49	6.38
XIX	4-MeO-3-Br-$C_6H_3CH_2CH_2$	CH_3	116.5–117	Prisms	Æ-H	$C_{11}H_{15}O_2N_2Br$	45.97	5.27	46.03	5.30
	Symmetrically substituted ureas									
XX	2-Me-4-Br-$C_6H_3NHCONHEt$		230–232	Tiny felted needles	HAc	$C_{10}H_{13}ON_2Br$	46.70	5.10	47.00	5.45
XXI	2,4-Me_2-$C_6H_3NEtCONHEt$		76	Stout prisms	H	$C_{12}H_{20}ON_2$	70.86	9.16	70.62	9.19
XXII	2-Et-$C_6H_4NEtCON(COC_6H_5)_2$		128–129	Needles	B	$C_{28}H_{24}O_3N_2$	74.97 (N = 7.00)	6.04	75.00 (N = 6.95)	6.38
	Secondary Aralkylamine Hydrochlorides $R_1R_2NH\cdot HCl$									
XXIII	4-MeO-3-Cl-$C_6H_3CH_2$	CH_3	201–201.5	Needle prisms	A	$C_9H_{13}ONCl_2$	48.64	5.90	48.76	6.03
XXIV	4-MeO-3-Br-$C_6H_3CH_2$ (hydrobromide)	CH_3	202–203	Needles	A	$C_9H_{13}ONBr_2$	34.73	4.21	35.08	4.44
XXV	4-MeO-3-Cl-$C_6H_3CH_2CH_2$	CH_3	196	Felted needles	Æ	$C_{10}H_{15}ONCl_2$	50.84	6.41	51.00	6.50
XXVI	4-MeO-3-Br-$C_6H_3CH_2CH_2$	CH_3	215–216	Fine needle prisms	A	$C_{10}H_{15}ONClBr$	42.78	5.39	42.94	5.49

[a] All melting points corrected. [b] A = ethanol; Æ = ethyl acetate; E = ether; H = hexane; Aq = water; HAc = acetic acid; B = benzene. [c] B. p. (13 mm.) of secondary amine, 136°. [d] B. p. (0.25 mm.) of secondary amine, 96–99°. [e] B. p. (27 mm.) of secondary amine, 141°. [f] B. p. (1 mm.) of secondary amine, 125°. [g] B. p. (17 mm.) of secondary amine, 137°. [h] B. p. (3 mm.) of secondary amine, 135°. [i] B. p. (22 mm.) of secondary amine, 122–123°. [j] B. p. (3 mm.) of secondary amine, 107°. [k] B. p. (0.25 mm.) of secondary amine, 111°.

The secondary amines corresponding to the ureas I, XI–XIII and XV are known. The amines corresponding to ureas XVI–XIX were characterized as salts and data thereon are also included in Table I. For the other secondary bases boiling points are given. The derived ureas are themselves satisfactory as compounds of characterization.

(1) Baltzly and Buck, THIS JOURNAL, 63, 1757 (1941).

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The unsymmetrically substituted ureas I–XIX were formed by the reaction of nitro-urea with the corresponding secondary amines. This reaction is not complete with aromatic secondary amines having ortho-substitution. Ordinarily unreacted amine can be separated by partitioning between ether or benzene and about 6% hydrochloric acid. When, however, there is halogen substitution the basicity of the amine is too low for this separation. Steam-distillation from saturated sodium chloride solution (at about 110°) proved to be adequate for the removal of the unreacted amine and it was then possible to crystallize the secondary ureas reported here. The *n*-butyl derivative analogous to the ureas III and IV was not obtained in crystalline form. Tested physiologically as a crude preparation it showed considerable hypnotic activity.

The dibenzoyl urea XXII resulted from benzoylation of the known N-ethyl-N-*o*-ethyl phenyl urea either by the Schotten–Baumann method or by heating with benzoyl chloride in pyridine.

BURROUGHS WELLCOME & CO., U. S. A. JOHANNES S. BUCK
EXPERIMENTAL RESEARCH LABORATORIES
RICHARD BALTZLY
TUCKAHOE, NEW YORK ALAN E. ARDIS

RECEIVED DECEMBER 10, 1943

Di-*n*-butyl-*n*-propylamine

This compound was prepared by the hydrolysis of γ-di-*n*-butylaminopropylmagnesium chloride with aqueous hydrochloric acid, and by the interaction of 2 moles of di-*n*-butylamine and 1 mole of *n*-propyl iodide in a sealed tube at 120° for four hours, removing the residual secondary amine by shaking with benzoyl chloride and 10% sodium hydroxide.

Both methods gave an identical product, with the following constants: b. p. (754 mm.) 193°; b. p. (8 mm.) 73–75°; d^{20}_4 0.7622; $n^{25}D$ 1.4248.

The picrate crystallized easily from 95% alcohol or from ether; m. p. 115.8–116.2°.

The picrate was analyzed for C and H. Calculated for $C_{17}H_{23}N_4O_7$: mol. wt., 400.42; C, 50.99; H, 7.05. Found: C, 50.90; H, 6.77.

NATIONAL INSTITUTE OF HEALTH
BETHESDA, MARYLAND, THEODORE D. PERRINE

RECEIVED DECEMBER 23, 1943

o-Phenylene Dioxyacetic Acid and its Ethyl Ester

The ethyl ester of *o*-phenylenedioxyacetic acid was prepared by refluxing dichloroethyl acetate with catechol in absolute ethanol solution in the presence of 2 moles of sodium and in an atmosphere of nitrogen until neutral to litmus. The reaction mixture was diluted with water, the ester extracted with ether, washed with sodium hydroxide solution and water, and isolated by fractionation; boiling point 115–117° at 12.5 mm.

Anal. Calcd. for $C_{10}H_{10}O_4$: C, 61.86; H, 5.15; mol. wt., 194. Found: C, 61.09; H, 5.70; mol. wt. (Rast), 191. The product gave no test for halogen nor phenolic hydroxyl.

The acid was prepared from its ester by hydrolysis with 1 *N* sodium hydroxide solution; melting point, 107–108° (uncor.) from ether–petroleum ether.

Anal. Calcd. for $C_8H_6O_4$: C, 57.84; H, 3.79. Found: C, 58.12; H, 3.91.

All attempts to effect direct preparation of *o*-phenylene dioxyacetic acid by condensation between catechol and dichloroacetic acid failed.

DEVELOPMENT LABORATORY
E. R. SQUIBB & SONS, W. G. CHRISTIANSEN
BROOKLYN, N. Y. M. A. DOLLIVER

RECEIVED NOVEMBER 23, 1943

A New Ammine of Basic Copper Chromate

The salt which most commonly separates from ammoniacal copper chromate solutions is $Cu(NH_3)_4CrO_4$. Other ammines have been described.[1] However, from solutions deficient in chromium and containing a considerable excess of ammonium hydroxide, there separates a previously undescribed compound, having the composition $2CuO \cdot 4NH_3 \cdot CrO_3 \cdot H_2O$. In a typical experiment, the crystals were obtained by adding to a suspension of 14.3 g. of basic copper carbonate in 20 ml. of water, 20 ml. of a solution containing 220 g. of ammonium dichromate per liter; 50 ml. of concentrated ammonium hydroxide was added and the mixture shaken thoroughly. Solution was complete except for a few bluish flecks. On standing at room temperature for several days, crystals of the new compound will frequently deposit. Once a crop has been obtained, preparation of the material may be ensured by seeding the solution with the compound. Cooling should be avoided, as at low temperatures green needles of $Cu(NH_3)_4CrO_4$ tend to separate. The yield, after washing with ammonium hydroxide, alcohol and ether, and drying, is about 6 g. The crystals of the new compound are 0.05–1.0 mm. on a side, thickly tabular, almost cubic in habit, greenish-black by reflected light and deep blue-green by transmitted light. The material slowly loses ammonia on exposure to the air, and stoppered preparations have a noticeable odor. On ignition at low temperatures, the crystals decompose with mild deflagration. The crystalline substance becomes coated with an orange-brown discoloration on exposure to air, and water decomposes it to a yellow basic copper chromate. It is insoluble in alcohol, ether, benzene and carbon tetrachloride, and soluble in ammonium hydroxide and acids, being decomposed by the latter; d^{25}_4 2.49.

Anal. Calcd. for $2CuO \cdot 4NH_3 \cdot CrO_3 \cdot H_2O$: CuO, 46.09; NH_3, 19.73; CrO_3, 28.96; H_2O, 5.22. Found: CuO, 46.21; NH_3, 19.55; CrO_3, 28.92; H_2O, 5.33.

RESEARCH LABORATORIES
MUTUAL CHEMICAL CO. OF AMERICA
BALTIMORE, MARYLAND WINSLOW H. HARTFORD

RECEIVED SEPTEMBER 29, 1943

(1) Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Longmans, Green and Co., London, 1931, Vol. 11, pp. 261–262.

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COMMUNICATIONS TO THE EDITOR

AN EQUATION OF STATE FOR SATURATED FLUIDS

Sir:

During a search for an equation of state for saturated fluids a simple relationship between pressure, temperature and specific volumes was found which seemingly is of general validity. In fact out of 59 substances tested only one, acetic acid, showed anomalous behavior. In this case the admittance of association, that is, double molecules, will explain the discrepancies. The test substances have molecular weights from 2 to 260, critical pressures from 2.3 to 218 atm., critical temperatures from −268 to +448° and critical densities from 0.03 to 1.15 g./cc.

Upon separating the roots of a more general, three constant, quadratic equation the following expression was arrived at

$$P = \frac{CT}{v_g + v_e + 2B}$$

where $C = R/M$ and $B = (CT_c/2P_c) - v_c$.

The symbols denote: p, the saturation pressure in atm.; T, the saturation temperature in °K. (ice point 273.16°K.); v_g and v_e the specific volume of saturated vapor and saturated liquid, respectively, in l. per gram; R, the gas constant (0.08206 for l., atm., g.-moles) and M, the molecular weight in grams (based on atomic weights of 1942). Subscripts c, indicate critical values.

The pressures calculated by the equation from corresponding v_g, v_e and T values are given for water from melting point to critical point. The critical data and constants for water are: T_c = 374.11°C., p_c = 218.167 atm., v_c = 3.1975 cc./g., C = 0.0045548 and B = 0.0035593.

TABLE I

T, °C.	p, atm. calcd.	lit.[1]	T, °C.	p, atm. calcd.	lit.[1]
0	0.0060307	0.0060273	200	15.910	15.332
20	.023089	.023042	220	23.800	22.897
40	.073126	.072748	240	34.356	33.044
60	.19742	.19656	260	48.049	46.322
80	.47070	.46740	280	65.290	63.343
100	1.0109	1.0000	300	86.583	84.776
120	1.9901	1.9595	320	112.34	111.40
140	3.6419	3.5669	340	143.09	144.14
160	6.2638	6.1032	360	180.59	184.26
180	10.216	9.896	374.11	(218.167)	218.167

Evidently the equation does not compare with the high accuracy afforded by several vapor pressure equations; however, the wide range of application, the great simplicity and the ease of calculation will render it useful for checking and supplementing experimental data. The agreement is considerably better for many of the substances tested and especially for the simpler gases such as helium, hydrogen, neon, nitrogen.

A complete report will be published later.

(1) Fales and Shapiro, THIS JOURNAL, 58, 2418 (1936); "Int. Crit. Tables," Vol. III, 1928.

COMMONWEALTH COLOR AND CHEMICAL CO.
BROOKLYN, N. Y. J. E. HAGGENMACHER

RECEIVED JANUARY 3, 1944

ELECTRON MICROSCOPE OBSERVATIONS OF CLAM MUSCLE FIBRILS

Sir:

Submicroscopic fibrils have been obtained from the adductor muscles of marine and fresh-water clams (Mya, Venus, Anodonta). In the dark-field microscope they appear as long, slender, needle-like fibrils. This fibrous protein has the solubility properties of myosin; it dissolves in 0.6 M potassium chloride to form a solution showing high viscosity and stream birefringence. Dilution with water produces a flocculent precipitate which can be redissolved in potassium chloride and which is apparently devoid of fibrils.

Electron micrographs show the fibrils to be very long and evenly contoured, having widths usually between 200 and 1000 Å., though sometimes less. In fibrils treated with osmic acid the density along the axis is not uniform but shows a periodic variation, producing a cross-striated appearance (Fig. 1). From measurements of 100 fibrils a distribution curve of "spacings" of this fiber axis repeat pattern was constructed. All the values lay between 290 and 470 Å., a surprisingly small range in view of the mechanical lability usually associated with muscle fibers. The most frequently occurring spacings were between 330 and 390 Å., the average value of all spacings being 360 Å.

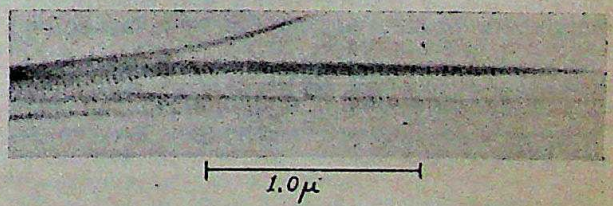

Fig. 1.—Electron micrograph of clam muscle fibrils, magnification × 27,000.

Subsequently Dr. R. S. Bear examined these muscles with X-rays and obtained diffraction evidence that the fiber-axis period in the intact dried muscle is 720 Å. It is improbable that this apparent difference is due to alterations produced in isolating the fibrils and preparing them for elec-

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tron microscope examinations. More likely, the larger X-ray period reflects density differences not yet resolved with the electron microscope but which may become apparent when special methods are applied. The structural problem, which is of great interest in connection with the mechanism of contractility, is one which requires for its solution both electron microscope and X-ray diffraction data. Details of the analysis will be reported in due course.

DEPT. OF BIOLOGY AND BIOLOGICAL ENGINEERING
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE, MASS.
M. A. JAKUS
C. E. HALL
F. O. SCHMITT

RECEIVED JANUARY 8, 1944

SPIROPENTANE

Sir:

The authors have made a Raman spectroscopic study of the low-boiling products obtained in the debromination of pentaerythrityl bromide by zinc. The first reduction was carried out in aqueous methanol.[1] In addition to lines assignable to methylenecyclobutane (I) and to 2-methyl-1-butene (II) the Raman spectrum of the product showed lines at 581 and 1033 cm.$^{-1}$ which arose from about 1–5% of a third component (III). Examination of the spectra of various fractions obtained in the distillation of the reduction mixture indicated that the boiling point of III should be near 37°. By means of this information and the known Raman spectra and generalizations therefrom it was possible, at least tentatively, to conclude that III did not correspond to any compound known to the authors. It seemed quite probable that the lines belong to spiropentane.

It was reasoned that if this were spiropentane and if it could be formed at all by zinc in aqueous methanol, in spite of the preponderance toward rearrangement, there should be other conditions, under which III would form in larger proportion. This proved to be the case. When the reduction was carried out by zinc in molten acetamide in the presence of sodium iodide and sodium carbonate[2] the product showed the same low-boiling substances but the compound responsible for the 581 and 1033 cm.$^{-1}$ lines was now a major component—approximately 40%.

Isolation of the pure compound involved removal of the accompanying olefins, first by repeated extraction with saturated aqueous silver nitrate, then with saturated aqueous silver perchlorate and finally by reaction with bromine. None of these reagents noticeably affected the new compound. The final, purified product has an odor similar to chloroform; b. p. 38.3–38.5°; n^{20}D 1.4117. *Anal.*[3] Calcd. for C_5H_8: C, 88.17; H, 11.83. Found: C, 87.91; H, 11.53. Its spectrum is given in Table I.

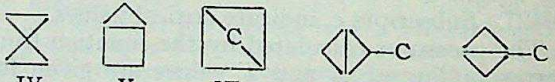
TABLE I

RAMAN SPECTRUM OF SPIROPENTANE

$\Delta\nu$, cm.$^{-1}$	I^a	$\Delta\nu$, cm.$^{-1}$	I^a
305	4	1397	5
581	16	1426	10
613	4	2836	0.4
779	4	2881[b]	
872	30	2991	100
1033	50	3065	30
1150	1		

[a] Intensities measured on Gaertner microdensitometer. [b] Intensity too low to measure.

Raman spectra considerations, boiling point, and non-reactivity with bromine conclusively eliminated acetylenes, diolefins and monocyclic olefins and left only the possibility that the compound was one of the following dicyclic hydrocarbons



IV V VI VII VIII

The authors favor formula IV because, 1, the product is formed in greater amount when conditions are less favorable to rearrangement and 2, the Raman pattern in the 2800–3100 cm.$^{-1}$ region indicates that all the hydrogens present are attached to cyclopropane rings and none either to cyclobutane rings (V, VI) nor to carbon in a methyl group (VII, VIII).

CHEMICAL LABORATORY
ILLINOIS INSTITUTE OF TECHNOLOGY
CHICAGO, ILLINOIS
M. J. MURRAY
EUGENE H. STEVENSON

RECEIVED JANUARY 21, 1944

(1) A report on this part of the work was presented before the Organic Division of the Pittsburgh Meeting of the American Chemical Society, September, 1943.

(2) Hass, McBee, Hinds and Gluesenkamp, *Ind. Eng. Chem.*, 28, 1178 (1936).

(3) Micro-analysis by Dr. T. S. Ma, University of Chicago.

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NEW BOOKS

How to Solve Problems in Qualitative Analysis. By JOSEPH A. BABOR, Associate Professor of Chemistry, The College of the City of New York, and J. KENNETH W. MACALPINE, Assistant Professor of Chemistry, New York University. Thomas Y. Crowell Company, 432 Fourth Avenue, New York, N. Y., 1943. iv + 93 pp. 14 × 21 cm. Price, $0.75.

The increasing importance of mathematical operations in chemistry has been producing a variety of "problem-solving" books, and this one is among the first dealing with qualitative analysis. Chapters composed of definitions, explanatory matter, examples and problems for the student, are presented under the titles: 1. Mathematical Operations, 2. Concentration of Solutions, 3. Weak Electrolytes, 4. Solubility-Product Principle, 5. Ionization Constant and Solubility Product, 6. The Water Equilibrium; Hydrolysis, 7. Complex Ions. The average sophomore student will have been exposed already to much of this material, but a lot of it will not have been retained. Diligent use of this condensed pamphlet will serve to revive and polish a student's faded comprehension into practically workable form.

ALLEN D. BLISS

Proteins, Amino Acids and Peptides as Ions and Dipolar Ions. By EDWIN J. COHN and JOHN T. EDSALL, Harvard Medical School. (A. C. S. Monograph Series.) Reinhold Publishing Corporation, 330 West Forty-second St., New York, N. Y., 1943. xviii + 686 pp. 15.5 × 235 cm. Price, $13.50.

At the present time, the outstandingly important general problem in the chemistry of natural products is the determination of the structure of proteins. Through the work of Emil Fischer and his predecessors, it has long been recognized that proteins consist of complicated condensation products of amino acids linked by peptide bonds, but of the ordinal distribution of these component units, and the effects of fine structure upon physicochemical properties, our knowledge is almost entirely conjectural. This state of affairs is ascribable to the complexity of the problem rather than to any neglect, for during the past decades much effort has been devoted to its elucidation.

The appearance of this treatise, written by a group of investigators who themselves have added, by observation and interpretation, to our knowledge of the physicochemical behavior of proteins, is therefore particularly welcome. Chapters on special aspects of the subject have been contributed independently or in collaboration with one of the authors by John D. Ferry, John G. Kirkwood, John W. Mehl, Hans Mueller, L. J. Oncley, and George Scatchard. No attempt has been made to present a systematic discussion of protein chemistry in all its phases, nor to describe experimental procedures.

The first half of the book deals with amino acids and peptides, consideration of which is an essential preliminary to the theoretical treatment of proteins. In an introductory chapter, Cohn and Edsall survey the modern theoretical views of dipolar ions and indicate the application of these to proteins. The second chapter, by Edsall, consists of a discussion of spectroscopic properties of dipolar ions; mere mention is made of the author's elegant demonstration that Raman spectra afford cogent evidence, supported by infrared and ultraviolet spectra, of the dipolar character of amino acids. In Chapter 3, Scatchard applies concentrated thermodynamics and simple electrostatic theory to dipolar systems. Chapter 4, by Edsall, relating to acid–base equilibria, contains a lucid description of Brönsted's theory as applied to amino acids and discusses in detail the ionization data of various types of amino acids and peptides; this discussion is continued in the fifth chapter, entitled Some Relations between Acidity and Chemical Structure, also by Edsall, who includes here a pertinent outline of the resonance theory. In Chapter 6, Edsall gives a comprehensive survey of work on the dielectric constants and dipole moments of dipolar ions; in Chapter 7 he discusses apparent molal volume, heat capacity, compressibility and surface tension of dipolar ions in solution. Chapter 8, by Edsall and Scatchard, relates to solubility in water and organic liquids, and includes a brief section on hydrogen bonding. Chapter 9, by Cohn and Edsall, treats of interactions between organic solvents and dipolar ions, as estimated from solubility ratios, in reference to the respective importance of the hydrophilic and hydrophobic groups in the amino acid molecule; the impressive volume of data permits the detection of striking quantitative trends in solubility relations. Chapter 10, by Cohn, is devoted to interactions between amino acids, peptides and related substances, and their effect on the activity coefficient. In Chapter 11, the same author considers the effect of interactions between ions and amino acids or peptides upon solubility, and discusses the theory of salting-out and salting-in. Chapter 12, by Kirkwood, is devoted to theoretical interpretation of the properties of solutions of dipolar ions which are characteristic of their electrical structure.

The second half of this volume bears the general title "The Size, Shape and Electric Charge of Protein Molecules." In Chapter 13, Edsall considers the structural basis of the protein molecule as inferred from analysis and from the action of proteolytic enzymes. Here the absence of clear-cut evidence of precise structure, in the organic chemist's sense of the word, combined with the inordinately complicated nature of the molecule, renders the author's task of summary difficult in the extreme; he has, however, so marshalled the pertinent facts as to present as clear a picture as seems humanly possible.

The succeeding chapters are devoted to more detailed discussion of restricted avenues of approach. In Chapter 14, Edsall considers the evidence concerning the peptide chain afforded by X-ray diffraction studies, discusses the structure of the "fibrous" and the "globular" proteins, gives a few paragraphs to the virus proteins, and concludes with brief sections on the cyclol hypothesis and on the deductions from Patterson projections. Chapter 15, by Cohn, consists of a survey of the natural amino acids, the special methods by which some of these are estimated in protein hydrolysates, and the amino acid composition of a few proteins. Chapter 16, by Cohn and Edsall, deals with the density of proteins and the molal volumes of their constituent amino acid residues. The osmotic pressure of proteins in solution and the deductions as to molecular weight are discussed in Chapter 17 by Edsall and Cohn. In Chapter 18, Edsall and Mehl take up the problems of translational diffusion and Brownian movement of proteins; in the succeeding chapter Edsall discusses sedimentation and diffusion in centrifugal fields and the results of ultracentrifugal studies on proteins.

Chapter 20, by Edsall, is devoted to the important subject of behavior of proteins as acids and bases. In the discussion of net charge and total charge in proteins, the author admits that his reasoning involves the addition or removal of protons and of no other ion, but he adheres to the custom of referring to the "binding" of "acid" and "base." This reviewer hopes that in future editions the authors will, in their theoretical treatment of the charges on dissolved proteins, exercise their world-wide authority and abandon this convention in favor of a terminology which suggests the participation of hydrogen or hydroxyl ions, and not that of undissociated molecules.

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In Chapter 21, Edsall discusses the determination of viscosity and double refraction of flow in protein solutions and the interpretation of the resulting information with respect to the shape of protein molecules. Chapter 22, by Oncley, is devoted to consideration of the estimation of electric moments and relaxation times by means of the dielectric constants of protein solutions. In Chapter 23, Cohn takes up the theory of the solubility of proteins and Edsall discusses the application of the phase rule to their solubility relations, a procedure of practical value in establishing criteria of homogeneity of protein preparations. In Chapter 24, Cohn and Ferry discuss the detection of interactions of proteins with ions and dipolar ions by determining the relations between solubility and various physical and chemical properties; salting-in and salting-out are here considered. Chapter 25, by Mueller, is devoted to the theory of electrophoretic migration, a subject of increasing practical importance in medicine as well as in protein chemistry.

The volume closes with an appendix containing factual information, a general subject index and tabular indexes of data in the text for certain important amino acids, peptides and proteins.

Like the other monographs in this series, this book is admirably edited and printed. It is, however, not easy reading for the general student, and probably few specialists exist who could take the whole work in their stride. The treatise has great educational value, for investigators as well as for students. It is, moreover, but one of the fruits of the close association, over more than fifteen years, of the unique group of experts in the authors' laboratory, where "freed from the necessity of considering practical applications" they could "make the excursion into the chemistry of protein prototypes which forms the background of this book. . . . ."

HANS T. CLARKE

Treatment of Experimental Data. By ARCHIE G. WORTHING, University of Pittsburgh, and JOSEPH GEFFNER, Weirton Steel Company. John Wiley and Sons, Inc., 440 Fourth Ave., New York, N. Y., 1943. ix + 342 pp. Illustrated. 15.5 × 23.5 cm. Price, $4.50.

Bringing to bear the resources of numerical mathematics for the treatment of experimental results is a relatively new procedure in some of the fields where experimental observations are gathered. The reviewer recalls asking a mature student some thirty years ago how he had obtained certain values which had obviously been subjected to a smoothing process. The reply was that "a curve had been drawn among the points." One may indeed sympathize with Professor Worthing when he refers to exasperations engendered over the years by the lack of knowledge on the part of the author of the methods by which experimental data may be fully digested and conveniently presented.

The material of the volume is the culmination in large part of a graduate course in the general treatment of a wide variety of observational material. Everyone who works with observational material, regardless of the particular field, will take a lively interest in the systematic and clear expositions for dealing with data. There are thirteen chapters of which the first three pertain to primary representations followed by one on methods of differentiation and integration. The practical applications and uses of Fourier series including a discussion of analyzers occupy one chapter, and then comes a very sensible presentation of the doctrine pertaining to normal frequency distribution, precision indexes and the technique of least square treatments of data. The concluding chapters contain a brief account of correlation and non-harmonic periodic functions, while an appendix giving the elementary expansion rules for determinants, useful tables, and a copious bibliography complete the volume.

The authors have incorporated a number of features which should prove particularly attractive to students and facilitate the book's use as a text. For example, all symbols used are listed along with ample information about their meaning before the first chapter and the fifth chapter (Fourier series). An abundance of illustrative material from widely different fields is used throughout, each chapter concludes with a summary and a series of problems, and the ensemble of material is knit together in simple direct language. The book is also illustrated with an unusually large number of figures. The authors have made an excellent contribution which will undoubtedly go far to promote the intelligent evaluation of experimental data in all fields of science.

Naturally the authors have had to exercise care not to overexpand the material. The reviewer believes, however, that George Rutledge's method of obtaining a derivative function (*Phys. Rev.*, **40**, 262 (1932)) is superior to that based on the Gregory–Newton formula, particularly for machine calculations. This remark holds also for Rutledge's interpolation formulae (*Trans. Am. Math. Soc.*, **31**, 807 (1929)). E. V. Huntington (*Am. Acad. Arts Sci.*, **63**, 421 (1929)) has also given convenient and extensive interpolation tables.

The printing, typography and form of the volume are excellent.

F. G. KEYES

BOOKS RECEIVED

December 10, 1943–January 10, 1944

G. F. D'ALELIO. "A Laboratory Manual of Plastics and Synthetic Resins." John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y. 134 pp. $2.00.

WILLIAM H. CHAPIN AND L. E. STEINER. "Second Year College Chemistry." Fifth Edition. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y. 575 pp. $3.75.

E. P. CLARK. "Semimicro Quantitative Organic Analysis." Academic Press, Inc., 125 East 23rd Street, New York, N. Y. 135 pp. $2.50.

FRITZ FEIGL. "Laboratory Manual of Spot Tests." Translated from the German Manuscript by Ralph E. Oesper. Academic Press, Inc., 125 East 23rd Street, New York, N. Y. 276 pp. $3.90.

CHARLOTTE A. FRANCIS AND EDNA C. MORSE. "Fundamentals of Chemistry and Applications." Second Edition. The Macmillan Company, 60 Fifth Avenue, New York, N. Y. 537 pp. $3.50.

HARRY N. HOLMES. "Out of the Test Tube." Fourth Edition, Revised and Expanded. Emerson Books, Inc., 251 West 19th Street, New York, N. Y. 312 pp. $3.00.

PIERCE W. SELWOOD. "Magnetochemistry." Interscience Publishers, Inc., 215 Fourth Avenue, New York, N. Y. 287 pp. $5.00.

HENRY TAUBER. "Enzyme Technology." John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y. 275 pp. $3.50.

ALEXANDER N. WINCHELL. "The Optical Properties of Organic Compounds." The University of Wisconsin Press, 811 State Street, Madison 6, Wisconsin. 342 pp. Photoprinted. $5.00.

"A. S. T. M. Standards on Plastics." American Society for Testing Materials, 260 S. Broad Street, Philadelphia 2, Pennsylvania. October, 1943. 431 pp. $2.00.

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Manuscripts for THIS JOURNAL should be submitted to the Editor ready for publication, typewritten (double space), with 2–3 cm. margins, on a good quality, durable paper, preferably of 8.5″ × 11″ size. In addition to the original typewritten copy, one or more carbon copies should be submitted so that the time required for examination by the Editorial Board may thus be considerably shortened. Care should be taken that all pages in a manuscript, including tables (but not the diagrams) be numbered consecutively. In preparing manuscripts authors are requested to observe, for reasons of economy, the utmost conciseness consistent with clarity of presentation. The manuscripts should be addressed to specialists in their particular field rather than to the general reader. Extensive reviews of the literature cannot be accepted. When well-known or previously published procedures have been followed in the experimental work they should only be designated or referred to.

Form of Presentation.—There should be one or more introductory paragraphs setting forth the occasion, significance and main objectives of the investigation and the method of attack. This should be followed by the experimental results and a discussion of them, either *seriatim* or at their conclusion. Finally, there should be a brief summary of the main achievements of the investigation. Sometimes, particularly when the subject matter is involved and there are many details which, though essential for a successful repetition of the experiments, are unnecessary for the main account of the investigation, these details can with advantage be relegated to an appendix or supplement, just preceding the Summary. In intermediate cases it is often advisable to retain a single, straightforward presentation but to intercalate sections in fine print giving the experimental details of procedure. This has the great advantage of keeping the experimental details close to the more general statements based upon them and yet at the same time permitting the reader if he wishes to pass over this section without inconvenience.

It will be of great assistance to the Editor's Office if the style, arrangement and orthography of the manuscripts are made to conform to the usages of the JOURNAL as exemplified in its recent issues and as set forth in the following paragraphs.

Center headings should be employed sparingly; side headings should be indented and run into the text to which they apply, using period and dash. References to the literature and all footnotes regardless of their nature (except those in tables) should be numbered in one consecutive series, repetition of notes being avoided by using simply the superscript number corresponding to the original reference. They should follow immediately in separate lines the line of text containing the text words to which they refer, and may be set off by short rules above and below. The items in the references to the literature should conform to the uniform usages of the Journal as regards order and punctuation, and to the abbreviations as given by *Chemical Abstracts* in its "List of Periodicals Abstracted." The names of all simple compounds rather than their formulas should be used whenever they occur in the text. Periods of time (unless fractional) should be written in words and quantities of material in Arabic numerals, unless occurring at the beginning of a sentence. Letters used to represent quantities in mathematical expressions should be underscored to indicate that they are to be printed in italics, and Greek or other unusual characters should be written plainly or should be explained by annotations. Simple fractional expressions should be written with a slant line rather than in the conventional manner, so that only a single line of type is required. All subscripts and superscripts should be carefully made and placed (the degree sign ° or a small o should not be used to represent zero). For economy, except in unusual circumstances the abbreviations %, °A., cm., cc., ml., g., Å., m. p., f. p., b. p., cal., kcal., expt. and Fig., should be used rather than the words.

Figures and graphs should be carefully prepared line drawings on plain white drawing paper, blue drawing cloth or coördinate paper printed in blue only. The

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original are preferable, but clear, well-prepared photographic prints or photostats are acceptable. Illustrations are most conveniently handled when made in the conventional 8.5″ × 11″ manuscript size; if they are of necessity larger, and therefore liable to damage in mailing, duplicate rough sketches or photographic prints of smaller size should be furnished for dispatch to the Referees. Diagrams should be designed to occupy a single column width and should therefore be tall rather than wide. Particular attention should be given to the correct proportions of the various parts of the figure, especially the experimental points, and if any letters, numbers, or legends must be placed on the diagram to their proportions also. In graphs the frame and actual curves should be ruled and inked more heavily than the coördinate lines, and these latter should not be too close together. Experimental points should always be given and should be indicated not by crosses but by circles or other symbols carefully drawn with drafting instruments. Where feasible it is often helpful to have the diameter of the circles indicate the precision of the measurements. The numbers and legends on coördinate axes are set up in type by the printer; the author, therefore, should place them in pencil outside the axes. The numbers and titles of figures should be placed below the diagrams, or on the back, or collected on a separate sheet. Small photographic prints should be mounted on cardboard and any composite series of photographic prints should be mounted in the order and arrangement desired. Each piece of illustration copy should be marked on the margin or back with the name of the author and brief title of the article (for identification purposes).

Tables.—Tables should not be used indiscriminately as they are much more expensive, line for line, than running text. If reasonably possible, they should be designed to occupy fully a single column (3 inches), which will take 50–75 characters and spaces. Tables occupying the full width can be used, but they are undesirable for the same reasons advanced with regard to page wide figures; their preparation should follow the same principles as for those of single width. Care should be taken to avoid any arrangement which unduly increases the depth of a table, and column heads should be made as small as possible, using abbreviations liberally. Lines of data should not be numbered nor run numbers given unless these numbers are needed for reference in the text. Columns should not be used to contain only one or two entries, nor should the same entry be repeated numerous times consecutively, since these cases may be taken care of more economically in footnotes, or by entries following the title of the table. Data should not be included in one column which are deducible easily by simple arithmetic from data in another column. Tables should be interspersed in the manuscript as near as possible to the places where they are referred to in the text, and need not be placed alone on separate sheets.

Formulas and Equations.—Empirical and structural formulas and mathematical and chemical equations should be arranged to fill adequately the width of a single column. This will often require a continuation of the equation in additional lines, and although this is a disadvantage it is in general preferable to intrusion into the adjoining column. Subscripts and superscripts, especially the latter, should be written with care and the conventional fractional arrangements should not be used in exponents. Organic structural formulas should be arranged to fill the space economically, and arrows should be used horizontally or vertically, not diagonally, wherever possible.

Notes do not differ fundamentally from Articles. They describe fragmentary or less complete studies and hence particular attention must be given to brevity and conciseness of presentation. Summaries are not included. They are collected in a special section near the end of each number of the Journal.

New Compounds.—This department is for brief accounts of new substances which do not appear of sufficient importance to justify separate publication and cannot be described appropriately as part of any other Article or Note. These accounts should report the preparation of the new compound succinctly, yet fully enough so that the operations can be duplicated. Significant properties, formulas and analytical data to establish the identity and purity of the substance should be given. Material appearing in this classification will not be accepted for subsequent publication.

Communications to the Editor are designed to afford prompt, brief, preliminary publication in our Journal of new and significant observations or discoveries. Their total length may in no case exceed 500 words or the equivalent. They will be given as rapid editorial consideration as possible, but at best it will usually be out of the question to include them in a given issue of the Journal if they arrive at the Editor's office later than the 20th of the preceding month. Communications like other contributions should be self-sustaining; that is, they should present experimental or other evidence adequate to establish the *prima facie* credibility of the results or conclusions stated or to permit their appraisal by an expert in the field although because of the 500-word limit a complete presentation cannot usually be expected. These requirements make Communications on many subjects impracticable, particularly those of an involved or theoretical nature.

Communications differ from ordinary Articles or Notes in that their publication does not prevent the re-publication of their subject matter in a later, more complete article in the Journal. In view of this special provision and their expedited publication, it is clear that the contribution made by the Communication should be of special interest or timeliness; mere abstracts of forthcoming articles cannot be accepted. Proof and reprint order will be sent to authors whenever possible, but as this cannot always be done, a memorandum as to the reprints desired should accompany the manuscript.

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VOLUME 66 MARCH 9, 1944 NUMBER 3

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 943]

Contribution to the Stereochemistry of Cryptoxanthin and Zeaxanthin

BY L. ZECHMEISTER AND R. M. LEMMON

Although the *cis–trans* isomerization of β-carotene has been studied in detail,[1] the investigation of its hydroxy derivatives, cryptoxanthin, $C_{40}H_{55}$·OH, and zeaxanthin, HO·$C_{40}H_{54}$·OH, is limited. Only those stereoisomerization phenomena which result from the iodine catalysis or heating of solutions have been studied.[2] Those spectral alterations which are caused by the bending of the molecule and take place in a certain section of the ultraviolet region[3,4] have not yet been examined.

In earlier experiments only one stereoisomer of natural (all-*trans*-) cryptoxanthin, *viz.*, "neocryptoxanthin," was reported. Three stereoisomers of natural zeaxanthin, the neo-forms A, B and C, were studied more extensively. In contrast to "neocryptoxanthin," the neozeaxanthins were found to possess a stronger adsorption affinity than the all-*trans* compound. The present reinvestigation of the stereoisomerization of zeaxanthin by methods which among others included melting of crystals and refluxing in higher boiling solvents has revealed no new members of this stereoisomeric set. However, two new isomers of cryptoxanthin were observed and named in accordance with analogous members of the β-carotene set. The minor isomer, neo B, is adsorbed on the Tswett column below "neocryptoxanthin" (now termed neo A). Neocryptoxanthin U which is adsorbed above the all-*trans* pigment appears upon careful development with petroleum ether–acetone mixtures. Its characteristics in many respects are similar to those of neo-β-carotene U[1] and neo-α-carotene U,[4] which likewise possess increased adsorbability relative to their all-*trans* forms.

In the present paper we wish also to report on the changes which occur in dilute solutions of cryptoxanthin and zeaxanthin (1 to 10 mg. per 100 ml.) during exposure to intense sunshine.[5] Under such conditions a gradual bleaching takes place, the rate of which for some reason is considerably greater for zeaxanthin than for cryptoxanthin (Table I).

TABLE I

LOSS OF COLOR INTENSITY OF BENZENE SOLUTIONS OF CRYPTOXANTHIN AND ZEAXANTHIN ON EXPOSURE TO INTENSE SUNSHINE

Duration of insolation, min.	Loss of color intensity (% of the initial value) Cryptoxanthin	Zeaxanthin
15	6	21
30	17	39
45	26	63
60	36	88

This loss in colorimetric intensity is a result of three processes: first, stereoisomerization; second, structural conversion to other pigments; and third, cleavage to colorless or nearly colorless substances. A short exposure to sunshine causes a small amount of *trans*→*cis* isomerization. While this rearrangement is taking place, the other reactions begin. Finally, the cleavage becomes the predominant process. Therefore, the proper duration of the insolation must be established for each carotenoid in order to study its photoisomerization.

(1) A. Polgár and L. Zechmeister, THIS JOURNAL, **64**, 1856 (1942).
(2) L. Zechmeister and P. Tuzson, *Biochem. J.*, **32**, 1305 (1938); *Ber.*, **72**, 1340 (1939); L. Zechmeister, L. Cholnoky and A. Polgár, *ibid.*, **72**, 1678 and 2039 (1939); H. H. Strain, "Leaf Xanthophylls," Washington, 1938.
(3) L. Zechmeister and A. Polgár, THIS JOURNAL, **65**, 1522 (1943).
(4) L. Zechmeister and A. Polgár, *ibid.*, **66**, 137 (1944).
(5) Insolation experiments have been reported for α-carotene, β-carotene, prolycopene, pro-γ-carotene, and capsanthin. *Cf.* Reference 4; L. Zechmeister, A. L. LeRosen, W. A. Schroeder, A. Polgár and L. Pauling, THIS JOURNAL, **65**, 1940 (1943); A. Polgár and L. Zechmeister, *ibid.*, **66**, 186 (1944).

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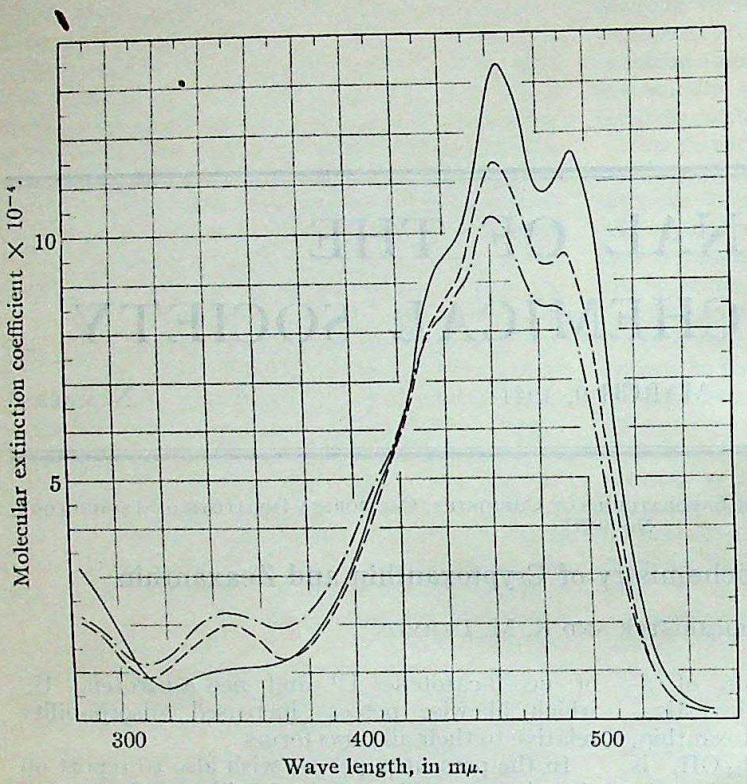

Fig. 1.—Molecular extinction curves of cryptoxanthin in benzene: —, fresh solution of the all-*trans* compound; ---, mixture of stereoisomers after refluxing for forty-five minutes; —·—·, after iodine catalysis at room temperature in light.

An insolation for forty-five minutes is adequate for cryptoxanthin; shorter exposures produce a slight stereoisomerization only. Zeaxanthin isomerizes to some extent in five minutes but an exposure of fifteen minutes was more satisfactory for the present stereochemical work. After thirty minutes of insolation most of the recovered pigment passed into the chromatographic filtrate under conditions under which any known member of the zeaxanthin set would have been adsorbed on the column.

The pigment mixture obtained upon insolation of zeaxanthin for fifteen minutes was composed of 48% unchanged all-*trans* compound, 11% neozeaxanthins, 12% minor zones, and 29% of a pigment which does not belong to the zeaxanthin set. The positions of the visual spectral bands of this latter pigment are approximately identical with that of the zeaxanthin bands. It is adsorbed between zeaxanthin and cryptoxanthin on the column. The investigation of this polyene, which was obtained in crystals in a yield of 17% from zeaxanthin, is not yet concluded.

We shall now consider the influence of *trans*→*cis* rearrangements on the spectral curves. As shown by Figs. 1 and 2, the molecular extinction curves of solutions which have been catalyzed with iodine resemble those of the carotenes in their essential features. There occurs upon catalysis a decrease of the extinction in the visible region which was observed earlier in heated solutions by Strain,[6] by Beadle and Zscheile,[7] and by White, Zscheile and Brunson[8]; partial spectral curves of some stereoisomers were given in those papers. We find that in the ultraviolet region a marked *cis*-peak appears at 348 mμ (in benzene). It must be stressed that light is required for *cis–trans* rearrangement of carotenoids induced by iodine[9]; neither cryptoxanthin nor zeaxanthin solutions showed a *cis*-peak when catalyzed in darkness. However, an irradiation with a lamp as short as five seconds developed a marked portion of the peak under conditions specified in the Experimental Part. The process is practically complete within two or three minutes.

The isolation of isomers from mixtures by chromatography permits the determination of the height of the *cis*-peak of each observed member of the set and, consequently, a tentative assignment of spatial structures.[4,5] The basis for the following discussion is given in Figs. 3, 4 and 5 as well as in Table II.

One *trans*→*cis* rotation usually shifts the longest wave length maximum of an all-*trans* carotenoid about 5 mμ toward the ultraviolet. Therefore, the neocryptoxanthins B and U are evidently mono-*cis*

Table II

Typical Spectroscopic Data for Some Members of the Stereoisomeric Cryptoxanthin and Zeaxanthin Sets in Benzene Solution (in the Sequence of Decreasing Adsorbability)

Member of the set	Diff. between the visually established longest wave length max. of the member and the all-*trans* form (mμ)	Mol. extinction coeff. at the *cis*-peak $E^{\text{mol.}}_{1\text{ cm.}} \times 10^{-4}$	Diff. between mol. ext. coeff. of the member and of all-*trans* form at *cis*-peak
	Cryptoxanthin		
Neo U	5	1.7	0.7
All-*trans*	0	1.0	0
Neo A	6.5	3.4	2.4
Neo B	4.5	4.6	3.6
	Zeaxanthin		
Neo A	5.5	4.4	3.7
Neo B	5.5	2.4	1.7
Neo C	8.5	3.9	3.2
All-*trans*	0	0.7	0

(6) H. H. Strain, ref. 2; *J. Biol. Chem.*, **127**, 191 (1938).
(7) B. W. Beadle and F. P. Zscheile, *ibid.*, **144**, 21 (1942).
(8) J. W. White, F. P. Zscheile and A. M. Brunson, This Journal, **64**, 2603 (1942); J. W. White, A. M. Brunson and F. P. Zscheile, *Ind. Eng. Chem., Anal. Ed.*, **14**, 798 (1942).
(9) *Cf.* A. Polgár and L. Zechmeister, This Journal, **66**, 186 (1944).

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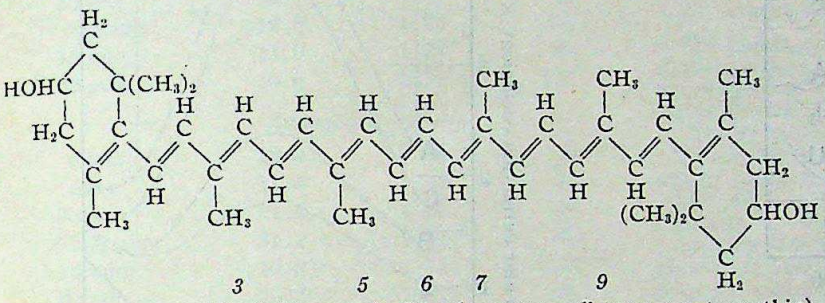
compounds. The very great difference in their *cis*-peaks suggests that the *cis* double bond is located in the center of the chromophore of neocryptoxanthin B but far from the center in that of neo U.[5] The most probable configurations are: neocryptoxanthin B = *6*-mono-*cis*-cryptoxanthin, and neocryptoxanthin U = *3*-mono-*cis*- or *9*-mono-*cis*-cryptoxanthin (see the formula). Neocryptoxanthin A seems to be a di-*cis* compound in which the central double bond is one of the *cis* bonds.



All-*trans*-zeaxanthin (with one hydroxyl group: all-*trans*-cryptoxanthin). The stereochemically effective double bonds[10] are numbered.

In the stereoisomeric zeaxanthin set the neo forms A and B are undoubtedly mono-*cis* compounds. On the basis of their *cis*-peaks the best assignment is: neozeaxanthin A = *6*-mono-*cis*-zeaxanthin and neozeaxanthin B = *5*-mono-*cis*-zeaxanthin. Neozeaxanthin C seems to be a di-*cis* isomer; it is possible that one of its *cis* double bonds is located in the center.

Experimental Part

Materials and Methods.—Cryptoxanthin solutions were chromatographed on calcium hydroxide (Shell Brand lime, chemical hydrate, 98% through 325 mesh) and those of zeaxanthin on calcium carbonate (Merck Heavy Powder). The visual spectral maxima were determined with an Evaluating Grating Spectroscope (Zeiss; light filter BG-7; 2 mm. thick). All pigments listed in the chromatograms below were tested spectroscopically before and after the addition of catalytic amounts of iodine. The spectra of cryptoxanthin and its isomers were taken in petroleum ether (b. p. 60–70°) and those of zeaxanthin and its isomers in benzene. The addition of iodine shifted spectra in the former set to 480, 449 mμ (± 1 mμ) and in the latter to 493, 460 mμ (± 1 mμ). The extinction curves were taken in a Beckman photoelectric spectrophotometer.[11] Solutions which had been catalyzed with iodine were irradiated from a distance of 60 cm. with a 3500° Mazda white fluorescent lamp (length of the tubes, 120 cm.). The solutions were placed in 25-ml. volumetric flasks (glass) in horizontal position on a white base. For insolation experiments transparent quartz test-tubes or small flasks were used which were filled with carbon dioxide. For more details concerning methods we refer to earlier reports.[12]

The cryptoxanthin and zeaxanthin samples were isolated from the berries of *Physalis alkekengi* and, after purification, were chromatographically homogeneous.

1. Cryptoxanthin

(a) ***cis–trans* Isomerization of Cryptoxanthin on Standing or Refluxing.**—Petroleum ether solutions of cryptoxanthin isomerize at room temperature in darkness to an extent of 1% within twenty-four hours.

A solution of 6 mg. of the pigment in 50 ml. of ligroin (b. p. 120°) was refluxed for thirty minutes in an all-glass apparatus in a slow stream of carbon dioxide. The chromatogram was developed on a column (20 × 3.5 cm.) with petroleum ether containing 10% acetone. (The figures on the left are the width of the zones in millimeters).

5	yellow, irreversible
65	colorless
22	orange, all-*trans;* 483.5, 452.5 mμ
2	almost colorless
14	yellowish orange, neo A: 477, 445.5 mμ
2	colorless
12	yellow, neo B: 479.5, 448 mμ

The loss of the initial colorimetric value was about 30%.

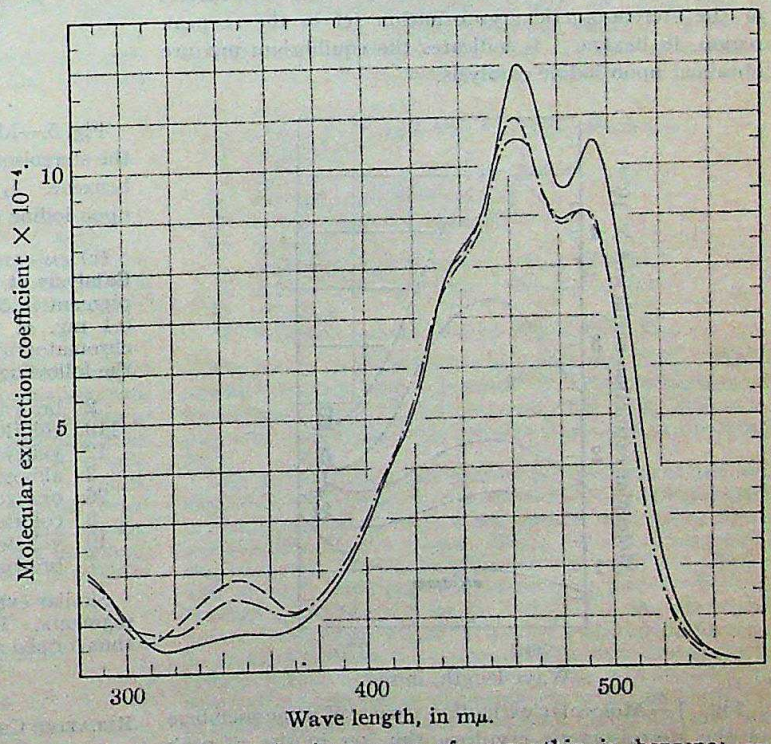


Fig. 2.—Molecular extinction curves of zeaxanthin in benzene: —, fresh solution of the all-*trans* compound; ---, mixture of stereoisomers after refluxing for forty-five minutes; and — · — ·, after iodine catalysis at room temperature in light. (The *cis*-peak obtained on refluxing is higher than that of the iodine equilibrium because much more neozeaxanthin A is contained in the refluxed solution than in the catalyzed mixture[2].)

(10) L. Pauling, *Fortschr. chem. organ. Naturstoffe*, **3**, 203 (1939); L. Zechmeister, A. L. LeRosen, F. W. Went and L. Pauling, *Proc. Natl. Acad. Sci.*, **27**, 468 (1941).

(11) H. H. Cary and A. O. Beckman, *J. Opt. Soc. Am.*, **31**, 682 (1941).

(12) *Cf., e. g.*, A. Polgár and L. Zechmeister, THIS JOURNAL, **64**, 1856 (1942); L. Zechmeister and A. Polgár *ibid.*, **65**, 1522 (1943).

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The colorimetric ratio was, unchanged all-*trans:* neo A: neo B = 62:32:6.

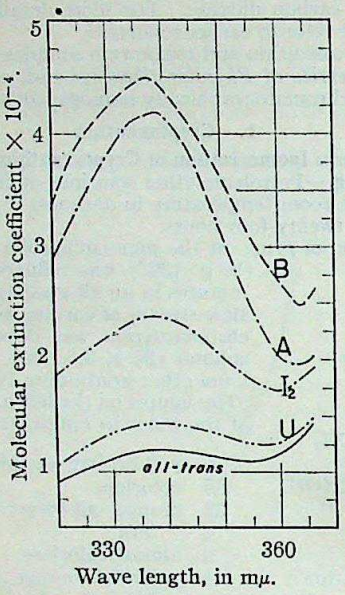

Fig. 3.—Molecular extinction curves of some members of the stereoisomeric cryptoxanthin set in the *cis*-peak region, in hexane. I_2 indicates the equilibrium mixture obtained upon iodine catalysis.

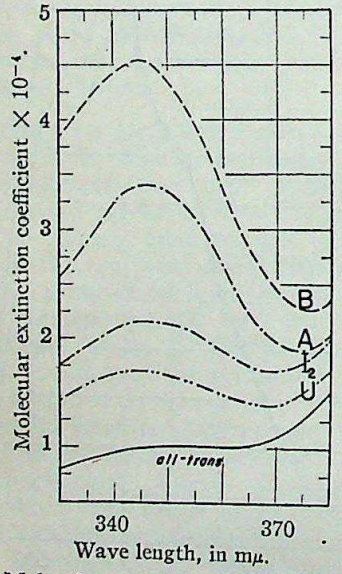

Fig. 4.—Molecular extinction curves of some members of the stereoisomeric cryptoxanthin set in the *cis*-peak region, in benzene. I_2 indicates the equilibrium mixture obtained upon iodine catalysis.

(b) *cis–trans* **Isomerization of Cryptoxanthin by Melting.**—Three milligrams of crystals was placed in a tube which was filled with carbon dioxide and then sealed. The tube was kept in a bath at 175° for fifteen minutes and then the melt was rapidly solidified in ice water. The petroleum ether solution of this material gave the following chromatogram (18 × 1.8 cm.) when the column was developed as in section (a).

1 brownish yellow, irrev.
75 colorless
15 yellowish orange, neo U: 478, 448 mμ
28 orange, all-*trans:* 483.5, 452 mμ
19 yellow, neo A: 477, 446 mμ
1 colorless
6 yellowish orange, neo B: 479, 448.5 mμ

The loss in the initial colorimetric value was 55%. The colorimetric ratio was, unchanged all-*trans:* neo U: neo A: neo B = 49:7:38:6.

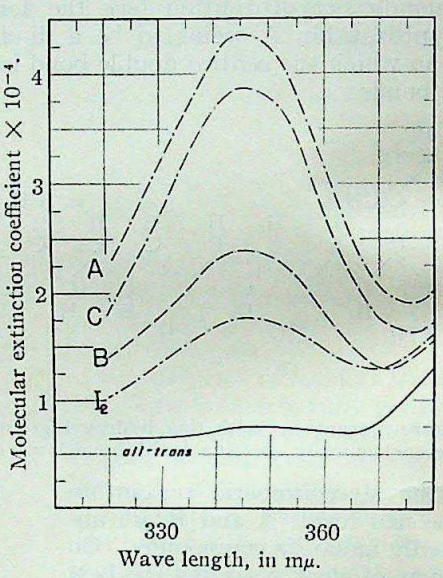

Fig. 5.—Molecular extinction curves of some members of the stereoisomeric zeaxanthin set in the *cis*-peak region, in benzene. I_2 indicates the equilibrium mixture obtained upon iodine catalysis.

(c) *cis–trans* **Isomerization of Cryptoxanthin by Iodine Catalysis at Room Temperature.**—A solution of 5 mg. of pigment in 30 ml. of petroleum ether was catalyzed with 0.1 mg. of iodine. An hour later the solution was chromatographed and, after development as above, gave the following zones (20 × 3.5 cm.).

2 brownish yellow, irrev.
110 colorless
12 yellowish orange, neo U: 478.5, 448 mμ
2 almost colorless
26 orange, all-*trans:* 483.5, 452.5 mμ
2 colorless
10 yellow, neo A: 477, 446 mμ
7 brownish yellow, neo B: 479.5, 449.5 mμ

Similar experiments were also carried out with the neo pigments. The relative colorimetric values of the zones thus formed are listed in Table III.

TABLE III

RELATIVE COLORIMETRIC VALUES OF CRYPTOXANTHIN AND SOME OF ITS STEREOISOMERS REVERSIBLY FORMED BY IODINE CATALYSIS AT 25° IN DIFFUSE DAYLIGHT

Starting material	Relative colorimetric values (% of the recovered pigment) neo U	all-*trans*	neo A	neo B
Neocryptoxanthin U	23	55	22	—
All-*trans*-cryptoxanthin	18	59	18	5
Neocryptoxanthin A	20	57	23	—
Neocryptoxanthin B	21	55	17	7

The influence of illumination on the iodine catalysis, especially on the *cis*-peak effect, is demonstrated in Table IV. In complete darkness no peak was observed one hour after the addition of iodine.

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TABLE IV

INFLUENCE OF LIGHT ON THE DEVELOPMENT OF THE *cis*-PEAK IN IODINE-CATALYZED BENZENE SOLUTIONS OF CRYPTOXANTHIN AND ZEAXANTHIN

Duration of the illumination	Mol. extinction coeff. $\times 10^{-4}$ at the longest wave length max.	Mol. extinction coeff. $\times 10^{-4}$ at the *cis*-peak wave length	Increase in the *cis*-peak (% of the greatest change)
	Cryptoxanthin		
0 sec.	13.4	0.70	0
5 sec.	13.1	.81	10
30 sec.	12.7	1.16	42
2½ min.	12.0	1.62	84
15 min.	11.0	1.77	98
30 min.	10.0	1.79	100
	Zeaxanthin		
0 sec.	12.0	0.89	0
5 sec.	11.8	1.25	42
30 sec.	11.4	1.47	68
2½ min.	11.1	1.64	88
15 min.	10.8	1.74	100
30 min.	10.5	1.71	96
60 min.	10.1	1.74	100

(d) *cis–trans* **Isomerization of Cryptoxanthin by Insolation.**—A solution of 2 mg. of pigment in 30 ml. of petroleum ether was exposed for forty-five minutes to intense sunshine. The final temperature was 34°. The following chromatogram was obtained (18 × 1.8 cm.).

4 yellowish brown, irrev.
83 colorless
26 orange, all-*trans:* 483.5, 453 mμ
13 yellow, neo A: 478, 446.5 mμ

The loss of color was about 30% of the initial value. In the recovered pigment the colorimetric ratio was, all-*trans:* neo A = 86:14. In parallel experiments the presence of a small amount of neocryptoxanthin B was also noticed.

2. Zeaxanthin

(a) *cis–trans* **Isomerization of Zeaxanthin on Refluxing.**—The isomerization produced by refluxing benzene solutions has been described earlier.[2] When 5 mg. of zeaxanthin in 50 ml. of ligroin (b. p. 120°) was refluxed in darkness in an atmosphere of carbon dioxide, for thirty minutes, only small amounts of the usual main isomers, neo A and neo B, were formed whereas a considerable fraction was converted into pigments which do not belong to the zeaxanthin set. The following chromatogram was obtained on a carbonate column (20 × 3.5 cm.) after development with a mixture of equal volumes of petroleum ether and benzene.

8 pale yellow, irrev.
9 yellowish orange, neo A: 489.5, 457.5 mμ
5 almost colorless
6 yellowish orange, neo B: 490, 458 mμ
12 almost colorless
13 yellowish orange, irrev.: 489.5, 457.5 mμ
14 colorless
9 orange, all-*trans:* 494, 462.5 mμ
21 colorless
5 yellowish orange, irrev.: 491.5, 458.5 mμ

The loss in the initial color intensity was 57%. The colorimetric ratio was, all-*trans:* neo A: neo B = 73:14:13. About 35% of the total recovered pigment was distributed among the two irreversible zones whose spectra are listed. These pigments shifted their spectral bands upon addition of iodine in the expected manner but did not behave as dihydroxy compounds in the partition test.

(b) *cis–trans* **Isomerization of Zeaxanthin by Melting.**—A mixture of 5 mg. of crystals and 20 mg. of naphthalene was placed in a tube (filled with carbon dioxide). The sealed tube was kept in a bath at 160° for fifteen minutes and then rapidly cooled in ice water. The material was dissolved in cold benzene, diluted with petroleum ether, drawn into a column (20 × 3.5 cm.) and developed with a benzene–petroleum ether mixture (1:1).

22 almost colorless
6 yellowish orange, neo A: 489, 458 mμ
2 almost colorless
6 yellowish orange, neo B: 489, 457.5 mμ
6 colorless
4 yellowish orange, irrev.: 489.5, 457.5 mμ
5 colorless
5 yellow, neo C: 486, 454.5 mμ
9 colorless
13 orange, all-*trans:* 494.5, 462.5 mμ

The loss in color intensity was about 60%. Nearly ⅛ of the recovered pigment consisted of the irreversible zone which did not behave like a dihydroxy compound in the partition test. The colorimetric ratio was, all-*trans:* neo A: neo B: neo C = 56:17:17:10.

In another experiment, at 220° without naphthalene, almost complete bleaching occurred.

(c) *cis–trans* **Isomerization of Zeaxanthin by Iodine Catalysis at Room Temperature.**—The data published previously[2] have been confirmed. In addition, experiments showed no *cis*-peak in the presence of iodine within half an hour in darkness. The influence of irradiation on this process is illustrated in Table IV.

(d) *cis–trans* **Isomerization of Zeaxanthin by Insolation.**—A solution of 5 mg. of zeaxanthin in 50 ml. of benzene was exposed to intense sunshine for fifteen minutes. When this solution was developed with pure benzene on a column (20 × 3.5 cm.) the following zones resulted.

3 almost colorless
2 yellowish orange, neo A: 490.5, 459.5 mμ
2 colorless
2 yellowish orange, neo B: 490, 459 mμ
60 blurred, traces of pigment
10 orange, all-*trans:* 494, 462.5 mμ
13 colorless
4 yellowish orange, irrev.: 491.5, 458 mμ
8 yellowish orange, irrev.: 491.5, 458 mμ
26 colorless
2 yellowish orange, irrev.: 492.5, 460.5 mμ

The loss in the initial color intensity was 20%. The recovered pigment was composed of 48% unchanged all-*trans*-zeaxanthin, 11% neozeaxanthins A + B, 12% minor pigments, and 29% of the pigment contained in the 8 mm. zone.

The latter, irreversibly formed polyene was eluted with methanol, transferred into benzene and, after evaporation, crystallized from the minimum amount of benzene by the addition of excess methanol. When 100 mg. of zeaxanthin was insolated, the yield of the new recrystallized pigment was 17 mg. This pigment forms long plates which are tapered on both ends; m. p. 129–131° (cor., electrically heated Berl block; sealed tube filled with carbon dioxide). In the partition test the compound is intermediate between cryptoxanthin and the carotenes. The visually observed spectral maxima were: in petroleum ether, 482, 451 mμ; in benzene, 496.5, 463 mμ; in alcohol, 483.5, 452 mμ; and in chloroform, 495, 462 mμ. Except in alcohol solution, the addition of iodine caused a 2 to 4 mμ displacement of the maxima toward shorter wave lengths.

Summary

The *cis–trans* isomerization of cryptoxanthin and zeaxanthin has been investigated further. Earlier observations concerning neozeaxanthins were confirmed. Cryptoxanthin yielded two new stereoisomers, one of which is adsorbed above the all-*trans* compound on the Tswett column. In addition to previous methods, stereoisomerization also occurs upon the melting of

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crystals or exposure of solutions to sunshine. Zeaxanthin is more photosensitive than cryptoxanthin. Extinction curves are given for fresh, refluxed, and iodine-catalyzed solutions. Cryptoxanthin and zeaxanthin develop *cis*-peaks at 348 mμ (in benzene); however, no peak was observed upon iodine catalysis in darkness. On the basis of optical data the most probable configurations are: neocryptoxanthin B = *6*-mono-*cis*-cryptoxanthin, and neocryptoxanthin U = *3*-mono-*cis*- or *9*-mono-*cis*-cryptoxanthin; neo A is a di-*cis* compound; neozeaxanthin A = *6*-mono-*cis*-zeaxanthin and neozeaxanthin B = *5*-mono-*cis*-zeaxanthin; neozeaxanthin C is probably a di-*cis* isomer.

PASADENA, CALIF. RECEIVED SEPTEMBER 27, 1943

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 945]

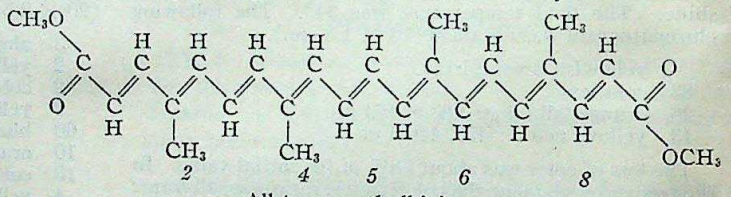
A Stereochemical Study of Methylbixin

BY L. ZECHMEISTER AND R. B. ESCUE

Bixin, $CH_3OOCC_{22}H_{26}COOH$, the main pigment in the seeds of the Annato tree (*Bixa orellana*, L.), was the first polyene for which stereoisomerism was demonstrated. Herzig and Faltis[1] in a single unreproducible experiment obtained from the seeds, instead of the well-known bixin, an isomer, termed "β-bixin," with higher melting point and greater stability than bixin, and with spectral maxima at longer wave lengths than those of bixin. Karrer and his associates[2] reported later that natural bixin can be converted into β-bixin by iodine, and they correctly interpreted this reaction as a *cis*→*trans* rearrangement. According to Kuhn and Winterstein[3] catalytic amounts of the halogen are sufficient to effect this transformation. Furthermore, they showed that both bixins yield the same dihydro compound, which is oxidized in air into β-bixin.

The following names have been used[4] for the two bixins and, in an analogous manner, for the two free carboxylic acids (norbixins) and the two dimethyl esters (methylbixins): ordinary bixin = natural bixin = *cis*-bixin = α-bixin = labile bixin = lower melting bixin = bixin II; isobixin = *trans*-bixin = β-bixin = stable bixin = higher melting bixin = bixin I.

Since no other isomer seems to have been described[5] and since the reversibility of the bixin isomerization by iodine catalysis so far as we know has not been claimed, we have re-investigated this field[6] by making use of some methods which were first applied to C_{40}-carotenoids.[7,8] Methylbixin was the most suitable starting material because of its greater solubility and markedly weaker adsorbability than that of bixin. Furthermore, because of its symmetrical molecule (see the formula) methylbixin can exist in only twenty stereoisomeric forms, whereas the corresponding number for bixin is thirty-two.[9,10]



All-*trans*-methylbixin

(The stereochemically effective double bonds are numbered.)

In the course of our experiments five members of the methylbixin set (and traces of other isomers) have been observed in chromatograms[11]; two new pigments, the neomethylbixins A and C, have been isolated as crystals. We designate

TABLE I

VISUALLY OBSERVED SPECTRAL MAXIMA OF SOME STEREOISOMERIC METHYLBIXINS LISTED IN THE SEQUENCE OF DECREASING ADSORPTION AFFINITIES

	In petroleum ether (b. p. 60–70°), mμ		In benzene, mμ	
Natural methylbixin	485	453.5	503	470
All-*trans*-methylbixin	490	457	508.5	475
Neomethylbixin A	485	454	502.5	469
Neomethylbixin B	471	444.5	491	458
Neomethylbixin C	479.5	449	496	463

(1) J. Herzig and F. Faltis, *Ann.*, **431**, 40 (1923).

(2) P. Karrer, A. Helfenstein, R. Widmer and Th. B. van Itallie, *Helv. Chim. Acta*, **12**, 741 (1929).

(3) R. Kuhn and A. Winterstein, *Ber.*, **65**, 646 (1932), and **66**, 209 (1933).

(4) *Cf.* L. Zechmeister, "Carotinoide," J. Springer, Berlin, 1934, pp. 239–251.

(5) A third bixin termed "isobixin" could not be reproduced; *cf.* J. F. B. van Hasselt, *Rec. trav. chim. Pays-bas*, **30**, 1 (1911), and **33**, 192 (1914); P. Karrer and T. Takahashi, *Helv. Chim. Acta*, **16**, 287 (1933).

(6) L. Zechmeister and R. B. Escue, *Science*, **96**, 229 (1942).

(7) *Cf. e. g.*, A. Polgár and L. Zechmeister, THIS JOURNAL, **64**, 1856 (1942); L. Zechmeister and A. Polgár, *ibid.*, **66**, 137 (1944).

(8) L. Zechmeister, A. L. LeRosen, W. A. Schroeder, A. Polgár and L. Pauling, *ibid.*, **65**, 1940 (1943).

(9) L. Pauling, *Fortschritte Chem. organ. Naturstoffe*, **3**, 203 (1939).

(10) L. Zechmeister, A. L. LeRosen, F. W. Went and L. Pauling, *Proc. Natl. Acad. Sci.*, **27**, 468 (1941).

(11) A. Winterstein mentioned in Klein's "Handbuch der Pflanzenanalyse," Vol. IV, p. 1403 (1933), that *cis*- and *trans*-bixin can be separated chromatographically; no experimental directions were given; *cf.* A. Winterstein and R. Stein, *Z. physiol. Chem.*, **220**, 247 (1933).

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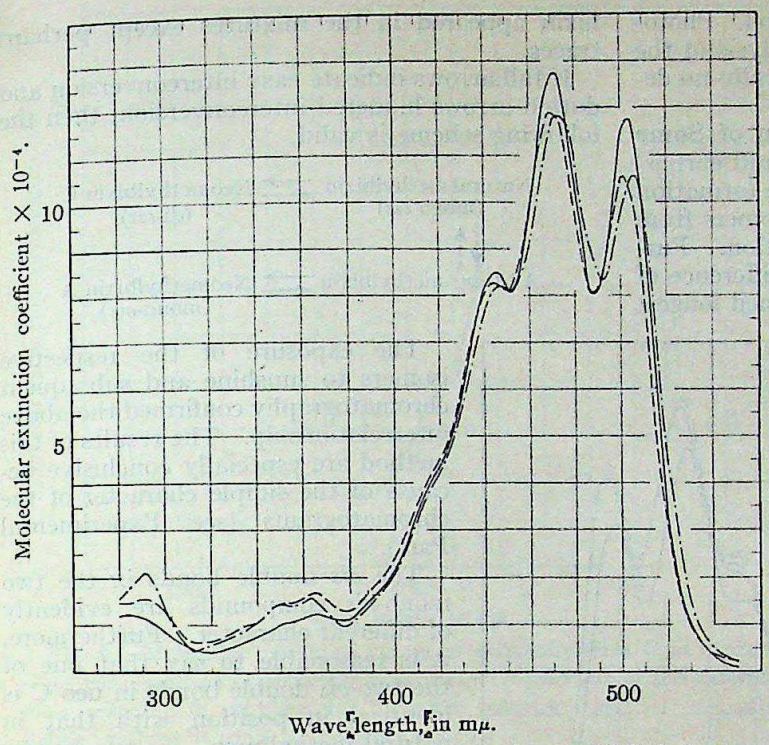

Fig. 1.—Molecular extinction curves of natural methylbixin in benzene: ——, fresh solution of natural methylbixin; – – –, mixture of stereoisomers after refluxing in darkness for forty-five minutes; and — · — ·, after iodine catalysis at room temperature in light.

(Table I) that stereoisomer whose double bonds have the same configuration as those in naturally occurring bixin (=norbixin II-monomethyl ester) as "natural methylbixin"; the methyl ester of β-bixin (=norbixin I-monomethyl ester) is termed "all-*trans*-methylbixin."

The position of natural methylbixin in chromatograms strongly reminds us of neo-β-carotene U, whereas the neo-forms A, B and C are adsorbed below the all-*trans* member in both sets.

Extinction curves of the bixins and methylbixins have been reported in the literature.[12] Figures 1 to 4 show the alterations of the curves of the four main isomeric methylbixins under the influence of refluxing and iodine catalysis. The iodine equilibrium curves obtained from the isomers are identical within experimental error. However, the curves taken after refluxing are not identical because under the conditions applied true equilibria are not reached.

A characteristic "*cis*-peak" appears in benzene solutions in each case at 363–364 mμ. As in the corresponding lycopene curve, the *cis*-peak maximum of methylbixin shows a fine structure. Natural methylbixin possesses only a slight peak and neo C a moderately high one, whereas neo A is responsible for the main effect observed in the iodine equilibrium mixture (Fig. 8).

Light is needed for the development of the *cis*-peak in the presence of iodine.[13] The extinction of all-*trans*-methylbixin remained practically unaltered in the *cis*-peak region when the catalyzed solution was kept in darkness; however, a five-second illumination caused a major effect (Fig. 5).

In the absence of catalysts, a fifteen-minute exposure to sunshine did not essentially alter the extinction curve of all-*trans*-methylbixin; natural methylbixin proved also to be relatively photo-stable under similar conditions. However, the configurations of the neo forms A and C are much more photosensitive (Figs. 6 and 7). The alterations which are represented in these curves are nearly

(12) *Cf. e. g.*, A. Smakula, *Angew. Chem.*, **47**, 657 (1934); P. Karrer and E. Würgler, *Helv. Chim. Acta*, **26**, 116 (1943); the original of the latter paper was not available to us.

(13) *Cf.* A. Polgár and L. Zechmeister, THIS JOURNAL, **66**, 186 (1944).

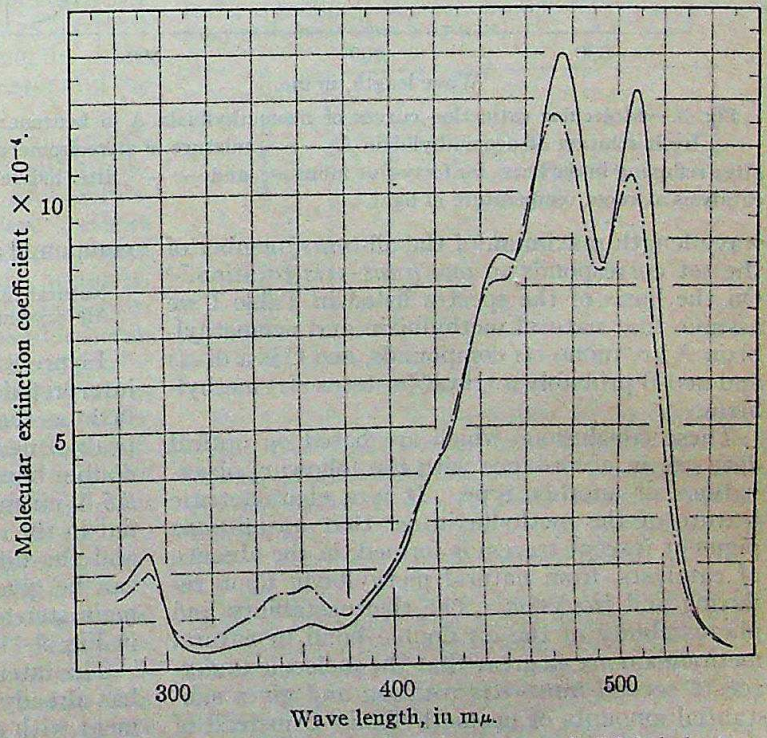

Fig. 2.—Molecular extinction curves of all-*trans*-methylbixin in benzene: ——, fresh solution of the all-*trans* compound; and — · — ·, after iodine catalysis at room temperature in light. (The latter curve is practically identical with that obtained after refluxing forty-five minutes in darkness.)

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exclusively caused by stereoisomerization. Photometric measurements after iodine catalysis of the insolated solutions proved that practically no destruction of pigment had taken place.

Interrelationship and Configuration of Some Stereoisomers.—It has been pointed out earlier[8] that there is a high probability for the formation of substantial amounts of mono-*cis* isomers from an all-*trans* carotenoid by isomerization. Furthermore, it has been stated that a difference of about 5 mμ from the visually established longest wave length maximum of the all-*trans* member of the set corresponds to one *trans*→*cis* rotation.[7,8] On the basis of the spectra listed in Table I we assume that natural methylbixin and neomethylbixin A are mono-*cis* compounds, neo C is a di-*cis* and neo B probably a tri-*cis* (or tetra-*cis*) methylbixin.

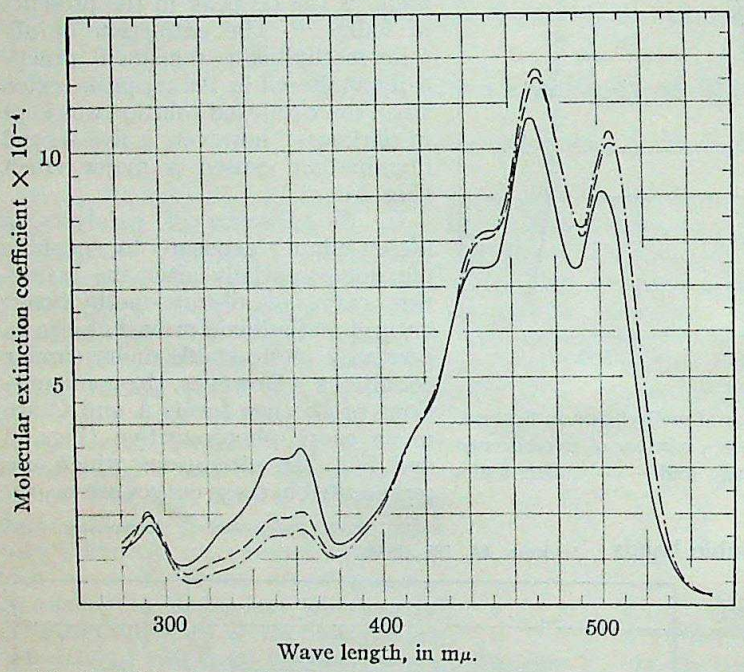
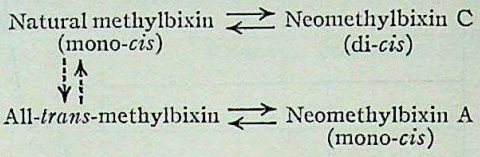


Fig. 3.—Molecular extinction curves of neomethylbixin A in benzene: ——, fresh solution of neomethylbixin A; – – –, mixture of stereoisomers after refluxing in darkness for forty-five minutes; and —·—·, after iodine catalysis at room temperature in light.

These conclusions which are based on optical data are in accordance with the following observations of another type. It is a characteristic feature of the methylbixin set that no all-*trans* pigment (except traces) is formed, in the absence of catalysts, from natural methylbixin upon refluxing and *vice versa*. The thermostability and photostability of the *cis* double bond in natural methylbixin are so great that the molecule undergoes a second *trans*→*cis* rotation and gives substantial amounts of neomethylbixin C instead of yielding any marked amounts of the all-*trans* pigment. On the other hand, the neomethylbixin A is easily formed when all-*trans* methylbixin is refluxed and *vice versa;* no natural methylbixin appeared in the mixtures except perhaps traces.

If full arrows indicate easy interconversion and dotted arrows hindered interconversion, then the following scheme is valid.



The exposure of the respective isomers to sunshine and subsequent chromatography confirmed the above interrelationship. The results of this method are especially conclusive because of the simple character of the chromatograms (see Experimental Part).

The *cis* double bonds in the two mono-*cis* compounds are evidently of different character. Furthermore, it is reasonable to say that one of the two *cis* double bonds in neo C is identical in position with that in natural methylbixin.

It has been pointed out[8] that in long conjugated systems a central mono-*cis* isomer is expected to show the highest *cis*-peak. As a rough approximation, the *cis*-peak effect of each member of the set can be taken proportional to the square of the distance between the center of the chromophore and the mid-point of the straight line between its ends. The values for the molecular extinction coefficients × 10^{-4} at the *cis*-peak wave length minus the corresponding value for the all-*trans* compound are

Natural methylbixin : 0.4	Neomethylbixin A : 2.8
All-*trans*-methylbixin : 0	Neomethylbixin C : 1.4

Figure 8 shows that neomethylbixin A must be interpreted as the 5-mono-*cis* and natural methylbixin as the 2-mono-*cis* isomer. The considerable peak of neo C indicates the presence of a central double bond and we suggest that this isomer is 2,5-di-*cis*-methylbixin. The curve of neo B is flat in the *cis*-peak region but because its lability and the difficulties of separation, no exact data can be given. The skeleton models of the four main stereoisomeric methylbixins are represented in Fig. 9.

The intensity of the principal absorption peak has already been used by Pauling[9,10] in the assignment with confidence of the all-*trans* structure to the natural C_{40}-carotenoids. Pauling pointed out, using the example of lycopene and neolycopene A for the discussion, that the integrated absorption coefficients should be approximately proportional

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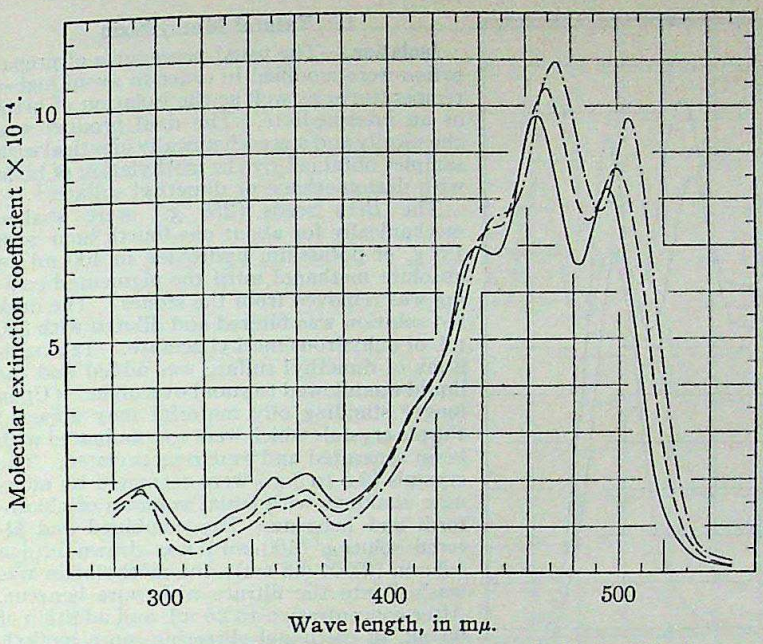

Fig. 4.—Molecular extinction curves of neomethylbixin C in benzene: ——, fresh solution of neomethylbixin C; – – –, mixture of stereoisomers after refluxing in darkness for forty-five minutes; and —·—·, after iodine catalysis at room temperature in light.

to the squares of the actual distances between the ends of the system. For the four members of the methylbixin set, we found experimentally that the maximum intensity ratios are, all-*trans*:natural: neo A:neo C = 1:0.93:0.80:0.82 while the ratios calculated on the basis of the models (with the single bond-double bond angles taken as 125°16′) are 1:0.87:0.82:0.79; the agreement is satisfactory, considering the experimental error and the approximate nature of the theory.

The configuration proposed for natural methylbixin is in contradiction with some results published (with reservation) by Karrer and Solmssen.[14] In a remarkable paper, these authors concluded, on the basis of the stereochemical relationship of some partial oxidation products, that natural bixin (or methylbixin) contains a *cis*-double bond in the 7-position. This double bond, however, belongs to the sterically hindered type.[9,10]

Some other data of the older literature are in very good accordance with the content of the present paper. Van Hasselt[5] found that two different methyl ethyl esters of "natural" norbixin can be prepared. Although he attributed this observation to a structural difference in the two molecule halves, it was shown by Karrer, *et al.*,[15] that the cause for the lack of symmetry is stereochemical and that a symmetrical structural formula must be given to norbixin. The existence of the two methyl ethyl esters shows independently of our configurational assignments that natural methylbixin cannot contain a centrally located *cis* double bond.

(14) P. Karrer and U. Solmssen, *Helv. Chim. Acta*, **20**, 1396 (1937).
(15) P. Karrer, P. Benz, R. Morf, H. Raudnitz, M. Stoll and T. Takahashi, *Helv. Chim. Acta*, **15**, 1218 and 1399 (1932), *cf.* footnote 3.

We believe that the experiments described below are in accordance with previous observations concerning the C_{40}-carotenoids and that they provide us with an enlarged basis for further conclusions. The experimental data for methylbixin indicate that, as was found also for the lycopene set,[8] the *trans* configuration around any double bond investigated is thermodynamically more stable than the *cis*.

Acknowledgment.—We wish to thank Professor Linus Pauling for valuable advice, furthermore Professor A. J. Haagen-Smit and Dr. G. Oppenheimer for microanalyses.

Experimental Part

Materials and Methods.—The designation "petroleum ether" refers to Skellysolve B (b. p. 60–70°). Calcium carbonate (Merck, Heavy Powder) was used as the adsorbent. Bixin is so strongly adsorbed on this material even from benzene solutions that a separation from methylbixin is easily accomplished. Ether or methanol does not completely elute these bixin adsorbates. For the separation of the methylbixin stereoisomers, development with a benzene–petroleum ether mixture (1:3) was used unless otherwise specified. These pigments can be conveniently chromatographed when dissolved in any mixture of benzene and petroleum ether if the former does not exceed 25%; a lower benzene content is distinctly advantageous since it secures a narrow pigment zone for the subsequent development. The best available eluent is acetone. Spontaneous crystallization may occur from petroleum ether solutions.

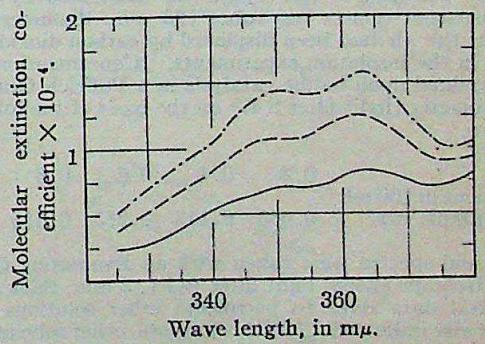

Fig. 5.—Influence of illumination on the development of the *cis*-peak effect in an iodine catalyzed solution of all-*trans*-methylbixin in benzene: ——, molecular extinction curve after standing for thirty minutes in darkness with iodine; – – –, after five seconds illumination; and —·—·, after thirty seconds illumination.

For melting point determinations the pigments were sealed in tubes filled with carbon dioxide. The samples were introduced into an electrically heated Berl block 20° below the melting point and the temperature was increased 2 to 3° per minute. The melting point values may be influenced by isomerization.

Refluxing experiments were carried out in darkness while a slow stream of carbon dioxide was introduced into the all-glass apparatus. In isomerization experiments by melting crystals, the pigments were sealed under carbon dioxide, kept fused in a dibutyl phthalate bath, and then

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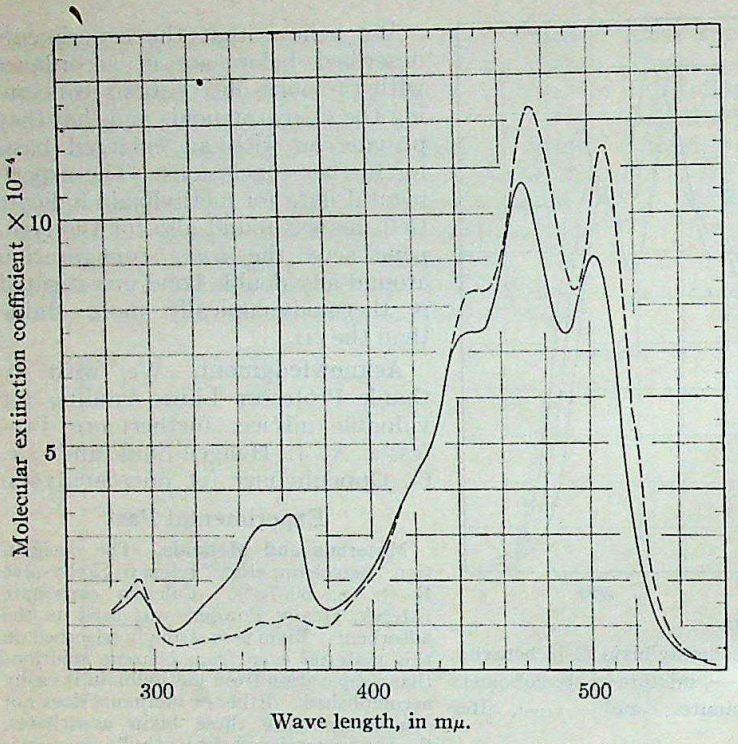

Fig. 6.—Photochemical isomerization of neomethylbixin A in benzene: ——, fresh solution of neomethylbixin A; and – – –, mixture of stereoisomers after fifteen minutes insolation.

cooled rapidly in ice water. The iodine catalyzed solutions (contained in 25-ml. glass volumetric flasks) were exposed to diffuse daylight for thirty minutes or illuminated by a 3500° white fluorescent Mazda lamp (tube length, 120 cm.) at 60 cm. distance for fifteen minutes. This same procedure was used in the experiment illustrated by Fig. 5. Transparent quartz test-tubes (22 mm. diameter) from which the air had been displaced by carbon dioxide were used in the insolation experiments. Concentrations were determined upon iodine catalysis in a Pulfrich Gradation Photometer (light filter S 47) on the basis of the following values.

k	0.2	0.4	0.6	0.8	1.0
Pigment in 100 ml. benzene, mg.	0.065	0.145	0.215	0.315	0.390

Visual spectra were taken with an Evaluating Grating Spectroscope (Zeiss, light filter BG-7, 2 mm. thick). The spectral data refer to petroleum ether solutions unless otherwise indicated. For this purpose, other solvents were displaced from the column by washing with petroleum ether immediately before extrusion. Each pigment listed below in the chromatograms as a member of the methylbixin set shifted its maxima to visually observed 488, 455 mμ (±0.5 mμ) when catalyzed with iodine. The extinction curves were determined in a Beckman Photoelectric Spectrophotometer.[16]

All crystalline samples were dried in high vacuum. The concentration of solutions was established in many cases from the equilibrium curve (Table II) upon iodine catalysis with an accuracy of ±2.5%. Since the columns were developed with benzene-petroleum ether mixtures but the concentrations had to be established in pure benzene, the adsorbates were washed after cutting with petroleum ether (b. p. 28–38°). The latter was eliminated by means of a vacuum pump and the pigment was eluted with ice cold acetone and transferred into benzene.

(16) H. H. Cary and A. O. Beckman, *J. Optical Soc. Am.*, **31**, 682 (1941).

1. Natural Methylbixin

Isolation.—The usual procedures of preparation were modified in order to avoid higher temperatures as well as the isolation of bixin as an intermediate. The final product was chemically and stereochemically identical with samples obtained by the methylation of bixin with diazomethane or dimethyl sulfate.

The *Bixa* seeds (250 g.) were shaken mechanically for about one-fourth hour with 1.5 g. of potassium hydroxide in 400 ml. of absolute methanol until the pigmented coating was removed from the stones. The dark red solution was filtered and diluted with 200 ml. of anhydrous methyl acetate. Ten milliliters of dimethyl sulfate was added and the liquid was allowed to stand overnight. (Upon longer standing oily material may appear.) Purple crystals which were contaminated with bixin separated and were remethylated. The crystals (2.5 to 3 g.) were extracted by alternate shakings with equal volumes of chloroform and benzene. The combined and filtered solution (100 ml.) was drawn into a column (23 × 4.8 cm); the methylbixin was washed into the filtrate with pure benzene. After concentration to 25 ml. and addition of 90 ml. of methanol glittering, pure methylbixin crystallized (Fig. 10). After cooling to −10° the crystals were filtered, washed with ice cold methanol and dried in high vacuum; m. p. 161–161.5° (cor.). The yield was 1.4 g. but it is dependent upon the quality of seeds.

Anal. Calcd. for $C_{24}H_{26}O_2(OCH_3)_2$: C, 76.44; H, 7.90; OCH_3, 15.19. Found: C, 76.45, 76.33; H, 7.93, 7.98; OCH_3, 14.98, 15.08.

TABLE II

MOLECULAR EXTINCTION COEFFICIENTS OF SOME MEMBERS OF THE STEREOISOMERIC METHYLBIXIN SET AND OF THE IODINE EQUILIBRIUM MIXTURE AT THE MAXIMA (*italicized*) AND MINIMA IN BENZENE

Wave length, mμ		Wave length, mμ	
Natural methylbixin		Neomethylbixin A	
284	1.20	*293*	1.76
320	0.4(0)	308	0.8(8)
366	1.21	*362*	3.5
378	1.10	380	1.31
445	8.5	*444–8*	7.4
452	8.1	*470*	10.7
471	12.8	489	7.4
488	8.0	*502*	9.1
503	11.7		
		Neomethylbixin C	
All-*trans*-methylbixin		*297*	1.98
292	2.45	314	0.9(4)
316	0.3(0)	*363*	2.17
363	0.8(0)	378	1.50
374	0.7(3)	*438*	7.0
448	8.7	446	6.8
454	8.6	*465*	9.8
475	13.0	482	6.6
493	8.5	*495*	8.2
508	12.2		
Iodine equilibrium mixture			
363	1.6		
450	8.1		
473	11.5		
505	10.3		

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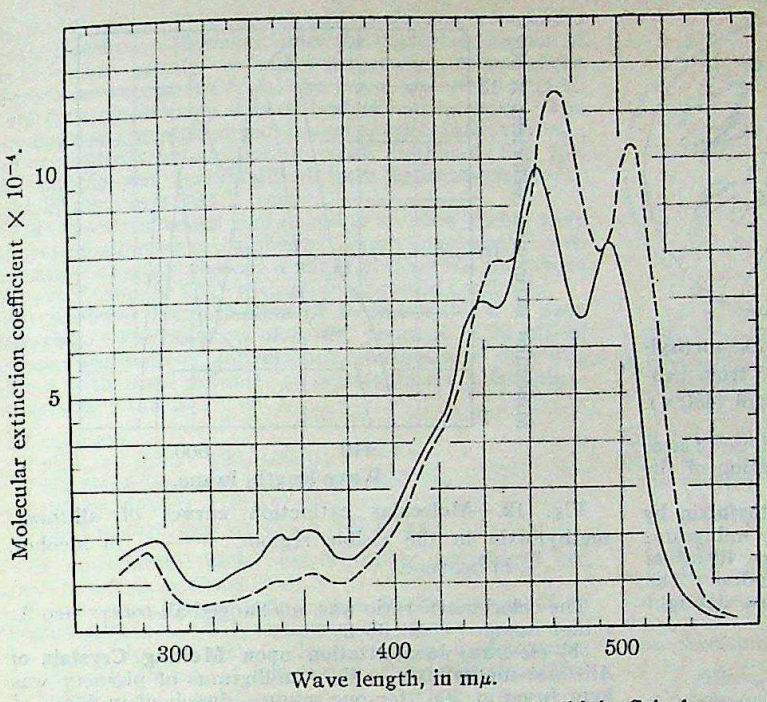

Fig. 7.—Photochemical isomerization of neomethylbixin C in benzene: ——, fresh solution of neomethylbixin C; and – – –, mixture of stereoisomers after fifteen minutes insolation.

The molecular extinction coefficients are compared with those of some other members of the set in Table II.

(a) ***cis–trans* Isomerization of Natural Methylbixin upon Standing and Refluxing.**—The extent of spontaneous isomerization in benzene–petroleum ether solution at 25° is about 3% in twenty-four hours. It must be remarked that even fresh solutions occasionally show a separation into blurred regions when chromatographed. The fractions could not be differentiated by any means, and extended development may cause them to recombine.

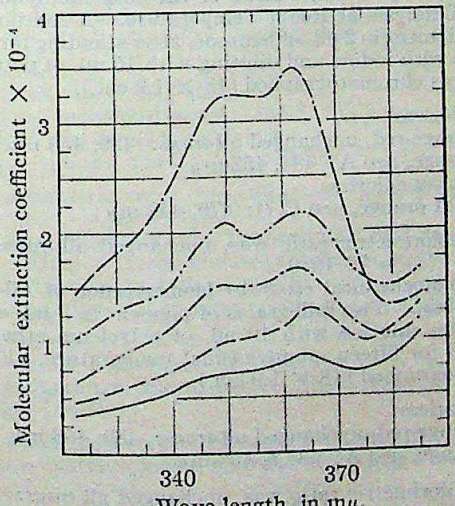

Fig. 8.—Molecular extinction curves of some members of the stereoisomeric methylbixin set in the *cis*-peak region in benzene: ——, all-*trans*-methylbixin; – – –, natural methylbixin; — · — ·, iodine equilibrium mixture; — · · —, neomethylbixin C; and · — · — ·, neomethylbixin A.

A solution of 5 mg. of methylbixin in 20 ml. of benzene was refluxed for an hour, concentrated to 2 ml., diluted with 15 ml. of petroleum ether, and chromatographed (size of column 18 × 1.9 cm.). (The figures on the left designate zone width in millimeters.)

25 colorless
34 orange-red, unchanged methylbixin: 486, 454 mμ
1 colorless
1 pink, all-*trans:* 488.5, 456 mμ
1 orange-red, neo A: 485, 453 mμ
1 orange, neo B(?)
1 colorless
40 yellow-orange, neo C: 479, 449 mμ

The colorimetric ratio of unchanged starting material: stereoisomers (essentially neo C) was 74:26.

(b) ***cis–trans* Isomerization upon Melting Crystals of Natural Methylbixin.**—When the pigment was kept fused for fifteen minutes, 95% of the initial color intensity disappeared. However, fusion for one minute was found to be satisfactory. Eight milligrams was kept at 165°, then dissolved in 5 ml. of benzene and, after dilution with 3 vol. of petroleum ether, developed on a column (18 × 2.5 cm.) with benzene–petroleum ether 1:5 and later with the usual 1:3 mixture.

15 yellow, irreversible
3 colorless
5 pink, traces
50 red-orange, unchanged starting material: 485, 454 mμ
10 pink, all-*trans:* 489, 456.5 mμ
10 orange, neo A: 485, 453 mμ
9 yellow, mainly neo B: 474, 444.5 mμ
2 darker orange (see below)
32 orange, neo C: 479, 448.5 mμ
Filtrate: yellow, irreversible pigment

The colorimetric ratio was, unchanged natural methylbixin: all-*trans:* neo A:neo B:neo C = 28:17:16:8:31.

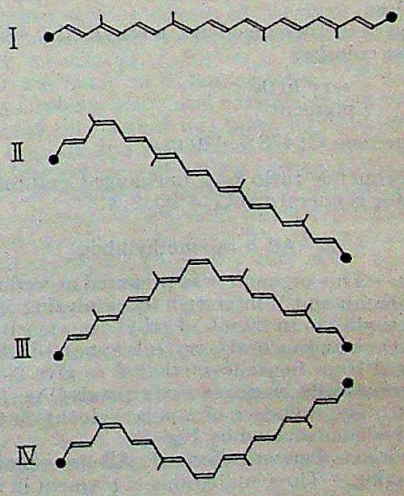

Fig. 9.—Suggested configurations of the four crystallized members of the methylbixin set: I, all-*trans*-methylbixin; II, natural methylbixin; III, neomethylbixin A; and IV, neomethylbixin C. (The carboxyl groups are represented by black circles.)

The by-product contained in the 2-mm. zone was obtained in larger quantity by melting 100 mg. of methylbixin. It is not a member of the methylbixin set and shows a characteristic spectral curve. The first two of its four

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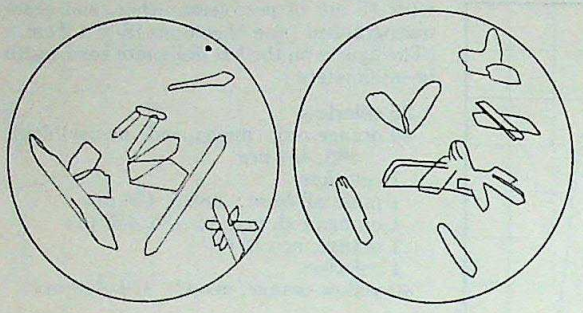

Fig. 10.—Natural methylbixin, crystallized from benzene and methanol (100×).

Fig. 11.—All-*trans*-methylbixin, crystallized from benzene and methanol (430×).

main maxima are identical in location with those of neomethylbixin B. The chromatographic separation of the two pigments is very difficult.

(c) *cis–trans* **Isomerization of Natural Methylbixin by Iodine Catalysis at Room Temperature.**—Two milligrams of pigment in 1 ml. of benzene was diluted with 10 ml. of petroleum ether and catalyzed with 20 μg. of iodine. The solution was kept for fifteen minutes in diffuse daylight and chromatographed (18 × 1.9 cm.).

25 colorless
39 red-orange, mainly all-*trans:* 489, 457 mμ
10 orange, neo A: 484, 453 mμ
1 yellow (traces), neo B: 473, 444.5 mμ
21 orange, neo C: 479, 448.5 mμ

(The uppermost section of the 39-mm. zone showed 2 mμ shorter wave-length maxima than indicated.) The colorimetric ratio was, all-*trans:* neo A:neo C = 72:19:9.

(d) **Photochemical** *cis–trans* **Isomerization of Natural Methylbixin.**—Two milligrams of pigment dissolved in 3 ml. of benzene and diluted with 10 ml. of petroleum ether was insolated for fifteen minutes (final temperature, 30°), and developed on a column (18 × 1.9 cm.) first with 20 ml. of benzene–petroleum ether 1:5 and then with 40 ml. of 1:3 mixture.

32 colorless
68 orange-red, unchanged nat. methylbixin: 485, 453 mμ
1 almost colorless
1 pink, 1 orange, 1 yellow } very little pigment
30 orange, neo C: 478.5, 449 mμ

The colorimetric ratio was, unchanged natural methylbixin: minor isomers:neo C = 90:2:8.

2. All-*trans*-methylbixin

Isolation.—This pigment was prepared according to the method of Kuhn and Winterstein by catalyzing 500 mg. of natural methylbixin in 20 ml. of ethyl acetate with 30 mg. of iodine. On standing at 0°, crystals appeared which were recrystallized from benzene–methanol to give 200 mg. of chromatographically homogeneous crystals (Fig. 11); m. p. 198° (cor.). The influence of a polar solvent on the spectral curve is demonstrated by Fig. 12.

(a) *cis–trans* **Isomerization of All-*trans*-methylbixin upon Refluxing.**—Three milligrams of pigment in 20 ml. benzene was refluxed for an hour. The solution was concentrated to 3 ml., diluted with 5 vol. of petroleum ether and chromatographed (18 × 1.9 cm.).

20 colorless
30 orange-red, unchanged all-*trans:* 490, 458 mμ
9 orange, neo A: 485, 453 mμ
0.5 yellow
1.5 colorless
2 orange
2 colorless minor isomers: 480.5, 449 mμ
2 orange

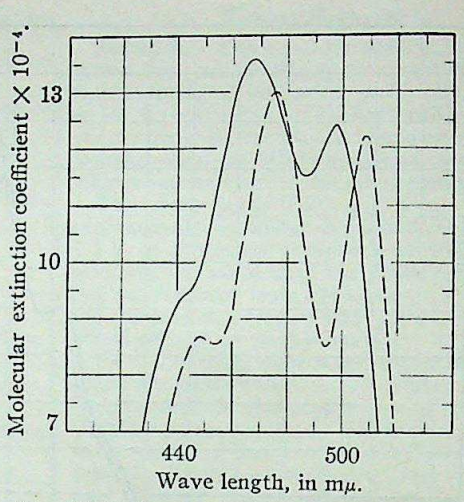

Fig. 12.—Molecular extinction curves of all-*trans*-methylbixin in the visible region: ———, in alcohol; - - - - -, in benzene.

The colorimetric ratio was, unchanged all-*trans:* neo A: minor isomers = 63:35:2.

(b) *cis–trans* **Isomerization upon Melting Crystals of All-*trans*-methylbixin.**—Eight milligrams of pigment was kept fused at 200° for one minute, dissolved in 5 ml. of benzene, diluted with 20 ml. of petroleum ether and chromatographed (18 × 2.5 cm.).

24 yellow, irreversible
45 colorless
25 orange-red, unchanged all-*trans:* 489, 456 mμ
8 orange, neo A: 485, 453 mμ
3 almost colorless
15 lemon-yellow, mainly irreversible
20 orange, neo C: 479, 449 mμ
2 almost colorless
2 faint orange (traces)

The colorimetric ratio was, unchanged all-*trans:* neo A:neo C = 55:20:25.

(c) *cis–trans* **Isomerization of All-*trans*-methylbixin by Iodine Catalysis at Room Temperature.**—A solution of 2 mg. of pigment in 2 ml. of benzene, after standing for thirty minutes with iodine and diluting with 15 ml. of petroleum ether, was chromatographed (18 × 1.9 cm.).

50 colorless
30 orange-red, unchanged all-*trans:* 489, 456 mμ
5 orange, neo A: 484, 452 mμ
5 almost colorless
25 light orange, neo C(?): 479, 448 mμ

The colorimetric ratio was, unchanged all-*trans:* neo A: neo C(?) = 72:19:9.

(d) **Photochemical** *cis–trans* **Isomerization of All-*trans*-methylbixin.**—Two milligrams of pigment in 3 ml. of benzene, after dilution with 10 ml. of petroleum ether, was insolated for fifteen minutes (final temperature, 31°) and chromatographed (18 × 1.9 cm.).

25 colorless
25 orange-red, unchanged all-*trans:* 489, 458 mμ
2 orange, neo A: 485.5, 453 mμ

The colorimetric ratio was, unchanged all-*trans:* neo A = 94:6.

3. Neomethylbixin A

Isolation.—A solution of 100 mg. of natural methylbixin in 10 ml. of benzene was catalyzed with 0.5 mg. of iodine and kept in daylight for thirty minutes at 25°. After dilution with 3 vol. of petroleum ether it was chromatographed (27 × 5.8 cm.). The broad orange layer located directly below the all-*trans* zone was eluted with acetone and rechromatographed immediately on a smaller column

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(24 × 4.8 cm.). This chromatogram showed only traces of other isomers. However, since the uppermost section of the neo A zone usually contains considerable amounts of the all-*trans* isomer, about 1/5 of the main zone was rejected. A third chromatogram showed perfect homogeneity. The pigment was transferred into benzene, evaporated to 2 ml., and crystallized by addition of excess methanol (Fig. 13). The sample was recrystallized from benzene–methanol; yield, 20 mg.; m.p. 190–2° (cor.).

This isomer is much more soluble and less stable than natural or all-*trans*-methylbixin. Fresh solutions of even the purest crystals showed a slight contamination (about 3%, exceptionally 6%) with all-*trans*-methylbixin.

(a) *cis–trans* **Isomerization of Neomethylbixin A upon Refluxing.**—The solution of 3 mg. pigment in 20 ml. of benzene was refluxed for an hour, concentrated to 3 ml., diluted with three volumes of petroleum ether and chromatographed (18 × 1.9 cm.).

22 colorless
50 pink, all-*trans:* 490, 458 mμ
22 orange, unchanged neo A: 485, 453 mμ
2 yellow, neo B: 475, 447 mμ
9 light orange, neo C: 477.5, 447.5 mμ

The colorimetric ratio was, all-*trans:* unchanged neo A:neo B:neo C = 63:32:2:3.

(b) *cis–trans* **Isomerization upon Melting Crystals of Neomethylbixin A.**—Five milligrams of pigment was fused, kept at 195° for one minute, dissolved in 5 ml. of benzene, diluted with 15 ml. of petroleum ether and chromatographed (18 × 2.5 cm.).

20 yellow, irreversible
20 colorless
30 pink, all-*trans:* 488.5, 455.5 mμ
10 orange, unchanged neo A: 484.5, 453 mμ
15 greenish-yellow, neo B (+irreversible): 474, 447 mμ
22 yellow-orange, neo C: 479, 449 mμ

Irreversibly formed pigments passed into the chromatographic filtrate. The neo C zone showed some tendency to separate into three sections with blurred borders; however, an examination did not reveal any spectral differences.

The colorimetric ratio was, all-*trans:* unchanged neo A:neo B (+irreversible):neo C = 53:25:6:16.

(c) *cis–trans* **Isomerization of Neomethylbixin A by Iodine Catalysis at Room Temperature.**—Three milligrams of pigment in 5 ml. of benzene was catalyzed and chromatographed (18 × 1.9 cm.) after standing half an hour.

40 colorless
44 pink, all-*trans:* 490, 456.5 mμ
16 orange, unchanged neo A: 484.5, 453.5 mμ
2 yellow, neo B: 474, 446.5 mμ
28 yellow-orange, neo C: 478, 448.5 mμ

The colorimetric ratio was, all-*trans:* unchanged neo A:neo B:neo C = 64:25:2:9.

(d) **Photochemical** *cis–trans* **Isomerization of Neomethylbixin A.**—After a fifteen-minutes insolation of 3 mg. of pigment in benzene and dilution with 5 vol. of petroleum ether, the mixture was chromatographed (18 × 1.9 cm.).

60 colorless
33 pink, mainly all-*trans:* 490, 458 mμ
25 pinkish-orange, mainly neo A: 484.5, 453 mμ
1 yellow (traces)

Due to unsatisfactory separation, the following ratio is only approximately correct, all-*trans:* unchanged neo A = 45:55.

4. Neomethylbixin B

Small amounts of this isomer may be obtained by iodine catalysis or by refluxing neomethylbixin A solutions. Its extinction maxima were located at 490, 460 mμ, in benzene and shifted to 505, 472 mμ upon the addition of iodine. From one fusion experiment with natural methylbixin, a pigment of a different type was separated from the neo B zone. Its benzene solution showed four extinction maxima in the visual region (490, 461, 419 and 404 mμ), the two first being identical in position with those of neomethylbixin B. The addition of iodine did not produce the spectrum which is characteristic for the methylbixin set.

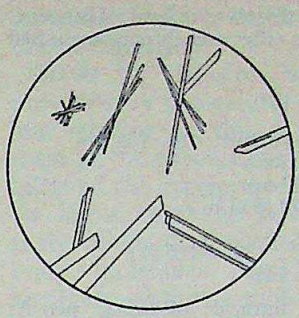

Fig. 13.—Neomethylbixin A, crystallized from benzene and methanol (430×).

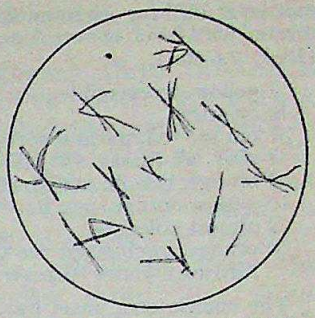

Fig. 14.—Neomethylbixin C, crystallized from benzene and methanol (430×).

5. Neomethylbixin C

Isolation.—A solution of 300 mg. of natural methylbixin in 100 ml. of benzene–petroleum ether (1:1) was refluxed for an hour, diluted with petroleum ether to 250 ml. and developed (30 × 8 cm.) with 2.5 liters of a 1:4 mixture. The development required three hours.

7 yellow (traces)
5 colorless
130 orange-red, unchanged natural methylbixin
1 colorless
2 pink
1 colorless
2 orange
1 yellow
60 bright orange, neo C

In order to augment the yields, the zone of unchanged methylbixin was eluted with acetone, transferred into benzene, refluxed again, and chromatographed. The natural methylbixin zone of this second chromatogram was submitted to a third refluxing and adsorption analysis after the addition of a 50-mg. portion of starting material.

The combined acetone eluates of the three zones of neo C were developed with benzene–petroleum ether (1:5) on a smaller column (27 × 5.8 cm.). Except for traces, the pigment was found to be homogeneous. It was transferred into petroleum ether and completely evaporated *in vacuo*. The red, oily residue was taken up in the minimum amount of benzene and transferred to a centrifuge tube; the solvent was evaporated with a carbon dioxide stream at 25°. When methanol was added gradually with stirring, an oily suspension appeared which crystallized upon scratching and cooling. Upon seeding, the crystals appear directly. After cooling to −10°, they were centrifuged and recrystallized (Fig. 14). The intensely colored mother liquors may be reworked. The yield of crude neomethylbixin C crystals was 50 mg.; however, this quantity decreased to 25–30 mg. upon recrystallization; m. p. 150–1° (cor.).

(a) *cis–trans* **Isomerization of Neomethylbixin C upon Refluxing.**—The benzene solution of 1 mg. pigment was refluxed for an hour, concentrated to 2 ml., diluted with 15 ml. of petroleum ether and chromatographed (18 × 1.9 cm.).

15 colorless
5 red-orange, natural methylbixin: 485, 453.5 mμ
4 pink, all-*trans:* 490, 458 mμ
4 orange, neo A: 485, 453.5 mμ
3 yellow, neo B: 471.5, 444.5 mμ
36 yellow-orange, unchanged neo C: 479, 448.5 mμ

The colorimetric ratio was, natural methylbixin: all-*trans:*neo A: neo B: unchanged neo C = 33:12:6:3:46.

(b) *cis–trans* **Isomerization upon Melting Crystals of Neomethylbixin C.**—Five milligrams of pigment was kept

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molten at 155° for one minute, dissolved in 5 ml. of benzene, diluted with 5 vol. of petroleum ether and chromatographed (18 × 2.5 cm.).

7 yellow, irreversible
40 colorless
37 orange-red, natural methylbixin: 485, 454 mμ
4 pink, all-*trans:* 489, 457.5 mμ
4 orange, neo A: 485.5, 452 mμ
10 yellow-orange, neo B: 471, 444 mμ
2 almost colorless
50 orange, unchanged neo C: 480, 448.5 mμ
Filtrate: yellow (irreversible)

The colorimetric ratio was, natural: all-*trans:* neo A: neo B: unchanged neo C = 51:4:4:5:36.

(c) ***cis–trans* Isomerization of Neomethylbixin C by Iodine Catalysis at Room Temperature.**—Three milligrams of pigment was catalyzed in benzene with 20 μg. of iodine. After standing for thirty minutes the solution was developed with benzene–petroleum ether (1:5) on a column (18 × 1.9 cm.).

20 colorless
49 orange-red, all-*trans:* 489, 456.5 mμ
20 orange, neo A: 484, 452.5 mμ
2 yellow
23 yellow-orange, unchanged neo C: 478, 448 mμ

The colorimetric ratio was, all-*trans:* neo A: unchanged neo C = 63:25:12.

(d) **Photochemical *cis–trans* Isomerization of Neomethylbixin C.**—A solution of 2 mg. of pigment in 3 ml. of benzene was insolated for fifteen minutes and after dilution with 10 ml. of petroleum ether, chromatographed (18 × 1.9 cm.).

23 colorless
15 orange-red, natural methylbixin: 485, 453.5 mμ
11 colorless
4 pink, neo A: 484.5, 453 mμ
3 colorless
65 yellow-orange, unchanged neo C: 478.5, 448 mμ

The colorimetric ratio was, natural: neo A: unchanged neo C = 21:2:77.

Summary

Besides "labile methylbixin," now named "natural methylbixin," and "stable" termed "all-*trans*-methylbixin," two other stereoisomers, neo A and C, have been isolated in crystals; several minor members of this set were observed in solution. The mutual conversion of the stereoisomers can be carried out by means of thermal methods, iodine catalysis or insolation. Natural and all-*trans*-methylbixin are practically not interconvertible by refluxing or exposure to sunshine. In contrast, the reversible formation of neo C from natural methylbixin and of neo A from the all-*trans* form takes place easily under similar conditions. On the basis of spectroscopic data, especially "*cis*-peak" measurements, configurations are suggested for the four main observed methylbixins.

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[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 947]

The Serological Properties of Simple Substances. VI. The Precipitation of a Mixture of Two Specific Antisera by a Dihaptenic Substance Containing the Two Corresponding Haptenic Groups; Evidence for the Framework Theory of Serological Precipitation

BY LINUS PAULING, DAVID PRESSMAN AND DAN H. CAMPBELL

The framework theory (lattice theory) of serological precipitation and agglutination, first proposed by Marrack,[1] was shown by Marrack and by Heidelberger and Kendall[2] to account for many experimental observations. Because of its simplicity and its compatibility with the available information about intermolecular forces, this theory was incorporated in his general theory of the structure and process of formation of antibodies by one of the present authors.[3]

Strong support of the framework theory has been provided during the past two years by the results of extensive studies of the reactions of antibodies and simple substances,[4] based upon the observations by Landsteiner and Van der Scheer[5] of the precipitation of antibody by certain simple substances containing two haptenic groups. It was found[4] from experiments with about fifty substances that all of those (about twenty) containing two or more haptenic groups (azophenylarsonic acid groups) per molecule gave precipitates with antiserum homologous to this haptenic group, and that none of the monohaptenic substances gave a precipitate. This fact is most readily accounted for by the framework theory.

The argument might be made, however, that no more than one of the haptenic groups of a molecule of a polyhaptenic substance is involved in interaction with antibody molecules, and that the difference in precipitability of polyhaptenic and monohaptenic substances with antiserum is due to some difference in properties of these two classes of substances, such as a tendency to asso-

(1) J. R. Marrack, "The Chemistry of Antigens and Antibodies," Report No. 194 of the Medical Research Council, His Majesty's Stationery Office, London, 1934; Second Edition, Report No. 230, 1938.

(2) M. Heidelberger and F. E. Kendall, *J. Expll. Med.*, **61**, 559, 563; **62**, 467, 697 (1935); M. Heidelberger, *Chem. Rev.*, **24**, 323 (1939).

(3) Linus Pauling, THIS JOURNAL, **62**, 2643 (1940).

(4) Linus Pauling, David Pressman, Dan H. Campbell, and collaborators, THIS JOURNAL, **64**, 2994, 3003, 3010, 3015 (1942); **65**, 728 (1943).

(5) K. Landsteiner and J. Van der Scheer, *Proc. Soc. Expll. Biol. Med.*, **29**, 747 (1932).

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ciate into colloidal particles.[6] In order to test this point, we have carried out a new experiment, the results of which show that each of the two haptenic groups of a dihaptenic substance enters into specific combination with antibody in the formation of the precipitate.

The experiment[7] was made with use of two different antisera, one of which (anti-R serum) was prepared by injecting rabbits with azoprotein containing R groups (*p*-azophenylarsonic acid groups) and the other (anti-X serum) by injecting with azoprotein containing X groups (*p*-azobenzoic acid groups). A substance was used as precipitating antigen which had one R group and one X group per molecule. It was found that this RX substance does not give a precipitate with either anti-R serum or anti-X serum alone, but does give a precipitate with a mixture of these two antisera. Similar results were obtained also with another RX substance.

This striking experimental result corresponds exactly to the behavior predicted by the framework theory: according to this theory the RX substance cannot give a precipitate with anti-R serum because its molecules contain only one R group, and are hence univalent with respect to anti-R antibodies and so are unable to form a framework with them; and similarly it can not give a precipitate with anti-X serum. (Indeed, it is predicted, and verified by experiment, that this effectively monohaptenic substance can inhibit the precipitation of either anti-R serum or anti-X serum by corresponding polyhaptenic simple substances or azoproteins.) But the RX substance is effectively dihaptenic and bivalent with respect to a mixture of anti-R serum and anti-X serum, since each molecule can form two bonds, one with an anti-R antibody molecule and one with an anti-X antibody molecule; and accordingly a specific framework precipitate, containing equal numbers of the two kinds of antibodies, can be formed with the mixed antiserum.

Let us now ask to what extent this experimental result supports the framework theory—whether it might not be equally compatible with some other theory. The answer is that our experiment shows that both of the two haptenic groups R and X of the RX molecule enter into specific combination with antibody, that the molecule of precipitating antigen is hence truly bivalent, and that this bivalence is necessary for precipitation. This, however, is common to two theories—the framework theory, which requires that the antibody molecules, as well as the antigen molecules, be bivalent or multivalent, and an alternative theory, which is based on the assumption that a complex of a multivalent antigen molecule and two or more univalent antibody molecules is for some reason or other insoluble, and constitutes the precipitate.[8]

Basis for decision between these theories is provided by the results of two other experiments, one relating to the antibody–antigen molecular ratio in the precipitate and the other to the solubility of the precipitate in excess antibody. Since we know that the RX precipitating antigen is truly bivalent, the effective valence of the antibody molecules can be calculated from the antibody–antigen molecular ratio. The value found by analysis for this ratio is 0.7, which corresponds to an average effective antibody valence of $2/0.7 = 2.8$; for univalent antibody the molecular ratio would be 2. (The assumption is made here that the antigen molecules are not associated into complexes, which might then form a precipitate with antibody with use of only some of the haptenic groups. Evidence against association of this sort is furnished by the failure of the RX substances to precipitate with anti-R serum or anti-X serum alone.)

The second experiment is based on the following argument. If antibody molecules are univalent, and the precipitate consists of RX antigen molecules each of which has two attached antibody molecules, increase in antibody concentration, with amount of antigen held constant, would necessarily increase the amount of precipitate; decrease in the amount of precipitate, which could occur only by formation of a soluble complex, would not occur because the antigen molecules in the precipitate would be already saturated with antibody, and so could not increase their valence, and the antibody molecules could not decrease their valence (below the value 1) and remain attached to antigen. But a framework precipitate with multivalent antibody could dissolve in excess antibody by formation of soluble complexes, the effective valence of the antibody molecules in these complexes being less than that in the precipitate (1 instead of 2 or 3), and the antibody–antigen ratio being greater than that for the precipitate; according to the principles of chemical equilibrium, increase in the antibody concentration would then lead to solution of the precipitate. The observation that increase in the amount of mixed antiserum results in pronounced decrease in the amount of precipitate formed with the RX substance accordingly eliminates the theory of univalent antibody and provides further proof of the framework theory.

A detailed discussion of these experiments and of other experiments with the RX substance (hapten inhibition, etc.) is given below, following the section on experimental methods and results.

Experimental Methods and Results

The following substances containing groups R =

(6) K. Landsteiner, "The Specificity of Serological Reactions," Charles C. Thomas, Baltimore, Md., 1936, p. 120.

(7) A brief statement about this work has been published in *Science*, **98**, 263 (1943).

(8) The "occlusion" theory proposed by W. C. Boyd, *J. Exptl. Med.*, **75**, 407 (1942), is a theory of this sort. See also F. Haurowitz and P. Schwecin, *British J. Exptl. Path.*, **23**, 146 (1942).

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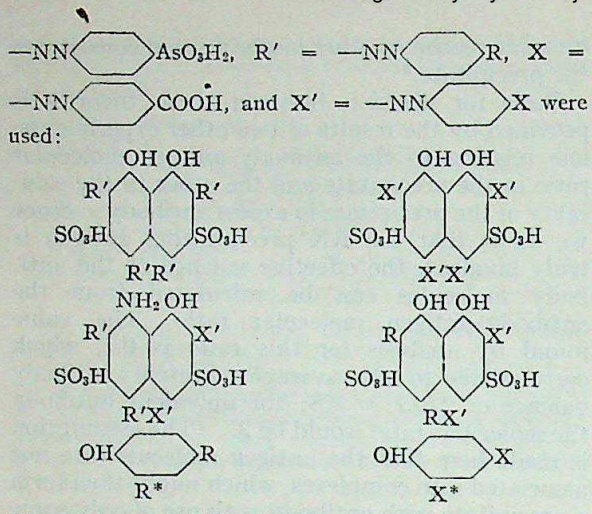
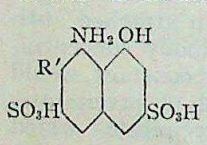


The substances R′X′ and RX′ are the "RX substances" referred to in the preceding discussion.

Preparation.—The substances R′R′ and R* have already been described,[4] and X′X′ and X* are described in a paper to be published soon.[9] The substance R′X′ was prepared by diazotizing 1.3 g. (0.0038 mole) of *p*-(*p*-aminophenylazo)-phenylarsonic acid, removing excess nitrite with urea, and coupling with 1.35 g. (0.0040 mole) of recrystallized "H-acid" in acetate buffer. The intermediate red compound was precipitated by addition of hydrochloric acid and washed twice with 500 ml. of water containing 10 ml. of 6 *N* hydrochloric acid and 3 g. of sodium chloride. The substance was then dissolved in sodium carbonate solution and added to a diazotized solution of 0.312 g. (0.0012 mole) of *p*-(*p*-aminophenylazo)-benzoic acid.[9] The product was precipitated with hydrochloric acid, dissolved in 500 ml. of sodium hydroxide solution, and reprecipitated with hydrochloric acid and sodium chloride and an equal volume of ethanol, leaving most of the remaining intermediate in solution. The process of solution and precipitation was repeated until the solution showed constant color, and sodium chloride was then removed from the product by extraction with 90% ethanol. Although the product was not crystallized, there is little doubt of its identity and purity; the method of preparation is based on the fact that at low *p*H substitution occurs in the 7 position of H-acid, ortho to an amino group, and not in the 2 position, ortho to a hydroxyl group, reaction at the latter position occurring in basic solution.



The RX′ compound was made by diazotizing 4.0 g. (0.020 mole) of *p*-arsanilic acid and adding it very slowly to 6.0 g. (0.019 mole) of chromotropic acid in solution with sodium carbonate (final *p*H 9). After one hour a diazotized and neutralized solution of 1.3 g. (0.005 mole) of *p*-(*p*-aminophenylazo)-benzoic acid was added and the *p*H was adjusted to 9. The product was purified in the way described above; this process removes any RR compound which is formed.

Anti-R, anti-R′, and anti-X sera were prepared as described elsewhere,[4,9] and the precipitation experiments were carried out in the usual way.[4] Several pools of antisera were tested; the same pools of anti-R and anti-X antisera were used for all of the quantitative experiments reported in this paper.

The substance RX′ was found not to precipitate with anti-X serum, anti-R serum, or anti-R′ serum, or with a mixture of anti-R′ serum and anti-X serum; it formed heavy precipitates with a mixture of anti-R serum and anti-X serum.

(9) David Pressman, Stanley M. Swingle, Allan L. Grossberg and Linus Pauling, paper to be submitted for publication in THIS JOURNAL.

The substance R′X′ gave no precipitate or only very slight precipitates with various pools of anti-X serum, anti-R serum, or anti-R′ serum; heavy precipitates were formed with mixtures of anti-R serum and anti-X serum and with mixtures of anti-R′ serum and anti-X serum. The quantitative experiments reported in Tables I to V were carried out with pools of sera which separately gave no precipitate with R′X′.

The failure of the substance RX′ to precipitate with a mixture of anti-R′ serum and anti-X serum is related to the fact[4] that anti-R′ serum in general does not precipitate with polyhaptenic substances containing R groups.

It was found that the substances RX′ and R′X′ act as monohaptenic substances in inhibiting the specific precipitation of R′R′ with anti-R′ serum or anti-R serum and of X′X′ with anti-X serum. Data showing the effect of haptens R* and X* on some precipitation reactions are given in Table II.

TABLE I

PRECIPITATION OF ANTIGENS R′R′, X′X′, R′R′ + X′X′, AND R′X′ WITH MIXTURES OF ANTI-R SERUM AND ANTI-X SERUM

Antigen solution, 2 ml.; mixed antiserum, 1 ml.; 1 hour at room temperature and 2 nights in refrigerator; *p*H of supernates 8.1.

Ratio anti-R serum: anti-X serum[a]	Antigen	Moles of antigen × 10^9 6	18	54	167	500
		Amount of precipitated antibody, μg.[b]				
93:7	R′R′	52	522	1134	721	162
	X′X′	0	0	0	0	0
	R′R′ + X′X′[c]	14	136	913	1070	564
	R′X′	48	60	72	60	60
62:38	R′R′	44	(261)	(446)	(169)	25
	X′X′	4	22	80	50	23
	R′R′ + X′X′[c]	8	104	439	481	236
	R′X′	22	158	792	821	623
17:83	R′R′	(12)	16	9	5	4
	X′X′	9	23	706	756	280
	R′R′ + X′X′[c]	9	12	137	1024	906
	R′X′	12	16	25	66	90

[a] The ratio 62:38 was selected as that for which the optimum concentrations of the antigens R′R′ and X′X′ are the same; the other ratios are 8 and 1/8 times as great, respectively. [b] Average of triplicate analyses, with mean deviation ±2%; duplicate analyses in parentheses. [c] In equimolal amounts, with totals as given above.

Discussion of Results and Comparison with Theory

The qualitative behavior of the substances RX′ and R′X′ in precipitation and in hapten inhibition, as described above, is just that predicted by the framework theory. The quantitative data given in Tables I and II are also in accord with this theory. In particular, there is some verification of the prediction of the framework theory that the precipitate with R′X′ should contain equal numbers of anti-R molecules and anti-X molecules; this would require that the amount of precipitate be small in case that either anti-R or anti-X serum be present in small amount, in agreement with observation.

It is also predicted, and verified by experiment, that precipitation of mixed antiserum with R′X′ can be completely inhibited by the presence of either hapten R* or hapten X*, whereas precipitation with a mixture of R′R′ and X′X′ is only partially inhibited by either of these haptens.

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TABLE II

INHIBITION BY HAPTENS R* AND X* OF PRECIPITATION OF ANTIGENS WITH MIXTURES OF ANTI-R SERUM AND ANTI-X SERUM

Antigen solution, 1 ml.; mixed antiserum, 1 ml.; hapten solution, 1 ml.; 1 hour at room temperature and 2 nights in refrigerator; *p*H of supernates 8.1.

Ratio anti-R serum: anti-X serum	Antigen[a]	Moles of hapten R* × 10^9				Moles of hapten X* × 10^9			
		0	37	111	333	1000	37	111	333	1000
		Amount of precipitated antibody, μg.[b]								
93:7	R′R′ + X′X′[c]	985	441	102	20	0	956	949	944	1004
	R′X′	64	41	(21)	(10)	0	50	27	19	5
62:38	R′R′	321	85	19	5	0	315	311	305	292
	X′X′	(71)	(61)	(59)	57	56	(43)	(15)	0	0
	R′R′ + X′X′[c]	344	132	61	52	51	316	342	302	300
	R′X′	827	527	290	88	15	553	219	48	15
17:83	R′R′ + X′X′[c]	496	502	470	434	319	223	48	11	11
	R′X′	49	39	31	21	11	34	17	9	7

[a] Total moles of antigen used: R′R′, 50 × 10^{-9}; X′X′, 50 × 10^{-9}; R′R′ + X′X′, 100 × 10^{-9}; R′X′, 100 × 10^{-9}. [b] Average of triplicate analyses, with mean deviation ±2%; duplicate analyses in parentheses. [c] In equimolal amounts.

TABLE III

ANTIBODY–ANTIGEN MOLECULAR RATIO IN PRECIPITATES FORMED BY R′X′ ANTIGEN AND A MIXTURE OF ANTI-R SERUM AND ANTI-X SERUM

Ratio of antisera 62:38; equal volumes of antigen solution and mixed antiserum: 1.5 ml. of each for first series, 2.0 ml. for second; 1 hour at room temperature and 2 nights in refrigerator; *p*H of supernates 8.1.

Moles of antigen × 10^9	Amount of precipitated antibody[a]		Amount of precipitated antigen[a]		Molecular ratio, antibody/antigen[a]
	μg.	moles	μg.	moles	
100	1421	8.89 × 10^{-9}	10.8	11.7 × 10^{-9}	0.76
33	456	2.85	4.2	4.5	.63

[a] Average of triplicate analyses, mean deviation ±2% for antibody, ±2% for antigen, ±2% for ratio. Assumed molecular weight of antibody 160,000, of antigen 927.

TABLE IV

PRECIPITATION OF MIXTURES OF NORMAL SERUM AND ANTISERUM AT CONSTANT AMOUNT OF ANTIGEN

Antigen solution, 2 ml., containing either 5 × 10^{-9} moles of antigen R′R′ (series A) or 6.7 × 10^{-9} moles of antigen R′X′ (series B); mixture of antiserum and normal serum, 2 ml.; 1 hour at room temperature and 2 nights in refrigerator; *p*H of all supernates 8.1.

Antiserum concentration in mixture[a]	Amount of antibody precipitated, μg.[b]	
	Series A[c]	Series B[d]
1.00	39	39
0.67	35	106
.45	93	120
.30	128	109
.20	133	81
.13	120	47
.088	90	23
.059	51	6

[a] Anti-R serum (Series A) or 62:38 mixture of anti-R serum and anti-X serum (series B) diluted with normal rabbit serum to the extent indicated in this column. [b] Averages of triplicate analyses, with mean deviation ±3%. [c] Blank of anti-R serum and buffer, 5 μg.; blank of normal serum and antigen R′R′, 5 μg. [d] Blank of 62:38 antiserum mixture, 6 μg.; blank of normal serum and antigen R′X′, 5 μg.

An interesting feature of the data in Tables I and II is that the 62:38 mixture of antisera gives a larger amount of precipitate with the R′X′ antigen than with R′R′ and X′X′ together. This is presumably related to the fact that the amount of precipitate formed with antigen R′R′ (or X′X′) alone falls off very rapidly with decrease in the fraction of anti-R (or anti-X) antiserum in the mixture; for example, the amount of precipitate formed by X′X′ with the 62:38 mixture is only about one-ninth of that formed with the 17:83 mixture, although the first mixture contains nearly one-half as much anti-X antibody as the second. The amount of precipitate formed by antigens R′R′ and X′X′ together would be expected to be about equal to the sum of the amounts formed by these antigens separately, since the two precipitates are mutually independent. But a single precipitate is formed by R′X′, containing equal amounts of the two kinds of antibody, and accordingly the amount of precipitate would be expected to be about equal to that formed by R′R′ or X′X′ with a mixture containing double the amount of anti-R serum or anti-X serum as is, indeed, observed.

It has been noted in general that simple antigens, in contradistinction to protein antigens, are far from completely precipitated by antisera, and that the fraction of the antigen remaining in solution at the optimum region increases on dilution of the antiserum with normal serum or heterologous antiserum; this effect, as discussed above, is to be noted in Table I. We have not yet carried out a sufficiently detailed experimental study of these phenomena to justify an extended discussion of them.

A mathematical discussion based on the simplified model treated previously[4,10] can be carried out for the RX precipitation reaction, leading to results in general correspondence with experiment. Let A represent the R′X′ antigen, $B^{(1)}$ and $B^{(2)}$ the anti-R and anti-X antibodies, respectively, which are assumed to be bivalent and homogeneous, and $H^{(1)}$ and $H^{(2)}$ the haptens R* and X*, respectively. It is assumed that, in addition to the precipitate $A_2B^{(1)}B^{(2)}$, certain soluble complexes exist, and that their equilibrium constants of formation have the values given below; these values have been assigned on the basis of structural considerations, with inclusion of the entropy term arising from the symmetry numbers of the molecules.

$$A + B^{(1)} = AB^{(1)} \qquad 2K_1$$
$$A + B^{(2)} = AB^{(2)} \qquad 2K_2$$
$$2A + B^{(1)} = AB^{(1)}A \qquad K_1^2$$
$$2A + B^{(2)} = AB^{(2)}A \qquad K_2^2$$
$$2A + B^{(1)} + B^{(2)} = AB^{(1)}AB^{(2)} \qquad 4K_1^2K_2''$$
$$2A + B^{(1)} + B^{(2)} = AB^{(2)}AB^{(1)} \qquad 4K_1''K_2^2$$

(10) Linus Pauling, Dan H. Campbell, and David Pressman, *Physiol. Rev.*, **23**, 203 (1943).

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$$\begin{aligned} H^{(1)} + B^{(1)} &= H^{(1)}B^{(1)} & 2K_1' \\ H^{(2)} + B^{(2)} &= H^{(2)}B^{(2)} & 2K_2' \\ 2H^{(1)} + B^{(1)} &= H^{(1)}B^{(1)}H^{(1)} & K_1'^2 \\ 2H^{(2)} + B^{(2)} &= H^{(2)}B^{(2)}H^{(2)} & K_2'^2 \\ A + B^{(1)} + H^{(1)} &= AB^{(1)}H^{(1)} & 2K_1K_1' \\ A + B^{(2)} + H^{(2)} &= AB^{(2)}H^{(2)} & 2K_2K_2' \end{aligned}$$

By straightforward solution of the equilibrium equations there is obtained for the case that no hapten is present a set of simultaneous equations

$$\beta_1^2(1 + K_1\alpha)^2 - \beta_1(B^{(1)}_{total} - B^{(2)}_{total}) - S(1 + K_2\alpha)^2/\alpha^2 = 0 \quad (1)$$

$$A_{total} - B^{(1)}_{total} - B^{(2)}_{total} - \alpha + \beta_1(1 - K_1^2\alpha^2) + S(1 - K_2^2\alpha^2)/\alpha^2\beta_1 = 0 \quad (2)$$

$$A_2B^{(1)}B^{(2)}(pp) = B^{(1)}_{total} - \beta_1(1 + K_1\alpha)^2 - s \quad (3)$$

These three equations are to be solved for three unknown quantities, the amount of precipitate $A_2B^{(1)}B^{(2)}(pp)$ and the two auxiliary variables α, the concentration of molecular species A in solution, and β_1, the concentration of molecular species $B^{(1)}$; the other quantities are the equilibrium constants K_1 and K_2, the solubility product $S = [A]^2[B^{(1)}][B^{(2)}]$ of the precipitate, and the solubility s of the precipitate as the complexes $AB^{(1)}AB^{(2)}$ and $AB'^{(2)}AB^{(1)}$, with $s = 4(K_1''K_2^2 + K_1^2K_2'')S$. A convenient method of solving the equations is to leave A_{total} undetermined, and to introduce numerical values of the other parameters; introduction in Equation 1 of a trial value of α permits solution for β_1, after which A_{total} may be evaluated from Equation 2 and $A_2B^{(1)}B^{(2)}(pp)$ from Equation 3.

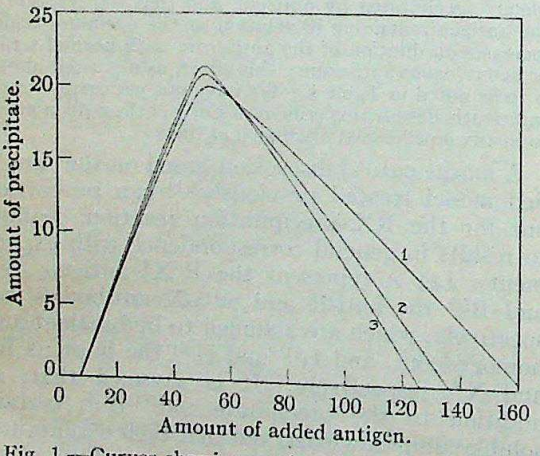

Fig. 1.—Curves showing results of theoretical calculations of amount of precipitate formed by antigen RX with an equimolal mixture of anti-R serum and anti-X serum, as function of amount of antigen: $B^{(1)}_{total} = B^{(2)}_{total} = 25$, $s = 2$, and $K_1 = K_1'' = 1$ for all curves; $K_2 = K_2'' = 0.2$ for curve 1, 1 for curve 2, and 5 for curve 3.

Curves showing dependence of amount of precipitate on amount of antigen with equal amounts of the two kinds of antibody present (Fig. 1) are similar to those for the precipitation of one kind of antibody by homologous dihaptenic antigen.[4] As the ratio of the amounts

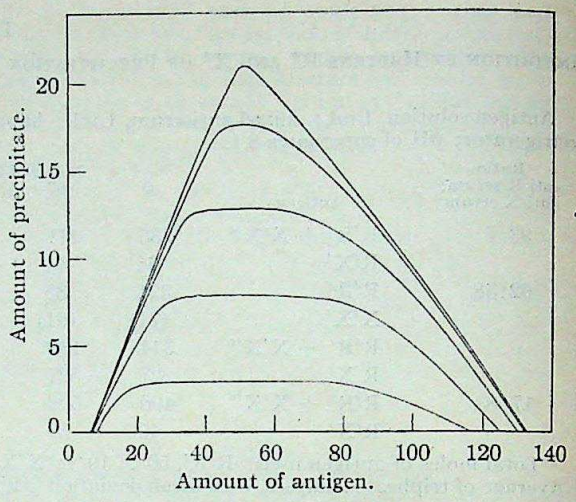

Fig. 2.—Curves showing calculated amount of precipitate as functions of amount of antigen RX for various relative amounts of anti-R and anti-X antibody. All curves are for $K_1 = K_1'' = K_2 = K_2'' = 1$ and $s = 2$. From top to bottom the curves correspond to the following pairs of values of $B^{(1)}_{total}$ and $B^{(2)}_{total}$: 25, 25; 20, 30; 15, 35; 10, 40; 5, 45.

of the two kinds of antibody is varied more and more from unity, the calculated curves of the amount of precipitate show broader and broader regions of approximate constancy (Fig. 2), resulting from the buffering action of the antibody present in excess, which combines with excess antigen to form a soluble complex, and thus interferes with the reaction of solution of the precipitate in excess of antigen; it is seen that the antigen concentration at which the amount of precipitate reaches its approximate maximum is determined by the amount of that kind of antibody which is present in smaller quantity, and that the antigen concentration at which the amount of precipitate begins to decrease is determined by the amount of the other kind of antibody. Experimental verification of these details of prediction cannot be expected until essentially homogeneous antibody solutions have been made by fractionation of antisera; however, the predicted general difference in nature is shown by the R'X' data given in Table I for the 93:7 mixture (broad region with nearly constant amount of precipitate) and the 62:38 mixture (rather narrow optimum region). Verification of the existence of the broad region of nearly constant amount of precipitate was obtained by the repetition of the experiment with the 93:7 mixture, with inclusion of points for smaller and larger amounts of the antigen R'X'; the amount of precipitated antibody was found to be constant (80 ± 10 μg.) over the range 18 to 500 $\times 10^{-9}$ mole of antigen, and to decrease for smaller and for larger amounts of antigen (34 μg. at 6.2 $\times 10^{-9}$ mole of antigen, 60 μg. at 1500 $\times 10^{-9}$).

When hapten of one kind is also present in the system, the equilibrium expressions may be com-

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bined to form the set of simultaneous equations 4 to 7.

$$\beta_1^2(1 + K_1\alpha + K_1'\gamma_1)^2 - \beta_1(B_{\text{total}}^{(1)} - B_{\text{total}}^{(2)}) - S(1 + K_2\alpha)^2/\alpha^2 = 0 \quad (4)$$

$$\beta_1^2\{(1 + K_1'\gamma_1)^2 - K_1^2\alpha^2\} + \beta_1\{A_{\text{total}} - B_{\text{total}}^{(1)} - B_{\text{total}}^{(2)} - \alpha\} + S(1 - \Lambda_2^2\alpha^2)/\alpha^2 = 0 \quad (5)$$

$$H_{\text{total}}^{(1)} = \gamma_1 + 2K_1'\beta_1\gamma_1 + 2K_1'^2\beta_1\gamma_1^2 + 2K_1K_1'\alpha\beta_1\gamma_1 \quad (6)$$

$$A_2B^{(1)}B^{(2)}(\text{pp}) = B_{\text{total}}^{(1)} - \beta_1(1 + K_1\alpha + K_1'\gamma_1)^2 - s \quad (7)$$

Here $H_{\text{total}}^{(1)}$ is the total amount of hapten (of the first kind) added and $\gamma_1 = [H^{(1)}]$ is another auxiliary variable. A similar set of equations can be derived for the case that hapten of the second kind is present. Solution of these equations may be made by selecting a value of γ_1 and finding by successive approximations the values of α and β_1 which satisfy Equations 4 and 5, and then determining $H_{\text{total}}^{(1)}$ and $A_2B^{(1)}B^{(2)}(\text{pp})$ from Equations 6 and 7, respectively.

The calculated curves for hapten inhibition by either kind of hapten when equal amounts of antibodies of the two kinds are present are closely similar to those for the simpler systems previously treated.[4] However, an interesting effect is predicted to occur when one antiserum predominates in the mixture and a small amount of antigen is present: a normal inhibition curve, linear in amount of hapten added, is found from the equations for one hapten, whereas the other hapten, that homologous to the antibody present in the larger amount, is predicted to be ineffective in small amounts, and to produce inhibition of precipitation only after enough of the hapten has been added to neutralize the excess of antibody in solution; calculated curves are given in Fig. 3. To test this prediction experiments were carried out, in triplicate, for the 93:7 mixture with the R′X′ antigen (antigen solution, 2 ml., containing 200 × 10^{-9} moles of R′X′ antigen; mixed antiserum, 2 ml.; hapten solution, 2 ml.; one hour at room temperature and two nights in refrigerator; pH of supernates 8.1; mean deviation of triplicate analyses ± 2%); the results are shown in Fig. 4. It is seen that there is a small initial region for which inhibition by the R* hapten does not occur. (In the comparison of Figs. 3 and 4 it should be remembered that the curves for Fig. 3 are calculated for haptens of equal bond-strength constant K', whereas K' for hapten R* is considerably larger than that for X*.) It is likely that the predicted effect would be shown more strikingly by fractionated antibody solutions than by the heterogeneous antisera used in these experiments.

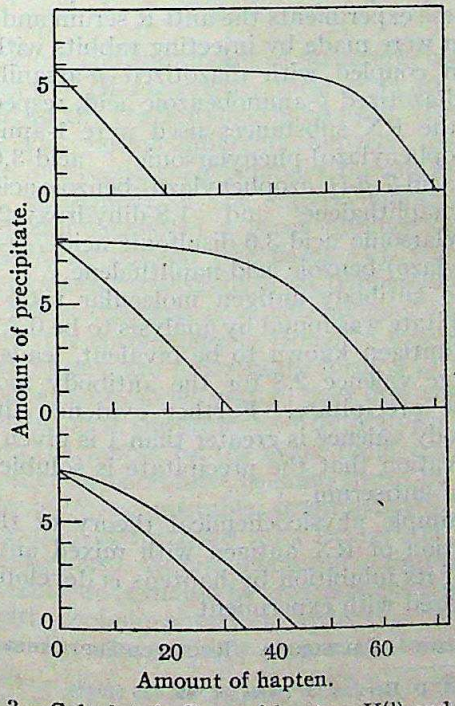

Fig. 3.—Calculated effects of haptens $H^{(1)}$ and $H^{(2)}$ on precipitation of antigen RX with an antiserum mixture containing four times as much anti-R antibody as anti-X antibody ($B_{\text{total}}^{(1)} = 10$, $B_{\text{total}}^{(2)} = 40$). From top to bottom the curves are for $A_{\text{total}} = 20$, 50, and 100; of each pair the curve at the left is for hapten $H^{(1)}$ and the other for hapten $H^{(2)}$.

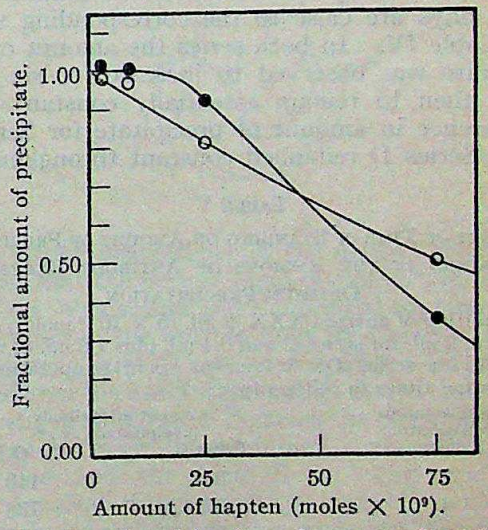

Fig. 4.—Experimental values of amount of precipitate formed by antigen R′X′ with 93:7 mixture of anti-R serum and anti-X serum in presence of hapten R* (solid circles) or hapten X* (open circles).

Experimental data bearing on the valence of the antibody molecules are given in Tables III and IV. The observed antibody/antigen molecular ratio of about 0.7 in both the equivalence zone and the region of antibody excess (Table III) corresponds, with antigen known to be bivalent, to 2/0.7 = 2.8 for the average valence of the antibody molecules in the precipitate.

The second of our arguments for the multivalence of antibody molecules is based on the solubility of antigen–antibody precipitates in

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excess antibody. This phenomenon has been reported for many antigen–antibody systems, especially with horse antibody. We have observed it to occur with rabbit antibody and simple polyhaptenic antigens; the results of an experiment of this sort, with anti-R serum and the substance R′R′, are given in Table IV. In this table there are given also data for a similar experiment with the substance R′X′ and a mixture of anti-R serum and anti-X serum; the observed decrease in the amount of precipitate with increase in amount of antiserum can be accounted for only with the theory of multivalent antibody.

It is known that excess of one component causes decrease in the rate of precipitation of antibody and antigen, and the question may be asked as to whether the effect of excess antibody reported in Table IV might be due to failure of the reaction to be completed in the time allowed. An experimental test of this possibility was made, with the results given in Table V. Tubes were set up corresponding to the first and fifth experiments of Series A of Table IV, representing, respectively, the region of antibody excess (Series C) and the region of optimum precipitation (Series D). These tubes were allowed to stand for times ranging from two to fifteen days, and then were analyzed. The values obtained after two days are close to the corresponding values of Table IV. In both series the amount of precipitate was observed to increase for six days, and then to remain essentially constant. The difference in amount of precipitate for Series C and Series D remained constant throughout the period; from these results we conclude that the effect of excess antibody in decreasing the amount of precipitate is real, and is not due to a difference in the rate of precipitation.

TABLE V

EFFECT OF TIME OF STANDING ON AMOUNT OF PRECIPITATE OBTAINED IN THE REGIONS OF ANTIBODY EXCESS AND OPTIMUM PRECIPITATION

Solution of antigen XXX, 2 ml. (5×10^{-9} mole); anti-R serum, 2 ml. for series C and 0.4 ml. plus 1.6 ml. of normal serum for series D; 1 hour at room temperature and indicated times in refrigerator.

Time of standing in refrigerator, days	Amount of antibody precipitated (μg.)[a] Series C	Series D
2	34	110
4	37	138
6	78	150
8	59	156
10	27	138
15	62	131

[a] Averages of triplicate analyses with mean deviation ±2 μg. Values are corrected by subtraction of the blanks for serum and buffer, which ranged between 14 and 23 μg. The large values of the blank in comparison with those of Table IV (5 μg.) may be due to change in the antiserum during the period of three months between the experiments.

Solubility of the precipitate in excess of antiserum has been reported for a few systems, such as diphtheria toxin and horse antitoxin, but not for antigen–antibody systems in general. Theoretical considerations[3,11] indicate that solubility in antibody excess should occur for antigens with small valence (such as the dihaptenic substances of Table IV) but not for antigens with large valence, which would only with difficulty be saturated with antibody to form a soluble complex.

This work was carried out with the aid of a grant from The Rockefeller Foundation. Dr. Stanley Swingle and Mr. Allan L. Grossberg helped with the experimental work.

Summary

It has been found by experiment that substances of the type RX, containing two different haptenic groups, do not form precipitates with either anti-R serum or anti-X serum alone, but do form precipitates with a mixture of the two specific antisera. This provides proof of the effective bivalence of the dihaptenic precipitating antigen, and thus furnishes further evidence for the framework theory of antigen–antibody precipitation. In these experiments the anti-R serum and anti-X serum were made by injecting rabbits with sheep serum coupled with diazotized *p*-arsanilic acid and diazotized *p*-aminobenzoic acid, respectively, and the RX substances used were 1-amino-2-*p*-(*p*-azophenylazo)-phenylarsonic acid-3,6-disulfonic acid-7-*p*-(*p*-azophenylazo)-benzoic acid-8-hydroxynaphthalene and 1,8-dihydroxy-2-*p*-azophenylarsonic acid-3,6-disulfonic acid-7-*p*-(*p*-azophenylazo)-benzoic acid-naphthalene.

The antibody–antigen molecular ratio in the precipitate was found by analysis to be 0.7, which, with antigen known to be bivalent, leads to the average valence 2.8 for the antibody molecules in the precipitate. Further evidence that the antibody valence is greater than 1 is given by the observation that the precipitate is soluble in excess of antiserum.

A simple physicochemical theory of the precipitation of RX antigen with mixed antiserum and of its inhibition by haptens is developed and compared with experiment.

PASADENA 4, CALIFORNIA RECEIVED SEPTEMBER 7, 1943

(11) A. D. Hershey, *J. Immunol.*, **42**, 455 (1941).

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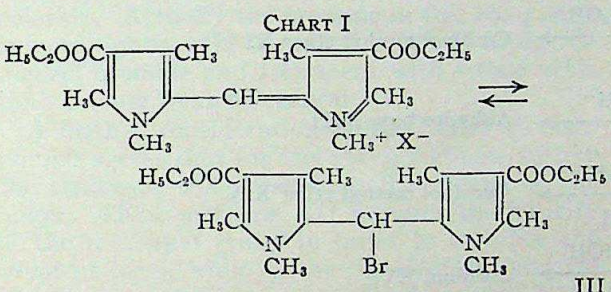
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

Effect of Substituents on the Structure of the Dipyrrylmethenes. Some Relationships between the Dipyrryl- and the Triphenylmethane Dyes[1,2]

BY KARL J. BRUNINGS AND ALSOPH H. CORWIN

Although a large number of dipyrrylmethene salts having a wide variety of substituents on the pyrrole rings have been prepared for the purpose of synthesizing naturally occurring pyrrole pigments,[3] the correlation of the effect of substitution and a study of the significance of these compounds to the general theory of organic dye salts has not been undertaken. General observations on the behavior of this large body of pigments has led to the conclusion that the dipyrrylmethene salts are best represented as coplanar resonating ionic structures (I), Chart I.

CHART I



I X = Br^-
II X = ClO_4

Thus, from the standpoint of structure, color and general dye characteristics these salts are closely related to the triphenylmethane dyes. However, there is a marked difference between these two classes of dyes in their behavior toward hydroxyl ions. Treatment of the dipyrrylmethene salts with alkali yields, in a great number of cases, stable highly colored free bases (VI, Chart II), whereas similar treatment of the triphenylmethane dyes yields colorless covalent carbinol bases instead of the corresponding Homolka bases. Such anhydro bases are not readily formed in the triphenylmethane series and go over into the colorless carbinols in the presence of hydroxyl ion. The dipyrryl carbinols, on the other hand, are practically unknown and have been suggested by several authors[3,4,5,6] as unstable intermediates in the preparation of methene salts by certain pyrrole condensations. In one instance,[7] a dipyrryl carbinol ether was isolated by treatment of a methene salt with alcoholic potassium hydroxide.

Recently, the authors prepared a stable carbinol from a di-N-methyl methene perchlorate II.[8] This system is similar to dimethylamino substituted triphenylmethane dyes in that it cannot exist in the form of a free base. Since the carbinol derivative was so unusual in the pyrrole series, a careful study of the properties of the parent methene salts was made. Evidence was found suggesting the existence of a covalent form of the di-N-methyl dipyrrylmethene bromide III. Thus, the unusual features of this methene system which gave rise to stability of the covalent carbinol also exerted their influence on the structure of the methene halide. Since the electronic interpretation of the effect of alkyl substitution on the nitrogens required that the stability of the ionic form of this system be enhanced, an explanation of the exactly opposite effect observed was sought elsewhere and found in a scale model of the coplanar resonating ion.

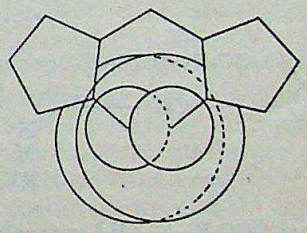


Fig. 1.

The strong interference of the methyl groups requires that the normal bond distances and angles, van der Waals radii and the normal coplanar configuration of the pyrrole rings be distorted in the resonating ion. These modifications must subtract from the usual stabilization due to resonance, thereby leading to a decrease in the margin of energy between the un-ionized covalent methyl bromide and the ionic form. Unfortunately, the covalent dipyrrylmethyl bromide could not actually be isolated in this case and therefore it seemed desirable to investigate the general effects of substitution on the structure of these pyrrole dyes and to attempt the preparation of a colorless covalent dipyrrylmethyl halide. The success of such an undertaking would be expected to lead to an explanation of the relationship of these compounds to the triphenylmethane dyes.

This paper reports the preparation of two covalent dipyrryl methyl bromides and presents a series of other derivatives which demonstrate the effect of pyrrole substituents on the structure of these methene dyes. All of the dipyrrylmethene salts and the dipyrrylmethyl halides were prepared by bromination of the corresponding di-

(1) Studies in the Pyrrole Series. XI; Paper X, Corwin and Brunings, THIS JOURNAL, 64, 2106 (1942).
(2) A portion of this paper was presented at the Buffalo meeting of the American Chemical Society, September, 1942.
(3) Fischer and Orth, "Chemie des Pyrrols," Bd. II, p. 3., Akad. Verlag, Leipzig, 1937.
(4) Fischer and Fries, *Z. physiol. Chem.*, **231**, 231 (1935).
(5) Fischer and Scheyer, *Ann.*, **434**, 237 (1923).
(6) Corwin and Andrews, THIS JOURNAL, **58**, 1086 (1936).
(7) Corwin and Andrews, *ibid.*, **59**, 1975 (1937).
(8) Brunings and Corwin, *ibid.*, **64**, 593 (1942).

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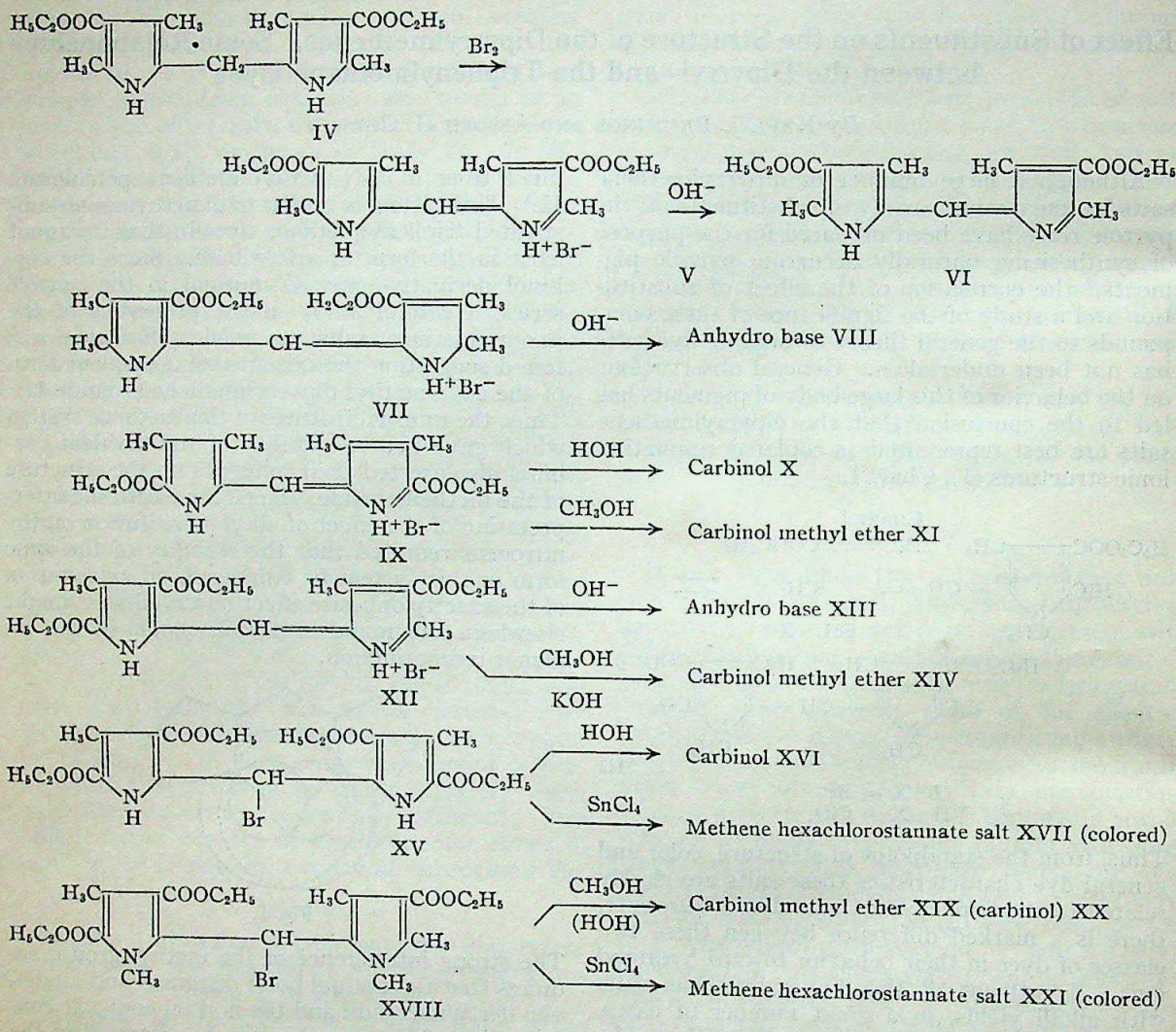
CHART II



pyrrylmethane leuco bases in carbon tetrachloride solution. Each methene was studied with respect to its behavior toward hydroxyl ion and alcoholic potassium hydroxide. The results are described by the structural formulas and equations in Chart II.

A comparison of the behavior of the methene bromides V, VII, and IX demonstrates the importance of the position of groups on the tendency toward stable dipyrryl carbinol formation. The methenes (V and VII) having a single carbethoxy group in either of the beta (3 or 4) positions of each pyrrole ring yield stable methene free bases VI and VIII in the manner of a great variety of these compounds. The α,α'-dicarbethoxy methene IX, on the other hand, gives a quite stable colorless dipyrryl carbinol X by merely suspending the highly colored methene crystals in neutral water, while the dipyrryl carbinol methyl ether XI is obtained by dissolving the methene in methanol. Thus it may be argued that carbethoxy groups in the alpha positions increase the tendency toward covalency in these systems. The special effect of the alpha carbethoxy groups was first noted by H. Fischer[9,10,11] who stated that α,α'-dicarbethoxy methanes do not yield methenes by oxidation (ferric chloride) but rather tetrapyrrylethanes. Since the α,α'-dicarbethoxy methene hydrobromide IX was prepared by oxidation of the corresponding methane with bromine, it represents an exception to this empirical rule. However, it should be pointed out that the conditions (solvent, oxidizing agent, temperature, etc.) of the reaction used in this work are quite different from those employed by Fischer in the oxidation of dipyrrylmethanes.

The effect of the alpha-carbethoxy group would suggest that substitution of carbethoxy groups for methyl groups on the pyrrole rings generally leads to stabilization of the covalent forms of the methenes. This reasoning is substantiated by the

(9) Fischer and Baumgartner, *Ann.*, **493**, 1 (1932).
(10) Fischer and Halbig, *ibid.*, **447**, 125 (1926).
(11) Fischer-Orth, "Chemie des Pyrrols," Bd. II, p. 6, Akad. Verlag. Leipzig, 1937.

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previously reported isolation of a stable carbinol ether from the tricarbethoxy dipyrrylmethene XII in which the additional effect of a single carbethoxy group has been introduced. The prime importance of the alpha carbethoxy groups is stressed by the fact that this methene having only one carbethoxy group in the alpha position yields the usual methene free base XIII on treatment with alkali.

By utilizing the strong effect of the carbethoxy groups in both of the alpha positions and the additional effect of substituting carbethoxy groups in the 3 and 3′ positions it was possible to prepare the colorless covalent dipyrrylmethyl bromide XV. The behavior of this compound is analogous to that of the well-known triphenylmethyl bromide and, like the parent compound of the triphenylmethane dyes, it may be converted into the colored ionic form by treatment with anhydrous stannic chloride. Actually the bromine in this compound is more tightly held than in the case of triphenylmethyl bromide and treatment with strong acids leads to only weak coloration.

A further consideration of this series of compounds shows that for any given methene system the structure will depend on the nature of the anion. Thus, methene XII requires the basicity of the methoxyl group in order to stabilize the covalent form, while in the presence of hydroxyl ion the methene reverts to the free base XIII. In the case of methene IX both hydroxyl and methoxyl ion stabilize the covalent form. Finally, the tetracarbethoxy system XV remains in the covalent form even in the presence of the weakly basic bromide ion.

Now, since compound XII, containing three carbethoxy groups, shows its tendency toward covalent structures only in the form of its carbinol ether, it might be argued that the introduction of steric hindrance by methylation of the nitrogens would so decrease the stability of the coplanar ionic form that even the methene bromide would exist in the covalent dipyrryl halide structure. This prediction is fully borne out by the preparation of the colorless di-N-methyl dipyrrylmethyl bromide XVIII. Once again this compound is analogous to triphenylmethyl bromide and is converted to a highly colored form by solution in strong acids or by treatment with anhydrous stannic chloride. The bromine in this derivative is less tightly bound than in the case of the tetracarbethoxydipyrrylmethyl bromide XV and the carbon–bromine bond is hydrolyzed by water so rapidly that great care must be exercised in protecting the compound from the atmosphere in preparing it for analysis.

The present series coupled with the previously reported data on the di-N-methyl dipyrrylmethene system I permits the following conclusions: (1) the structure of the dipyrrylmethenes is profoundly influenced by the substituents on the pyrrole rings; (2) the position of the substituents is critical; (3) substitution of carbethoxy groups increases stability of the colorless covalent form of the methene; conversely alkyl substitution favors the ionic salt structure; (4) alkyl substitution on the pyrrole nitrogens results in steric interference causing a decrease in the stability of the ionic coplanar form and is, therefore, opposite to the effect predicted on the basis of the electrical effect of alkyl groups.

Now, these observations are almost precisely those which have been made in the triphenylmethane series and the effects in both classes of dyes are supported by the same electronic interpretations. Finally, a consideration of the structural differences of the two systems leads to a satisfactory explanation of the relationships discussed in the early part of this paper.

The tendency of the triphenylmethyl halides toward ionic dissociation is explained by the resonance stabilization of the carbonium ion. Essentially the resonance forms of the ion describe the ability of the system to distribute the positive charge on the ortho and para positions of the phenyl groups and the bridge carbon atom. By substituting amino or dimethylamino groups in the para position of the benzene rings we convert the triphenylmethyl halide system into dye salts (pararosaniline, crystal violet, etc.). The positive charge is now shared by the amino nitrogens and the coplanar resonating cation is highly stabilized since the energy of positively charged nitrogen is lower than that of positively charged carbon. On the other hand, if carboxy groups are substituted in the para positions, we should expect the resulting structures to be covalent and therefore colorless. Some para carboxy substituted triphenyl carbinols and triphenylmethyl halides have been prepared and are, in fact, colorless covalent compounds.[12,13,14] The tendency of the carbethoxy groups to enter into resonance with the benzene rings by the withdrawal of electrons opposes the withdrawal of electrons from the triphenylmethyl system required for ionization of the halogen. The substitution of alkyl groups which are electron repelling by inductance would be opposite in effect to the carboxyl substitution and should increase the stabilization of the ionic form although their influence would be small. On the basis of qualitative measurements the tritolylmethyl halides are found to be more dissociated than the parent triphenylmethyl halide.[15,16,17]

Now it is well known that only para substituted triphenylmethenes are chromophoric dye systems. This suggests that the position of substitution in the benzene rings is critical. It was Baeyer and Villiger who first recognized the importance of position of substitution in the triphenylmethyl

(12) Hamilian, *Ber.*, **19**, 3071 (1886).
(13) Limpricht, *Ann.*, **299**, 295 (1898).
(14) Gomberg, THIS JOURNAL, **26**, 1520 (1904).
(15) Gomberg, *ibid.*, **26**, 1517 (1904).
(16) Mothwurf, *Ber.*, **37**, 3153 (1904).
(17) Norris, *Am. Chem. J.*, **38**, 629 (1907).

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system.[18] These investigators prepared a series of ortho, meta and para methoxy derivatives and devised a rough quantitative method for comparing the tendency toward ionization of the carbinols. They observed that the degree of ionization of *p,p',p''*-trianisylcarbinol in a mixture of concentrated acetic and sulfuric acids was many times greater than that of the parent triphenyl carbinol; the ortho derivative was much less ionized than the para, while meta derivatives were hardly more ionized than triphenyl carbinol. The very weak effect of ortho substitution was not considered surprising by these authors and since that time it has been considered axiomatic that only para substitution gives triphenylmethane dyes.

On the basis of the electronic interpretation of the effect of these groups we should expect meta substitution to be relatively ineffective in influencing the structure of these dyes, but there is no apparent reason why ortho substitution should not be as potent as para in stabilizing the resonating cation. However, if we construct a model of the triphenyl carbonium ion (Fig. 2) similar to the type drawn for the di-N-methyl dipyrrylmethene[8] (Fig. 1), assuming coplanarity of the system and utilizing the accepted bond angles and distances in aromatic molecules, strong overlapping of the van der Waals radii of the ortho hydrogens is observed. This steric hindrance of

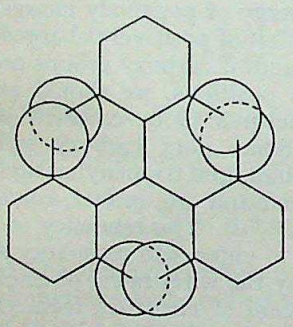
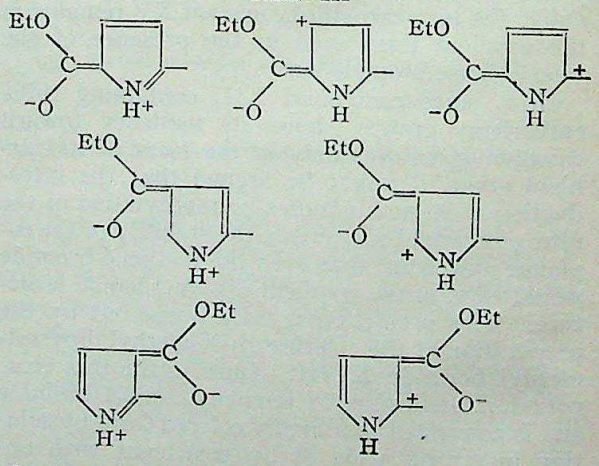


Fig. 2.

the ortho hydrogens has been pointed out recently by G. N. Lewis,[19] who suggests that deviation of the phenyl groups from complete coplanarity gives rise to isomerism in the triphenylmethane dyes. He finds evidence of two forms of crystal violet in the shoulder of its absorption maximum in the visible. It is not necessary to assume that this steric interference of the ortho hydrogens makes the concept of the resonance stabilized cation untenable since by bending of the carbon–hydrogen bonds, penetration of the van der Waals radii, and slight deviation from coplanarity the conditions of aromaticity can be approached. But these factors of accommodation can only occur with an expenditure of energy which must be subtracted from the energy of resonance stabilization. Replacement of the ortho hydrogens with still larger groups will decrease the resonance stabilization even more and it is not unreasonable to assume that this steric effect will eventually nullify whatever other influence the ortho substituent might have. The magnitude of the energy necessary to accommodate such sterically hindered structures and for that matter, the resonance energy of an unhindered system has not been determined and can only be inferred by comparison of the chemical and physical properties of a series of compounds.

The foregoing interpretation of the relationships in the triphenylmethane dyes provides an explanation of the observations on the dipyrrylmethenes reported in this paper. Thus, it is the pyrrole nitrogens with their ability to stabilize the positive charge of the cation by resonance which are responsible for the ionic character and finally the color of the dipyrrylmethene pigments. We may say that a pyrryl group is equivalent to a para aminophenyl group in stabilizing the carbonium ion. This tendency of the pyrrole rings to supply electrons for the ionization of the halogens in the dipyrrylmethyl halides will be opposed by the substitution of carbethoxy groups in the pyrrole rings. That the position of these groups is critical is apparent from an inspection of the resonance forms which can be written for the three types of carbethoxy substituted pyrrole rings in Chart III. It is observed that we can write

CHART III



three resonance forms in which electrons are removed from the ring in the case of alpha substitution while for the two beta (3 and 4) we can have only two. Thus, the alpha carbethoxy group will be most potent in attracting electrons from the dipyrrylmethyl system and, therefore, most effective in stabilizing the covalent colorless form of the methene halides. It may be equally well argued that the carbethoxy group increases the positive character of the methene bridge carbon, thereby strengthening the carbon–halogen bond with respect to ionic cleavage. Consideration of the interaction of the carbethoxy group with

(18) Baeyer and Villiger, *Ber.*, **35**, 3019 (1902).
(19) Lewis, Magel and Lipkin, THIS JOURNAL, **64**, 1774 (1942).

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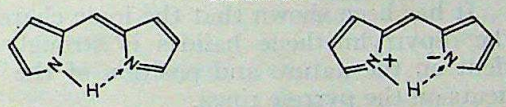
pyrrolenyl forms in the methene system shows that the β-carbethoxy can interact to give a higher energy form (two positive charges on one pyrrole ring) while the α-carbethoxy cannot. Again the difference favors a greater effect of the α-carbethoxy group in stabilizing the covalent form. A more careful analysis of all the possible resonance forms of the whole methene structure including higher energy forms will give a more accurate value of the ratio of effectiveness of the three positions and will, indeed, indicate differences between the two beta (3 and 4) positions. However, such an analysis is unnecessary for the large effects observed in the present study, but may be helpful in explaining fine differences in properties such as absorption spectra.

If we compare models of the N-free dipyrrylmethene ion (Fig. 1) and the triphenyl carbonium ion (Fig. 2), we observe that the interference of the hydrogens ortho to the bridge carbon is somewhat less for the former. This difference, however, is small and would represent only a minor contribution to the comparative effectiveness of dipyrryl groups in stabilizing the carbonium ion. Now in the formation of the free base of the dipyrrylmethene one of the hydrogens on the nitrogens is lost and with it the steric hindrance. Moreover, the distances are now favorable for the formation of an intramolecular six membered chelate ring involving the pyrrole nitrogens (Chart IV). Thus an additional factor must be

CHART IV



added to the resonance stabilization of the free base structure. In the case of the corresponding Homolka bases of the triphenylmethane dyes the normal steric repulsion of the ortho hydrogens is not released, nor does the possibility of intramolecular chelation exist. A consideration of the geometry of the resonating ions, therefore, gives us two factors which account for the ready formation of free bases in the pyrrole series and the relative instability of the Homolka bases of the triphenylmethane dyes.

The authors are indebted to the Rockefeller Foundation for a research grant which has made this investigation possible.

Experimental Section

Preparation of 3,5,3′,5′-Tetramethyl-4,4′-dicarbethoxydipyrrylmethene Hydrobromide (V).—A solution of 0.350 g. of 3,5,3′,5′-tetramethyl-4,4′-dicarbethoxydipyrrylmethane (II) in 500 cc. of dry carbon tetrachloride was prepared by refluxing the finely divided methane in the solvent for several hours. After the solution had been brought to room temperature 0.16 g. of bromine in 2 cc. of carbon tetrachloride was run in quickly while the flask was twirled. The solution was allowed to stand in the ice box overnight, after which time 0.390 mg. of fine red needles (92% of the theoretical) was filtered from the solution. The free base (VI) was obtained by shaking a chloroform solution of the hydrobromide salt with calcium hydroxide. The long red needles were recrystallized from benzene–hexane; m. p. (dec.) 189–190°.

3,3′-Dicarbethoxy-4,5,4′,5′-tetramethyldipyrrylmethene Hydrobromide (VII).—A solution of 1 g. of the corresponding dipyrrylmethane[20,21] in 100 cc. of dry carbon tetrachloride was placed in a 200-cc. Erlenmeyer flask; 0.51 g. of bromine in 5.1 cc. of carbon tetrachloride was run in quickly while the flask was twirled and the solution was allowed to stand several hours in the ice box; 0.910 g. of deep red crystals was obtained on filtration. Addition of petroleum ether to the mother liquors gave an additional 0.150 g. of the methene salt; total yield, 87%. The free base VIII was prepared by shaking a chloroform solution of the hydrobromide salt with calcium hydroxide.[22,23] Recrystallization from benzene–hexane gave beautiful orange-red crystals; m. p. (dec.) 164–165°.

3,4,3′,4′-Tetramethyl-5,5′-dicarbethoxydipyrrylmethene Hydrobromide (IX).—The corresponding dipyrrylmethane[24,25] (5 g.) was dissolved in one liter of dry carbon tetrachloride. After the solution had been brought to room temperature, 2.55 g. of bromine in 25.5 cc. of carbon tetrachloride was added rapidly with stirring. A rich crop of brilliantly colored crystals appeared in a few minutes. After cooling in an ice box 5.9 g. of fine red needles was filtered off; yield, 96%. The dipyrrylmethene salt decomposed at 160–165°. *Anal.* Calcd. for $C_{19}H_{25}N_2O_4Br$: C, 53.65; H, 5.93. Found: C, 53.64; H, 5.94. All attempts to prepare the free base yielded the dipyrrylcarbinol (X).

3,4,3′,4′-Tetramethyl-5,5′-dicarbethoxydipyrrylcarbinol (X).—The corresponding dipyrrylmethene salt (1 g.) was suspended in about 50 cc. of water, the mixture shaken thoroughly and allowed to stand overnight. The brilliant red color of the suspended crystals faded slowly until after six hours only a faint pink remained. The easily filtrable precipitate weighed 0.830 g. Recrystallization from benzene yielded a beautiful white compound melting with decomposition at 185–186°. *Anal.* Calcd. for $C_{19}H_{26}N_2O_5$: C, 62.97; H, 7.23. Found: C, 63.25; H, 7.18.

3,4,3′,4′-Tetramethyl-5,5′-dicarbethoxydipyrrylcarbinol Methyl Ether (XI).—The corresponding dipyrrylmethene salt (IX) (200 mg.) was dissolved in boiling anhydrous methanol. The red color of the methene disappeared rapidly and on cooling, 150 mg. of pearly crystals precipitated; yield, 85%. The material melts sharply with decomposition at 169–170°. *Anal.* Calcd. for $C_{20}H_{28}N_2O_5$: C, 63.81; H, 7.50. Found: C, 63.93; H, 7.46.

Both the dipyrrylmethyl carbinol (X) and the dipyrrylmethyl methyl ether (XI) described above may be converted back to the corresponding dipyrrylmethene hydrobromide (IX) by dissolving them in dry carbon tetrachloride and saturating the solution with dry gaseous hydrogen bromide. The identity of the methene salt was checked by analysis.

3,5,4′-Trimethyl-4,3′,5′-tricarbethoxydipyrrylmethene Hydrobromide (XII).—The corresponding dipyrrylmethane[26,27] (500 mg.) was dissolved in 500 cc. of dry carbon tetrachloride; 0.2 g. of bromine in 5 cc. of carbon tetrachloride was added quickly with stirring at room temperature. After standing several hours in the cold 500 mg. of fine orange red needles was filtered from the solution; yield, 83%. Conversion of the methene salt to the base (XIII) by the method described above gave a compound identical with the methene base prepared by several independent methods; m. p. (dec.) 125–126°.

3,5,4′-Trimethyl-4,3′,5′-tricarbethoxydipyrrylcarbinol Methyl Ether (XIV).—This compound was prepared by the method described by Corwin and Andrews.[28]

(20) Fischer and Nenitzescu, *Ann.*, **443**, 124 (1925).
(21) Fischer and Walach, *ibid.*, **450**, 127 (1926).
(22) Fischer and Beller, *ibid.*, **444**, 247 (1925).
(23) Fischer and Nussler, *ibid.*, **491**, 167 (1931).
(24) Fischer and Nenitzescu, *ibid.*, **443**, 124 (1925).
(25) Bue, Dissertation, The Johns Hopkins University, 1939.
(26) Fischer and Halbig, *Ann.*, **447**, 132 (1926).
(27) Corwin and Ellingson, THIS JOURNAL, **64**, 2098 (1942).
(28) Corwin and Andrews, *ibid.*, **59**, 1978 (1937).

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3,3′,5,5′-Tetracarbethoxy-4,4′-dimethyldipyrrylmethyl Bromide (XV).—A solution of 10 g. of the corresponding dipyrrylmethane[26,29,30] (thoroughly desiccated) in one liter of dry carbon tetrachloride was prepared in a 1.5 liter filter flask equipped with a one-holed rubber stopper containing a calcium chloride drying tube. The sidearm of the filter flask was tightly sealed with a piece of rubber tubing and a screw clamp; 3.5 g. of bromine in 35 cc. of dry carbon tetrachloride was run in rapidly with stirring and the flask quickly stoppered. The addition of the bromine caused no cloudiness and the color of the solution was simply that of the added bromine. Even after six hours an appreciable amount of bromine remained unreacted. After standing twenty-four hours the stopper was replaced by a rubber stopper containing a capillary with a drying tube attached to the end. The flask was then hooked up to a water pump by means of an intervening drying tube, and the carbon tetrachloride removed at room temperature. The slightly colored crystalline residue was recrystallized from dry benzene–hexane (purified); yield, 10.6 g. or 90%. Repeated recrystallization from benzene–hexane gave 8.0 g. of analytically pure compound; m. p. (dec.) 132–133°. The compound turns pink at 128–130°. *Anal.* Calcd. for $C_{23}H_{29}N_2O_8Br$: C, 51.02; H, 5.40; Br, 14.26. Found: C, 51.09; H, 5.42; Br, 15.45 (± 1%).

In the process of purification it was observed that benzene solutions of the dipyrrylmethyl bromide (XV) became highly colored when heated to the boiling point of benzene; on cooling, this color disappears. The same phenomenon was reported by Gomberg for the tritolylmethyl halides in benzonitrile.[31] It was also observed that cold colorless solutions of the dipyrrylmethyl bromide were capable of imparting a definite orange-red color to filter paper and to textiles in general. The color imparted to wool was the most intense.

When the dipyrrylmethyl bromide was dissolved in concentrated sulfuric acid only a weak coloration occurred. Chloroform solutions on the other hand became intensely colored when anhydrous stannic chloride was added. This color vanished immediately when water was added to the solution. The assumed dipyrrylmethene hexachlorostannate salt (XVII) was not isolated.

1,3,5,1′,4′-Pentamethyl-4,3′,5′-tricarbethoxydipyrrylmethyl Bromide (XVIII).—A solution of 3.9 g. of the corresponding dipyrrylmethane[27] (thoroughly desiccated) was prepared in a 500-cc. Erlenmeyer flask. 1.47 g. of bromine in 14.7 cc. of carbon tetrachloride was run in rapidly while the flask was twirled. After the addition the flask was stoppered immediately, and then placed in a desiccator and allowed to stand overnight. After this time a small amount of red oil had collected on the sides of the flask; the solution itself was clear. The following operations were then carried out in a dry air chamber. A nitrogen tank with a glass top and arm holes served as a dry air chamber. Compressed air, conducted through a tall column of calcium chloride, was passed through the chamber for one-half hour before operations were begun and continued until completed. The solution was transferred to a one-liter flask equipped with a one-holed rubber stopper containing a capillary with a drying tube attached to the end. The filter flask was then hooked up to a water pump by means of an intervening drying tube and the carbon tetrachloride pumped off at room temperature. The pink colored crystalline residue, weighing 3.5 g., was placed in an Erlenmeyer flask equipped with a tight fitting rubber stopper. The crystals were then covered with dry benzene–hexane in the ratio of ten to one, the flask well stoppered, and removed from the dry air chamber. After replacing the stopper with an air reflux condenser equipped with a drying tube, the mixture was gently refluxed until solution was complete. The flask was once again stoppered with a drying tube, returned to the dry air chamber and allowed to stand until crystallization was complete. Soft almost colorless crystals were then painfully collected on a Büchner funnel in the dry air chamber. The material melted, turning blood red at 135–136°.

Anal. Calcd. for $C_{23}H_{31}N_2O_6Br$: C, 54.01; H, 6.11; Br, 15.63. Found: C, 54.28; H, 6.11; Br, 16.11 (± 1%). It is absolutely necessary to follow the above precautions for the exclusion of water vapor in order to obtain analytical material. By merely suspending the compound in water and filtering over fifty per cent. of the bromine is lost.

The dipyrrylmethyl bromide readily dissolves in concentrated sulfuric and perchloric acid to yield brilliantly colored solutions. Likewise, the same intense color is obtained when a chloroform solution of the bromide is treated with anhydrous stannic chloride. Dilution of the acid solutions and addition of water to the stannic chloride solution discharges the color.

1,3,5,1′,4′-Pentamethyl-4,3′,5′-tricarbethoxydipyrrylcarbinol Methyl Ether (XIX).—This derivative was obtained by simply dissolving the corresponding dipyrrylmethyl bromide in hot methanol and allowing the solution to cool. The compound was recrystallized several times from the same solvent; m. p. 93–94°. *Anal.* Calcd. for $C_{24}H_{34}N_2O_7$: C, 62.32; H, 7.41. Found: C, 62.48; H, 7.42.

Summary

1. The effect of substituents on the structure of the dipyrrylmethenes has been studied by comparing the properties of a variety of these pigments.

2. It has been shown that the ionic character of the dipyrrylmethene halides is strongly dependent on the nature and position of the substituents on the pyrrole rings.

3. Several new dipyrryl carbinols have been prepared.

4. Two colorless dipyrrylmethyl bromides have been synthesized. These compounds, which are analogous in structure and behavior to triphenylmethyl bromide, have not been observed heretofore in the pyrrole series.

5. It has been shown that steric interference of hydrogens or substituents ortho to the bridge carbon atom exerts a strong influence on the structure of both the triphenyl and dipyrrylmethane dyes.

6. The present observations on the dipyrrylmethenes and previously established data on the triphenylmethane series have been correlated on the basis of a common electronic interpretation. A comparison of the structural geometry of the two dye systems completes the relationship.

BALTIMORE, MD. RECEIVED SEPTEMBER 17, 1943

(29) Corwin, Bailey and Viohl, THIS JOURNAL, **64**, 1270 (1942).

(30) Fischer and Ernst, *Ann.*, **447**, 158 (1926).

(31) Gomberg, *Ber.*, **35**, 2404 (1902).

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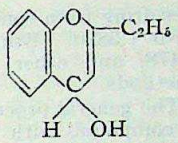
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

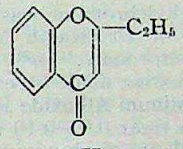
The Reduction of Ester Vinylogs[1]

BY ROBERT H. BAKER AND PATTY CAMPBELL WEISS

In an attempt to prepare 2-ethylchromen-4-ol, I, by methods more suitable than the one developed by Mozingo and Adkins,[2] it was observed that aluminum isopropoxide does not reduce 2-ethylchromone, II.[3] The failure of this reaction



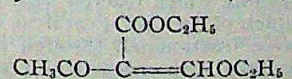
I



II

may be attributed to the fact that the ketone is a vinylog of an ester and hence has an oxidation potential which is numerically too far below that of acetone to allow it to oxidize isopropyl alcohol.[4]

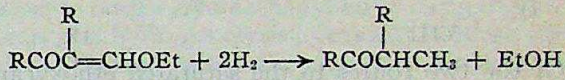
It appeared that open chain vinylogs might approach more nearly the properties of esters, and hence might exhibit alkoxyl exchange in the presence of aluminum alkoxides,[5] but no reaction of this type has been unequivocally demonstrated. Both 2-ethylchromone, II, and O-ethylbenzoylacetone, IV, were recovered unchanged after refluxing with isopropyl alcohol in the presence of aluminum isopropoxide. The latter compound was also unaffected by heating to 100° in the presence of pure aluminum *s*-butoxide. Ethyl α-ethoxymethyleneacetoacetate, III, was changed



III

by similar treatment but the only identifiable product was a small amount of a dimer and much tar was produced. This is not surprising in light of the ease of dimerization of methyl ketones[6] and the great instability of this compound when kept at room temperature.

The catalytic reduction of these compounds demonstrates the extraordinary lability of the alkoxyl group. Over palladium catalysts Kötz and Schaeffer[7] found that those which are easily hydrolyzed are hydrogenated according to the equation



In this reaction hydrogenolysis of the ethoxyl must precede the reduction of the ethylenic linkage, for there is no precedent for the reverse order which would require the hydrogenolysis of a saturated ether under mild conditions. It appeared that the hydrogenolysis reaction might be minimized and hydrogenation favored by use of catalysts less active than palladium which allow of greater selectivity. Some typical results of these experiments are shown in Table I.

TABLE I

SELECTIVE HYDROGENATION OF ESTER VINYLOGS

Compound	Temp., °C.	Time, min.	Cat.	Moles H_2 per mole cmpd.	% Product
Ethyl α-ethoxymethylene-acetoacetate	23	48[a]	Ni(R)	1.6	50 Ethyl α-methylaceto-acetate
Same	150	40[a]	CuCrO	0.8	Non-distillable tar
O-Ethylbenzoylacetone	118	40	Ni(R)	2.0	57 β-Ethoxypropylphenyl-carbinol VI
Same	120	120[a]	Ni(R)	1.0	64% Mixture of VI and β-ethoxybutyrophenone
Same	180	330	CuCrO	2.0	58 Butyrophenone, IX
Ethyl β-ethoxycrotonate	130	70	Ni(R)	0.9	86 Ethyl β-ethoxybutyrate
Same	170	120	CuCrO	0.6	45 Ethyl β-ethoxybutyrate

[a] Glass liner used.

Ethoxymethyleneacetoacetic ester, III, presents a very labile ethoxyl group, it being vinylogous to two carbonyl groups. Over nickel it underwent hydrogenolysis followed by hydrogenation of the carbon-to-carbon double bond under very mild conditions. Over copper–chromium oxide it is apparently polymerized before hydrogenation takes place.

In O-ethylbenzoylacetone, IV, the alkoxyl is vinylogous to only one carbonyl group, and it was possible to avoid hydrogenolysis with nickel or to make it the predominating reaction over copper–chromium oxide. Of the several ways that hydrogen might attack this molecule, the more plausible are shown below.

(1) This investigation was supported in part by a grant from the Abbott Fund of Northwestern University.

(2) Mozingo and Adkins, THIS JOURNAL, **60**, 669 (1938).

(3) This experiment was carried out by the senior author in 1939 while working under the direction of Prof. Homer Adkins.

(4) Baker and Schafer, THIS JOURNAL, **65**, 1675 (1943).

(5) Baker, *ibid.*, **60**, 2673 (1938).

(6) Wayne and Adkins, *ibid.*, **62**, 3401 (1940).

(7) Kötz and Schaeffer, *J. prakt. Chem.*, **196**, 604 (1913).

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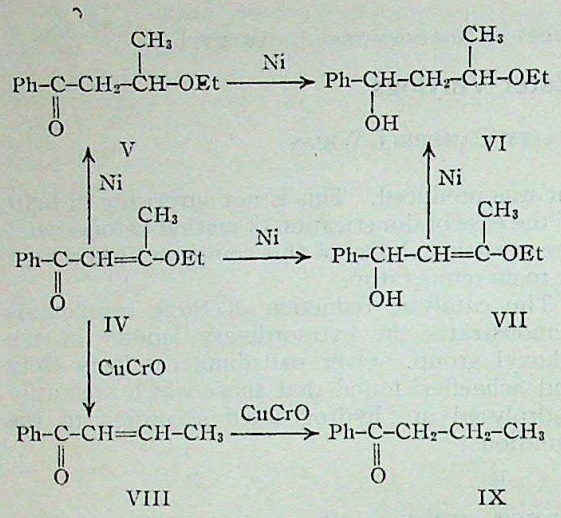
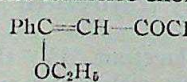


Of the two routes to the saturated ethoxycarbinol, VI, evidence that the preferred one is through the ethoxyketone, V, was obtained from experiments in which the hydrogen adding was limited to one mole. The boiling point of the ketone, V, is so near that of the alcohol, VI, that only the mixture was isolated; however, its presence was demonstrated in the mixture by polarographic and Grignard machine analysis. Evidence for the formation of the ethoxyvinyl carbinol, VII, was less conclusive, but its presence can hardly be discounted on the basis of the fact that nickel generally shows little preference for an ethylenic over a carbonyl linkage. Its presence was indicated by tests for unsaturation applied to some of the low boiling fractions resulting from various hydrogenations over nickel.

The third mode of hydrogenation leads to butyrophenone, IX, and this is brought about over copper–chromium oxide. No evidence for the formation of crotonophenone, VIII, was obtained, the runs with limited quantities of hydrogen seemingly resulting only in the production of butyrophenone.

Ethyl β-ethoxycrotonate presents a still less powerful group to activate the vinylogous ethoxyl and is hydrogenated entirely to β-ethoxybutyric ester over either of the two catalysts.

The structures of the products of hydrogenation of O-ethylbenzoylacetone, IV, confirm the structure originally claimed for this enol ether by Claisen,[8] and dispute the contention of Weygand[9] that regardless of the method of preparation the compound is the isomeric enol ether, X.



(X)

Experimental Part

Preparation of Compounds.—Ethyl α-ethoxymethyleneacetoacetate was prepared from one mole each of ethyl acetoacetate and acetic anhydride and two moles of ethyl orthoformate according to Claisen.[10] It was found to be desirable to distil the product rapidly from hydroquinone without the aid of a column. The product distilling at 149–151° (16 mm.) amounts to 76 g., 41%, and has $n^{20}D$ 1.4715–1.4720. It may be kept for a few weeks only if protected by hydroquinone at 0° and in the dark, one-half of it being destroyed by keeping under ordinary conditions at room temperature for one month.

O-Ethylbenzoylacetone was prepared by the method of Claisen.[8] A number of preparations indicated that seven minutes of refluxing of benzoylacetone and ethyl orthoformate with strictly dry ethyl alcohol and ferric chloride gives the best yield, 53% of product $n^{20}D$ 1.5610–1.5615, b. p. 119% (1 mm.), when distilled through a 16-plate column.

2-Ethylchromone was a sample resulting from some research of Dr. Ralph Mozingo,[2] $n^{25}D$ 1.5820. Ethyl β-ethoxycrotonate,[11] $n^{30}D$ 1.4471–1.4478, and other compounds were made by established methods.

Aluminum Alkoxide Reactions.—The general procedure was to treat 0.05–0.10 mole of the compound with three equivalents of aluminum alkoxide dissolved in its corresponding alcohol. Aliquots were taken at the beginning and after various periods of heating and analyzed polarographically. The height of the 2-ethylchromone wave[2,12] was not diminished after sixty hours of refluxing. The remainder of the solution after hydrolysis, isolation, and distillation through a 3-plate column yielded the major portion of unchanged 2-ethylchromone, $n^{25}D$ 1.5806.

The heights of the O-ethylbenzoylacetone wave[13] also showed that no reduction of this compound had occurred. After treatment with water and fractionation, the compound corresponded in boiling point and refractive index to starting material. As a further test to see if alkoxyl exchange is possible, this compound was heated with pure aluminum *s*-butoxide for two hours at 100°. Then just sufficient water was added to hydrolyze the alkoxide and the oil was isolated. This was distilled through a 3-plate micro column yielding fractions which appeared to be unchanged material. A small tail fraction was analyzed as follows:[14] Calcd. for O-ethylbenzoylacetone, $C_{12}H_{14}O_2$: C, 75.76; H, 7.41. Calcd. for O-*s*-butylbenzoylacetone, $C_{14}H_{18}O_2$: C, 77.03; H, 8.31. Found: C, 76.05; H, 7.67. Since the tail fraction represented 15% of the starting weight and the carbon analysis cannot admit of more than 25% of *s*-butyl derivative, the exchange in the whole fraction cannot have been greater than 4%, if any.

Ethyl α-ethoxymethyleneacetoacetate, when thus treated with aluminum isopropoxide in isopropyl alcohol, turned quite yellow after ten minutes at 60°. There was a sharp drop in the height of the polarographic wave which remained approximately equivalent to one-half of the original concentration after three hours. After treatment with water and isolation, there was obtained a viscous yellow oil 50% of which was distillable at 200–218° (1 mm.). This was an amber colored plastic mass which did not crystallize after standing a year. Its molecular weight, Rast, was 370, while that calculated for the starting material is 186.

Hydrogenations.—The catalysts, apparatus and procedures were similar to those which are particularly adapted to selective hydrogenations.[15,16] No solvents were used, and glass liners for the bombs appeared to be of no benefit except possibly in the case of ethyl α-ethoxymethyleneacetoacetate which reacted with metals to such an extent that much of the nickel catalyst was destroyed. The products were fractionated through either a 10- or 16-plate column and the recorded boiling points are subject to the usual errors attending slow fractionation through electrically heated, total condensation apparatus.

Identification of Hydrogenation Products.—Ethyl α-methylacetoacetate, $n^{21}D$ 1.5215, was converted into the

(8) Claisen, *Ber.*, **40**, 3903 (1907); **59**, 144 (1926).
(9) Weygand, *ibid.*, **58**, 1473 (1925).
(10) Claisen, *Ann.*, **297**, 1 (1897).
(11) Wislicenus and Schollkopf, *J. prakt. Chem.*, **203**, 269 (1917).
(12) Adkins and Cox, THIS JOURNAL, **60**, 1151 (1938).
(13) $\pi = -1.67$ volts, empirical in lithium chloride solution.
(14) Analysis by Dr. T. S. Ma, University of Chicago.
(15) Adkins, "Reactions of Hydrogen," University of Wisconsin Press, Madison, Wisconsin, 1937.
(16) Sprague and Adkins, THIS JOURNAL, **56**, 2669 (1934).

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2,4-dinitrophenylhydrazone, m. p. 59°, and into ethyl methyl ketone the semicarbazone of which melted at 136°.[17]

β-Ethoxypropylphenylcarbinol has not been previously described. It has the following constants: b. p., 82.5° (1 mm.); $n^{21}D$ 1.4995; d^{20}_4 0.994; M_D, found, 56.8; M_D, calcd., 52.0; mol. wt., cryoscopic in benzene 202, cryoscopic in camphor 198; mol. wt. calcd., 194; % hydroxyl, found, 8.76, 8.75[18]; calcd., 8.76. The Baeyer and iodoform tests are negative. We are unable to explain the anomaly in molecular refractivity except on the basis that this product is in all probability a mixture of two racemic forms.

β-Ethoxybutyrophenone was thought to be present in the reaction mixture resulting from limited hydrogenation of O-ethylbenzoylacetone over nickel. Nine fractions boiling 94–110° (1 mm.) were collected from a 3-plate distillation. The first six of these, 94–100°, showed a gradual drop in refractive index, $n^{20}D$ 1.5137–1.5075 and represented 64% of the weight of starting material. The last two fractions $n^{20}D$ 1.5645 represented 11% recovery of crude starting material. Fraction number three gave negative tests with bromine and with permanganate, and the presence of an aryl ketone in approximately 50% concentration was demonstrated by the polarograph, $\pi = -1.68$. Assuming the mixture to be pure alcohol and ketone the Grignard machine analysis indicated 56% of alcohol of molecular weight 195 and 44% ketone of molecular weight 194. The calculated molecular weights of the expected ketone and alcohol, V and VI, are 194 and 196, respectively.

Butyrophenone, $n^{20}D$ 1.5127, showed a polarographic wave in lithium chloride solution at −1.68 volts (empirical). It gave a semicarbazone, m. p. 189–190°, and a 2,4-dinitrophenylhydrazone, m. p. 190°, in agreement with the literature.[17]

Ethyl β-ethoxybutyrate, $n^{20}D$ 1.4076; d^{20}_4 0.925; M_D found, 42.6, calcd., 42.4; had the correct boiling point at 745 mm., 173°.[19]

(17) Huntress and Mulliken, "Identification of Pure Organic Compounds," Order I, John Wiley and Sons, Inc., New York, N. Y., 1941.

(18) Adkins, Frank and Bloom, THIS JOURNAL, **63**, 554 (1941).

Summary

1. Compounds which are open-chain vinylogs of esters are too much like esters to be reduced by aluminum alkoxides. They, however, are not sufficiently ester-like to undergo alkoxyl exchange with these reagents.

2. When the alkoxyl group is in a vinylogous position to both a keto-carbonyl and a carbethoxyl, it undergoes hydrogenolysis over nickel under very mild conditions. When the alkoxyl is vinylogous to only a keto-carbonyl it is more resistant to hydrogenolysis and the nature of the hydrogenation products may be controlled by selection of catalysts. The carbethoxyl group does not labilize such groups sufficiently to allow of hydrogenolysis prior to hydrogenation of the ethylenic linkage.

(19) Purdie and Marshall, *J. Chem. Soc.*, **59**, 478 (1891).

EVANSTON, ILL. RECEIVED OCTOBER 28, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

The Acetylation of Certain Unsymmetrical Aliphatic Ketones with Acetic Anhydride in the Presence of Boron Trifluoride[1,2]

BY CHARLES R. HAUSER AND JOE T. ADAMS

The acetylation of ketones with acetic anhydride in the presence of boron trifluoride to form 1,3-diketones has been carried out previously apparently only with ketones such as acetone,[3,4] diethyl ketone[3] or acetophenone,[3,5] each of which can yield but a single monoacetyl derivative. The purpose of this investigation has been to determine the products of acetylation, in the presence of boron trifluoride, of certain unsymmetrical aliphatic ketones each of which might form two different monoacetyl derivatives. Three types of unsymmetrical ketones have been studied, types I, II and III, represented below, with which it is possible to form, respectively, the methyl and methylene derivatives, the methyl and methinyl derivatives, and the methylene and methinyl derivatives, thus

$$\underset{\text{Type I}}{CH_3COCH_2R} \xrightarrow[BF_3]{Ac_2O} \underset{\text{Methyl deriv.}}{CH_3COCH_2COCH_2R} + \underset{\text{Methylene deriv.}}{CH_3COCHRCOCH_3}$$

$$\underset{\text{Type II}}{CH_3COCHR_2} \xrightarrow[BF_3]{Ac_2O} \underset{\text{Methyl deriv.}}{CH_3COCH_2COCHR_2} + \underset{\text{Methinyl deriv.}}{CH_3COCR_2COCH_3}$$

$$\underset{\text{Type III}}{RCH_2COCHR_2} \xrightarrow[BF_3]{Ac_2O} \underset{\text{Methylene deriv.}}{CH_3COCHRCOCHR_2} + \underset{\text{Methinyl deriv.}}{CH_3COCR_2COCH_2R}$$

Seven ketones have been acetylated, five of type I, methyl ethyl, methyl *n*-propyl, methyl isobutyl, methyl *n*-amyl and methyl *n*-hexyl ketones, and one each of types II and III, methyl isopropyl ketone and 2-methylcyclohexanone,[6] respectively. The yields of acetylation products isolated from these ketones were 28–59%, the

(1) Paper XXIII of series on "Condensations;" for paper XXII, see THIS JOURNAL, **66**, 309 (1944).

(2) This investigation was supported in part by a grant from the Duke University Research Council.

(3) Meerwein and Vossen, *J. prakt. Chem.*, **141**, 149 (1934).

(4) "Organic Syntheses," Vol. **20**, 6 (1940).

(5) Breslow and Hauser, THIS JOURNAL, **62**, 2385 (1940).

(6) Although this ketone has a cyclic, instead of the linear structure represented by the general formula above, it should react as a typical type III ketone.

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highest yields being obtained from methyl *n*-amyl and methyl *n*-hexyl ketones. Considerable amounts (15–25%) of the ketones were generally recovered and relatively little high boiling material was obtained. The only other product found was acetylacetone resulting from the self-condensation of the acetic anhydride as described previously.[3]

The acetylation products obtained from each of the ketones (except methyl ethyl ketone) were found to consist of a mixture of the two possible acetyl derivatives shown in the general equations represented above. A reasonably good separation of the isomeric 1,3-diketones has been realized by extracting ether solutions of the acetylation products with alkali, in which the methyl derivatives are relatively much more soluble than are the methylene derivatives, while the methinyl derivatives are insoluble in alkali. Essentially complete extraction of the methyl derivatives was indicated when the alkaline extracts no longer gave the red enol test (characteristic of the methyl derivatives),[7] but instead gave the purple enol test (characteristic of the methylene derivatives),[7] or gave no enol test (characteristic of isopropylacetylacetone[8] and the methinyl derivatives). Complete extraction of the methylene derivative of 2-methylcyclohexanone was indicated when the alkaline extract no longer gave the purple enol test. The methyl and methylene derivatives of ketones of type I were recovered with relatively little loss so that a fairly reliable estimate of the proportions in which these derivatives were present in the original acetylation products could be made. Alkali extractions of acetylation products from the ketones of types II and III, however, produced some cleavage apparently involving mainly the methinyl derivative. The proportions of the acetyl derivatives of methyl isopropyl ketone (type II) has been obtained by treating the original acetylation product with copper acetate, only the methyl derivative yielding a copper salt. This method has not been applicable to the acetylation product from 2-methylcyclohexanone (type III), since the copper salt of the methylene derivative could not be crystallized.

In Table I are given the relative percentages of the two isomeric acetyl derivatives comprising the original acetylation products. These values are probably reproducible within ±3% for the derivatives of the methyl *n*-alkyl ketones, within ±5% for the derivatives of methyl isobutyl ketone, and within ±10% for the derivatives of methyl isopropyl ketone and 2-methylcyclohexanone. Since the first alkaline extract of the acetylation product from methyl ethyl ketone gave the purple enol test we have concluded that this product consists essentially only of the methylene derivative.

The proportions of the two isomeric acyl derivatives produced from at least the ketones of type I are evidently independent of the anhydride used, since, in an investigation now in progress on the acylation of ketones with higher anhydrides, it has been found that methyl ethyl, methyl isobutyl and methyl *n*-amyl ketones with propionic and butyric anhydrides yield essentially the same proportions of the corresponding methyl and methylene derivatives as those given in Table I for the acetylation products.

TABLE I

THE RELATIVE PERCENTAGES OF THE TWO ISOMERIC ACETYL DERIVATIVES COMPRISING THE ACETYLATION PRODUCTS OF KETONES

Ketone acetylated	% Methyl derivative	% Methylene derivative	% Methiny derivative
Methyl ethyl	0	100	
Methyl *n*-propyl	10	90	
Methyl isobutyl	55[a]	45	
Methyl *n*-amyl	10	90	
Methyl *n*-hexyl	10	90	
Methyl isopropyl	32[b]		68
2-Methylcyclohexanone		50	50

[a] This is the average of the values found by the alkali extraction method and by the preparation of the copper salt directly from the original acetylation product. [b] This is the value obtained by the preparation of the copper salt directly from the original acetylation product.

It can be seen from Table I that the methyl *n*-alkyl ketones of type I yield largely the methylene derivatives with only small amounts (or none) of the methyl derivatives, whereas methyl isobutyl ketone, which has a branched chain, yields a little more of the methyl than methylene derivative. Methyl isopropyl ketone (type II) yields mainly the methinyl derivative, but also a considerable amount of the methyl derivative, while 2-methylcyclohexanone (type III) yields the methylene and methinyl derivatives apparently in about equal amounts. Thus, in the presence of boron trifluoride, ketones are capable of being acylated at the α-methyl, α-methylene or α-methinyl groups at which the α-carbon atom holds, respectively, three, two and one hydrogen atoms.

Although the α-hydrogen of a ketone is involved in the acylation, it would appear that the number of hydrogens present on the β-carbon atom in the ketones of type I, $CH_3CO-\underset{\alpha}{CH_2}-\underset{\beta}{C}\lessgtr$, determines the relative proportions of the methyl and methylene derivatives that result, the proportion of the methylene derivative decreasing and that of the methyl derivative increasing as the number of β-hydrogens is decreased.[9] Thus, methyl ethyl ketone, which has three β-hydrogens yields apparently only the methylene derivative; methyl *n*-propyl, methyl *n*-amyl or methyl *n*-hexyl ke-

(7) See Morgan, Drew and Porter, *Brr.*, **58**, 333 (1925).

(8) Morgan and Thomason, *J. Chem. Soc.*, **125**, 754 (1924).

(9) On the basis that these acylations are dependent on the conversion of the ketone into its enol form by the acidic mechanism (which may be regarded as a special case of the elimination reaction), these results may be explained by the application of the theory of Baker and Nathan that CH-bond electrons may participate in tautomeric electron displacements. For the application of this theory to the elimination reaction see Hughes and Ingold, *Trans. Faraday Soc.*, **37**, 675 (1941).

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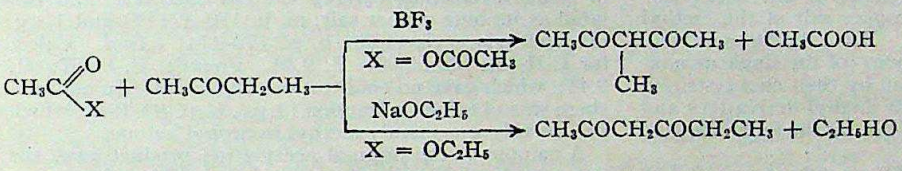
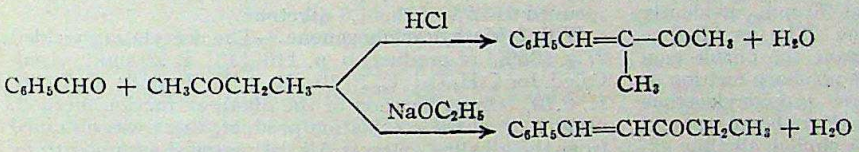
tone, which has two β-hydrogens yields 90% of the methylene and 10% of the methyl derivative; while methyl isobutyl ketone, which has only one β-hydrogen, yields 45% of the methylene and 55% of the methyl derivative. An attempt to acetylate methyl neopentyl ketone, which has no β-hydrogens, failed.

The fact that the methylene derivative is the main product with methyl *n*-alkyl ketones and acetic anhydride in the presence of the acidic reagent, boron trifluoride, is in contrast to the formation of only[10] the methyl derivative with these ketones and ethyl acetate in the presence of a base, which has been the more common method of acylation of ketones. A similar relationship exists for the aldol reaction between at least methyl ethyl ketone and benzaldehyde,[11] which yields chiefly the methylene derivative in the presence of hydrogen chloride, but the methyl derivative in the presence of sodium hydroxide.





The fact that the methinyl derivative is the main product with methyl isopropyl ketone and acetic anhydride in the presence of boron trifluoride is also in contrast to the formation of only the methyl derivative with this ketone and ethyl acetate in the presence of a base.[12] The contrast is not as great with methyl isobutyl ketone,[13] however, which yields a little more of the methyl than methylene derivative in the presence of boron trifluoride and only the methyl derivative in the presence of a base.[12]

The two different courses of the acylation or aldol reaction with methyl ethyl ketone in the presence of acidic and basic reagents are paralleled by the halogenations of this ketone, which, in the presence of chlorine and hydrochloric acid, yields mainly the methylene chloro derivative,[14] 3-chloro-2-butanone, but which, in the presence of alkali, undergoes the well-known haloform reaction involving the halogenation of the methyl hydrogens. Since the formation of the enol of the ketone is generally considered to be prerequisite for the halogenation,[15] it would appear that the formation of the enol form of the ketone is also prerequisite for the acylation and aldol reactions.

Thus, these carbon–carbon condensations effected by acidic reagents may involve the activation not only of the electron-accepting component,[16] the anhydride or aldehyde, but also of the electron-donating component,[16] the ketone. The activation of the anhydride or aldehyde consists in the coördination of the acidic reagent with the carbonyl oxygen thereby making the carbonyl carbon a stronger electron-acceptor. The activation of the ketone (which, in most cases, is probably the more weakly activated of the two) consists in the coördination of the acidic reagent with its carbonyl oxygen thereby facilitating the conversion of the ketone into the enol form, which presumably is a stronger electron donor. A base, however, can activate only the ketone; of course the base used as condensing agent may attack the carbonyl carbon of the anhydride or aldehyde but this should consist in a deactivation, rather than an activation, since the electron-accepting capacity of the carbonyl carbon would thereby be destroyed. It should be pointed out also, that although the Friedel–Crafts type of acylation of benzene with an anhydride is somewhat analogous to the acylation of a ketone in the presence of an acidic reagent, probably only the anhydride is activated in the former reaction.

Certain of the acetylations described in this paper are of value for the synthesis of 1,3-diketones. The use of these and other acylations in syntheses will be discussed in a later paper.

Experimental[17]

Acetylation.—One mole of acetic anhydride and one-half mole of the ketone were placed in a three-neck flask equipped with an inlet tube (1 cm. above the surface of the liquid), a mercury-sealed stirrer and a calcium chloride tube. The mixture was cooled in an ice-bath and stirred. Boron trifluoride was passed in at such a rate that the mixture was saturated (as indicated by the copious evolution of white fumes) within two to three hours. After the mixture was saturated, the boron trifluoride was passed in for fifteen to twenty minutes longer, and the reaction mixture

(10) See Hurd and Kelso, THIS JOURNAL, **62**, 2184 (1940).

(11) Harries and Muller, *Ber.*, **35**, 966 (1902).

(12) See Sprague, Beckham and Adkins, THIS JOURNAL, **56**, 2666 (1934).

(13) A study is in progress in this Laboratory to determine the products of reaction of benzaldehyde with such ketones as methyl isobutyl and methyl neopentyl ketones in the presence of an acidic reagent.

(14) Kling [*Bull. soc. chim.*, [3] **33**, 325 (1905)] found that on monochlorination in slightly acid medium, methyl ethyl ketone yields about 80% of the methylene chloro derivative and 20% of the methyl chloro derivative, 1-chloro-2-butanone. In this Laboratory Mr. R. Levine has found that in strong acid medium, the percentage of the methylene chloro derivative is even greater. Also, a preliminary experiment by Levine has indicated that, similar to the acylation in the presence of boron trifluoride, methyl isobutyl ketone yields on chlorination in strongly acid medium at least as much of the methyl chloro derivative as the methylene chloro derivative.

(15) See Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, pp. 231–233.

(16) See Hauser and Breslow, THIS JOURNAL, **62**, 2389 (1940).

(17) Analyses are by Dr. T. S. Ma, Microchemical Laboratory, Department of Chemistry, University of Chicago, Chicago, Illinois. Boiling points and melting points are uncorrected.

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then poured into a solution of 130 g. of sodium acetate in one liter of water. The mixture was steam distilled[18] until the distillate no longer gave an enol test with ferric chloride. The steam distillate was cooled and practically all of the acetic acid present was neutralized by adding dilute sodium hydroxide solution until the mixture just turned litmus red. The slightly acidic mixture was extracted with ether and, after drying over sodium sulfate, the solvent distilled. The residue was fractioned *in vacuo* and the acetylation products of the ketones were collected. The forerun generally contained acetylacetone.

Alkali Extraction Method.—The two isomeric acetyl derivatives of the ketones comprising the acetylation products were separated in the following manner. Samples (10–20 g.) of the acetylation products were dissolved in 100 cc. of ether and the solutions were extracted with 100-cc. portions of cold 1% aqueous sodium hydroxide until two successive alkaline extracts (after acidification) gave, respectively, the red and the purple enol tests, the red and no enol test, or the purple and no enol test. Generally several extractions were required. The ether solutions were then distilled, while the combined alkaline extracts were acidified, extracted with ether and the solvent distilled. The methylene and methinyl derivatives were recovered essentially pure but the recovered methyl derivatives generally contained a little of the methylene derivative; however, the pure copper salt of the methyl derivative was readily obtained. The 1,3-diketones were identified by boiling points, analyses (of the single or mixture of isomeric 1,3-diketones) and by their enol tests and copper salts (which are blue with methyl derivatives and gray with methylene derivatives)[7] or by the failure to give enol tests or copper salts.

With Methyl Ethyl Ketone.—The acetylation yielded 18 g. (32%) of product, b. p. 77–79° at 30 mm., evidently consisting of only methyl acetylacetone. The first alkaline extract (using 1% or 0.5% alkali) gave the purple enol test and gray copper salt, which gave no sharp melting or decomposition point. The isomeric propionylacetone (which is more soluble in alkali) gives the red enol test and blue copper salt, m. p. 197–198.[19] A similar alkaline extraction of the forerun (6 g., b. p. 73–76° at 30 mm.), obtained on fractionation of the acetylation product, gave only acetylacetone, isolated as its blue copper salt, which decomposes above 230°.[20]

With Methyl *n*-Propyl Ketone.—The acetylation yielded 22 g. (34%) of product, b. p. 78–81° at 20 mm. *Anal.* Calcd. for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.58; H, 9.27. The alkali extraction method showed that this acetylation product consisted of 10% *n*-butyrylacetone (giving the red enol test, isolated as its blue copper salt, m. p. 164–165°[21]) and 90% (by difference) of ethyl acetylacetone, b. p. 80–81° at 20 mm., which gave the purple enol test and gray copper salt, m. p. 209–211°.[22]

With Methyl Isobutyl Ketone.—The acetylation yielded 29 g. (41%) of product, b. p. 79–81° at 20 mm. *Anal.* Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.41; H, 9.50. The alkali extraction method showed that this product consisted of 60% of isovalerylacetone (b. p. 78–79° at 20 mm., giving the red enol test and blue copper salt, m. p. 154–155°[21]) and 40% of isopropyl acetylacetone (b. p. 183–185° at 750 mm. *Anal.* Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.92; H, 10.07), which gave no enol test or copper salt.

A sample of the original acetylation product gave the copper salt of isovalerylacetone in a yield which corresponded to 50% of the 1,3-diketone.

With Methyl *n*-Amyl Ketone.—The acetylation yielded 46 g. (59%) of product, b. p. 104–106° at 20 mm. This product was not extracted with alkali; instead, the experiment was repeated and the total ether extract was subjected directly to the alkali extraction method. In this manner, the acetylation product was found to consist of 10% of *n*-hexoylacetone (b. p. 102–103° at 20 mm., giving the red enol test and blue copper salt, m. p. 137–138°[23]) and 90% of *n*-butyl acetylacetone (b. p. 105–106° at 20 mm.) which gave the purple enol test and gray copper salt, m. p. 185–186°.

With Methyl *n*-Hexyl Ketone.—The acetylation yielded 45 g. (53%) of product, b. p. 112–113° at 15 mm. *Anal.* Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.12; H, 10.29. The alkali extraction method showed that this product consisted of 10% of *n*-heptoylacetone (giving the red enol test, isolated as its blue copper salt, m. p. 122–123°[24]) and 90% (by difference) of *n*-amyl acetylacetone (b. p. 112–113° at 15 mm.) which gave the purple enol test and gray copper salt, m. p. 177–178°.

With Methyl Isopropyl Ketone.—The acetylation yielded 18 g. (28%) of product, b. p. 73–76° at 20 mm. *Anal.* Calcd. for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.39; H, 9.18. On application of the alkali extraction method, using 5 g. of acetylation product, there was obtained 1 g. of isobutyrylacetone (giving the red enol test, and isolated as its blue copper salt, m. p. 170–171°[25]) and 1.4 g. of dimethylacetylacetone, b. p. 172–174° (*Anal.* Calcd. for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.57; H, 9.41), which gave no enol test or copper salt. In addition there was obtained a fraction (1 g.), b. p. 80–100°, which presumably was mainly methyl isopropyl ketone.

A sample of the original acetylation product gave the copper salt of isobutyrylacetone in a yield which corresponded to 32% of this 1,3-diketone.

With 2-Methylcyclohexanone.—The acetylation yielded 27 g. (35%) of product, b. p. 116–118° at 20 mm. *Anal.* Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.36; H, 9.19. On application of the alkali extraction method, using 10 g. of the acetylation product, there was obtained from the alkaline extracts 5 g. of material assumed to be 2-methyl-6-acetylcyclohexanone (giving the purple enol test and gray oily copper salt which could not be crystallized) and from the material insoluble in alkali, 1 g. of material (b. p. 168–183°) assumed to be mainly 2-methylcyclohexanone, and 2.5 g. of 2-methyl-2-acetylcyclohexanone (b. p. 190–222°, mostly at 220–222°). (*Anal.* Calcd. for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 69.75; H, 9.08) which gave no enol test or copper salt.

Summary

The acetylation of certain unsymmetrical aliphatic ketones with acetic anhydride in the presence of boron trifluoride to form 1,3-diketones has been carried out, and the proportions of the two possible acetyl derivatives have been determined.

Methyl ethyl ketone yields apparently only the methylene derivative; methyl *n*-alkyl ketones yield 90% of the methylene derivative and 10% of the methyl derivative; while methyl isobutyl ketone yields 45% of the methylene derivative and 55% of the methyl derivative. Methyl isopropyl ketone yields 68% of the methinyl derivative and 32% of the methyl derivative, while 2-methylcyclohexanone yields the methylene and methinyl derivatives in about equal amounts.

These results are compared with acylations effected by bases. Correlations are made between

(18) An alternate procedure was to extract the reaction mixture (after standing with the sodium acetate solution for a few hours) directly with ether, but apparently certain boron trifluoride complexes were not completely decomposed under these conditions and better yields of 1,3-diketones have been obtained by the steam distillation procedure.

(19) Griner, *Ann. Chim. Phys.*, [6] **26**, 362 (1892).

(20) Claisen, *Ann.*, **227**, 170 (1893).

(21) Morgan and Drew, *J. Chem. Soc.*, **125**, 731 (1924).

(22) Curtiss, *Am. Chem. J.*, **17**, 436 (1895).

(23) Morgan and Holmes, *J. Chem. Soc.*, **125**, 760 (1924).

(24) Claisen and Ehrhardt, *Ber.*, **22**, 1016 (1889).

(25) Conrad and Gast, *Ber.*, **31**, 1339 (1898).

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acylations, aldolizations and halogenations in the presence of acidic and basic reagents. Certain aspects of the theory of the reactions are considered.

DURHAM, N. C. RECEIVED SEPTEMBER 10, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

The Preparation of β,β-Trehalose Octaacetate

BY CHESTER M. MCCLOSKEY,[1] RONALD E. PYLE AND GEORGE H. COLEMAN

In connection with work in this Laboratory on the chromatographic separation of the azoyl derivatives of sugars, it was necessary to prepare β,β-trehalose. Since procedures previously reported did not prove satisfactory for preparing moderate quantities of this compound, modification of one of these methods was undertaken.

Fischer and Delbrück,[2] who discovered β,β-trehalose octaacetate, prepared it by the action of silver carbonate and a small amount of water upon an ether solution of tetraacetyl-α-D-glucosyl bromide, in a yield of about 1%; they also obtained it from the action of phosphorus pentoxide on a chloroform solution of 2,3,4,6-tetraacetyl-β-D-glucose in a yield of 2%.

In 1932 Schlubach and Schetelig[3] prepared β,β-trehalose octaacetate by the condensation of tetraacetyl-α-D-glucosyl bromide and 2,3,4,6-tetraacetyl-β-D-glucose in a chloroform solution with silver carbonate, calcium chloride and iodine. The reduction value of the crude reaction mixture was determined by Bertrand's method and the condensation was calculated as 50%, based on the reduction value of pure tetraacetyl glucose. The yield of crystalline product was not given.

The procedure of Schlubach and Schetelig was repeated several times in this Laboratory. The best yield of crystalline β,β-trehalose octaacetate was not more than 4%. The conditions described by these authors were duplicated as nearly as possible. However, it may be that some necessary precaution was omitted, since the reaction product showed a reduction value corresponding to only 18.8% condensation.

This preparation has been modified to conform more closely to the technique used by Kreider and Evans[4] in the Koenigs and Knorr synthesis. By effecting condensation in the presence of Drierite as drying agent, a 10% yield of crystalline product, m. p. 180.5–181.5° cor., has been obtained. The reduction value of the crude reaction product indicated a condensation of approximately 30%. The non-crystalline residues from which no more product could be obtained, still contained two-thirds of the original condensation product as shown by reduction values. This problem is being investigated further.

(1) Research Fellow of the Corn Products Refining Company.
(2) Fischer and Delbrück, *Ber.*, **42**, 2776 (1909).
(3) Schlubach and Schetelig, *Z. physiol. Chem.*, **213**, 83 (1932).
(4) Kreider and Evans, THIS JOURNAL, **58**, 707 (1936).

The use of iodine has been found essential for satisfactory condensation. Excessive amounts of glucosyl bromide and elevated temperatures did not produce appreciably higher yields.

In a series of several runs the percentage yields calculated from the reducing values varied from 30–40%. The actual yield of crystalline product did not, however, in any case exceed 10.5%. In one run in which only 4.5 g. of iodine was used the percentage yield calculated from the reducing value was 30%. The yield of crystalline material was only 3.4%.

Experimental Part

2,3,4,6-Tetraacetyl-α-D-glucosyl Bromide.—This compound was prepared by the method of Karjala and Link[5] or Redemann and Niemann[6] from pentaacetylglucose or its glucose equivalent. The crude reaction mixture prepared by this method from 120 g. of glucose pentaacetate was poured with rapid stirring into 1.5 liters of ice-water. The precipitate, which solidified, was filtered off and ground in a mortar in order to break up the lumps. It was then returned to the filter funnel and washed thoroughly with ice-water and sucked as dry as possible. The precipitate without further drying was dissolved in 300 ml. of ether. The aqueous layer was separated and the ether layer cooled in a freezing mixture. The crystals which formed were filtered off and the filtrate which had partially evaporated during the filtration was cooled as before. In this manner several crops of crystals were obtained. The crystallization of the last portion was facilitated by the addition of a little ligroin to the ether. The crystals were air dried a short time and then in a vacuum desiccator over phosphorus pentoxide. The product can be kept indefinitely without decomposition. The yield of product melting at 87–88° (uncor.) was 121 g. (96%).

2,3,4,6-Tetraacetyl-β-D-glucose was prepared by a modification of the method of Georg.[7] A solution of 125 ml. of anhydrous acetone and 82.2 g. of tetraacetylglucosyl bromide was cooled to 0° in an ice-bath and 2.3 ml. of water added. To the cold solution 46.5 g. of silver carbonate was added in small portions, with thorough shaking or stirring, during a period of fifteen minutes. After about thirty minutes more shaking the mixture was warmed to 50–60° and filtered. The silver salts were washed with 65 ml. of dry acetone, removed from the funnel and warmed in a flask with 65 ml. more acetone, filtered and washed again on the funnel. The combined filtrates were concentrated under reduced pressure and at room temperature. When most of the solution was filled with crystals the concentration was stopped and the mixture warmed until solution was complete. To this acetone solution an equal volume of absolute ether and a similar volume of ligroin were added. The solution so obtained was cooled in a freezing mixture with gentle stirring. The crystals of tetraacetate soon formed and after ten minutes in the ice-bath to ensure complete crystallization were filtered and air-dried. The

(5) Karjala and Link, *ibid.*, **62**, 917 (1940).
(6) Redemann and Niemann, "Organic Syntheses," Vol. 27, p. 1.
(7) Georg, *Helv. Chim. Acta*, **15**, 924 (1932).

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solution was kept as anhydrous as possible since moisture interfered with the crystallization. The product so obtained melted at 133–135° (cor.). The yield was 56 g. (79%).

β,β-Trehalose Octaacetate.—In a 2-liter three-necked flask equipped with a mechanical stirrer, mercury seal, calcium chloride tube, and a 500-ml. dropping funnel, was placed 110 g. of 2,3,4,6-tetraacetyl-β-D-glucose, 180 g. of silver carbonate, 12 g. of iodine, 100 g. of powdered Drierite (previously dried for three hours at 500°), and 400 ml. of alcohol-free chloroform. The flask was covered with a dark cloth to prevent the entrance of light and stirred for thirty minutes. In 400 ml. of alcohol-free chloroform was dissolved 150 g. of 2,3,4,6-tetraacetyl-α-D-glucosyl bromide and the solution shaken with 50 g. of powdered Drierite for thirty minutes. At the end of the shaking, the solution of glucosyl bromide was decanted and added dropwise to the first mixture over a period of two hours. This was followed by a 100-ml. portion of chloroform used to wash the Drierite and the mixture was stirred for twelve hours. At the end of the stirring, the solid matter was filtered off and washed with 100 ml. of chloroform. The chloroform from the combined filtrate was removed by evaporation of the solution on a water-bath. The residue was dissolved in 900 ml. of benzene and the solution washed twice with 2 liters of water. Each washing was shaken for thirty minutes. Without drying, the benzene was removed from the solution by evaporation on a steam-bath and the residue dissolved in hot ethyl acetate. Ligroin was then added until the warm solution became turbid. Upon cooling, long needles of β,β-trehalose octaacetate formed. After three recrystallizations the melting point was constant at 180.5–181.5° cor., $[\alpha]^{25}D$ −18.4° (c = 3) in U. S. P. chloroform. The yield was 12.5 g. (6.5%). By working up the residues, 6.7 g. of additional product was obtained, giving a total yield of 19.2 g. (10%). Reduction values were determined by the method of Lane and Eynon[8] and expressed as the percentage of the reducing value of pure tetraacetylglucose. The residues from washing the benzene solutions of the product had reduction values approximately equal to pure tetraacetyl glucose. The reduction values of the residues from recrystallization indicated that some non-reducing material was still present.

Summary

A satisfactory method has been developed for the preparation of crystalline β,β-trehalose octaacetate from 2,3,4,6-tetraacetyl-α-D-glucosyl bromide and 2,3,4,6-tetraacetyl-β-D-glucose.

(8) Lane and Eynon, *J. Soc. Chem. Ind.*, **42**, 32T (1923).

IOWA CITY, IOWA RECEIVED SEPTEMBER 10, 1943

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

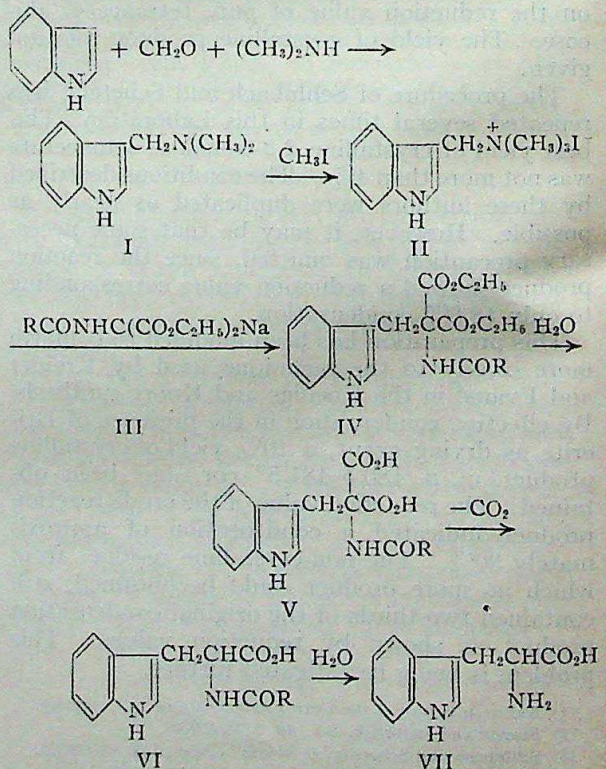
A Convenient Synthesis of *dl*-Tryptophan

BY H. R. SNYDER AND CURTIS W. SMITH

In an earlier work[1] it was discovered that quaternary salts containing a radical of the benzyl type can be used as carbon-alkylating agents. The methiodide of gramine (3-dimethylaminomethylindole, readily prepared from indole, formaldehyde and dimethylamine) was found particularly effective in the alkylation of active methylene compounds. This suggested that *dl*-tryptophan might be prepared by condensation of gramine methiodide with an alkali derivative of an acylaminomalonic ester. In view of the high yields previously obtained in reactions of gramine methiodide with malonic ester it seemed likely that the proposed synthesis would be much more practical than the earlier methods based on the condensation of indole-3-aldehyde with hippuric acid[2] or hydantoin.[3]

Gramine methiodide has been found to react smoothly with the sodium derivative of acetaminomalonic ester in the presence of dioxane. Ethyl α-acetamino-α-carbethoxy-β-(3-indole)-propionate (IV, R = CH_3) was obtained in yields of 63–70%. Saponification converted the ester to the acid (V, R = CH_3), and boiling a water suspension of the acid brought about decarboxylation. The resulting acetyltryptophan was converted to *dl*-tryptophan by alkaline hydrolysis. Two recrystallizations brought the product to analytical purity. The yield of *dl*-tryptophan, based on indole, was approximately 45%.

It is interesting to note that long boiling with 20% aqueous sodium hydroxide did not convert the substituted acetaminomalonic ester (IV) to the aminomalonic acid, but the acetyl group was



(1) Snyder, Smith and Stewart, THIS JOURNAL, **66**, 200 (1944).
(2) Ellinger and Flamand, *Ber.*, **40**, 3031 (1907).
(3) Boyd and Robson, *Biochem. J.*, **29**, 2256 (1935).

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removed easily after the decarboxylation of the acetaminomalonic acid (V).

Experimental

Ethyl Acetaminomalonate.—The isonitroso ester, prepared by a modification of the method of Redeman and Dunn,[4] was reduced and acetylated without isolation of any of the intermediates. A solution of 400 g. of malonic ester in 450 g. of glacial acetic acid, in a 3-liter three-necked flask, was cooled in an ice-bath. With stirring, a solution of 518 g. of sodium nitrite in 710 cc. of water was added over a period of one hour, the temperature of the mixture being kept below 20°. Gases which escaped were led to the hood. The mixture was stirred for four hours after the addition of sodium nitrite was completed. The reaction mixture was extracted with three 500-cc. portions of ether. The combined ether extracts were washed with three 250-cc. portions of 10% sodium carbonate and with two portions of water. The ether solution was dried over calcium chloride and the ether was removed by distillation under reduced pressure. The residual liquid was dissolved in 1000 cc. of absolute alcohol and 25 g. of Pd-charcoal catalyst (10% Pd) was added. The mixture was hydrogenated (1500 lb. pressure, room temperature, at start) and when absorption of hydrogen was complete the catalyst was removed by filtration. To the cooled filtrate was slowly added 204 g. of acetic anhydride, and the resulting solution was cooled in ice. When crystallization appeared complete the first crop (127 g.) of the product was collected. Concentration and cooling of the mother liquor produced additional crops, the total yield being 217 g. The first fraction was pure (m. p. 95–96°), but later crops required recrystallization.

Ethyl α-Acetamino-α-carbethoxy-β-(3-indole)-propionate (IV).—After 6.9 g. (0.30 mole) of sodium had been powdered in 100 cc. of dry xylene, most of the xylene was decanted. Then 500 cc. of dioxane which had been distilled from sodium and 68 g. (0.314 mole) of acetaminomalonic ester were added and the mixture was stirred for fourteen hours in an oil-bath at 92°. To the resulting light yellow suspension was added 101 g. (0.32 mole) of gramine methodide (II)[1] and the mixture was stirred in an oil-bath at approximately 108° for nineteen hours and then at 125° for three hours. The hot dioxane was separated from a brown pasty solid by filtration through a heated Büchner funnel. After standing overnight in a refrigerator (+5°) the solution had deposited 64.5 g. of the product (IV); m. p. 125–135°. A second fraction of 4.7 g. (m. p. 135–142°) was obtained by concentrating the mother liquor to one-fourth volume. A third fraction (6.4 g., m. p. 158°) was obtained by extracting the solid from the first filtration with 200 cc. of boiling 95% ethanol, diluting with 200 cc. of hot water, and cooling.

The two fractions of IV which had crystallized from dioxane (69.2 g.) were dissolved in 160 cc. of boiling 95% ethanol and 160 cc. of warm water was added to the solution. After standing overnight in a refrigerator at 5° the solution deposited 61.7 g. of IV; m. p., 156–8°. The total yield of IV, m. p. 156–8°, was thus 68.1 g. or 63%; other runs gave yields in the range 63–70%. An analytical sample of IV was prepared by recrystallization from *n*-butyl ether and then from 50% alcohol–water solution; m. p. 158°.

Anal. Calcd. for $C_{18}H_{22}N_2O_5$: C, 62.44; H, 6.40. Found: C, 62.42; H, 6.24.

α-Acetamino-α-carboxy-β-(3-indole)-propionic Acid (V).—The ester (IV) was saponified by refluxing 33.62 g. (0.097 mole) with 19.2 g. (0.48 mole) of sodium hydroxide in 192 cc. of water for four hours. After treatment with charcoal, the solution was cooled in an ice-bath and 50 cc. (0.6 mole) of cold concd. hydrochloric acid was added with cooling so that the temperature of the solution did not exceed 25°. The solution was cooled for four hours, and the light pink precipitate was filtered off and dried over calcium chloride in an evacuated desiccator for fourteen hours; the yield of crude material, containing some sodium chloride, was 32 g.; m. p. 136–139°. The acid could be purified by dissolving it in ten volumes of water (containing a trace of sodium hydrosulfite) at 50° and cooling. The analytical sample, after two recrystallizations from 20% ethanol, melted with decomposition at 144.5°.

Anal. Calcd. for $C_{14}H_{14}N_2O_5$: C, 57.93; H, 4.86. Found: C, 57.71; H, 5.02.

***dl*-Tryptophan (VII).**—A mixture of 28 g. of the crude malonic acid (V) and 120 cc. of water was heated under reflux for two and one-half hours. The N-acetyltryptophan (VI) produced was less soluble than the malonic acid and in some runs it partially crystallized from the solution as the reaction proceeded. After the decarboxylation was completed, 16 g. (0.4 mole) of sodium hydroxide in 40 cc. of water was added and the solution was refluxed for twenty hours. The alkaline solution was treated with charcoal and acidified with 24 g. (0.4 mole) of glacial acetic acid. A copious white precipitate formed immediately, but the solution was stored in the refrigerator for twelve hours before the solid was collected. It was dissolved in 200 cc. of water containing 5 g. of sodium hydroxide. After treatment with charcoal, 100 cc. of 95% ethanol was added to the solution. The solution was warmed to 70°, acidified with 7.5 cc. of glacial acetic acid, and allowed to cool slowly. The flat plates which separated from the solution were filtered off and washed with two 40-cc. portions of water, two 40-cc. portions of ethanol and two 30-cc. portions of ether; yield 14 g. (81% calculated on the basis of IV); m. p. 272–280° (dec.). An analytical sample, m. p. 275–282° (dec.), was prepared by two recrystallizations from 33% ethanol.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92. Found: C, 64.61; H, 5.90.

N-Acetyltryptophan (VI) was isolated from a similar run by allowing it to crystallize from the acidified solution after decarboxylation. For recrystallization, 11.7 g. of VI was dissolved in a solution of 100 cc. of water and 30 cc. of 95% ethanol, a few grains of sodium hydrosulfite were added, and the hot solution was treated with charcoal; yield, 8 g. (68.5%), m. p. 206° (lit.,[5] 206°). A sample recrystallized several times from very dilute ethanol was analyzed.

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.73. Found: C, 63.20; H, 5.61.

Summary

A convenient and economical synthesis of *dl*-tryptophan is described. Indole is converted to gramine (3-dimethylaminomethylindole) by condensation with formaldehyde and dimethylamine; the methiodide of gramine is condensed with the sodium derivative of ethyl acetaminomalonate to give ethyl α-acetamino-α-carbethoxy-β-(3-indole)-propionate; α-acetamino-α-carboxy-β-(3-indole)-propionic acid is obtained by saponification of the ester and is decarboxylated to acetyltryptophan by boiling in water; *dl*-tryptophan is obtained by alkaline hydrolysis of the acetyl derivative. The yield of tryptophan, based on indole, is about 45%.

Urbana, Illinois Received November 8, 1943

(4) Redeman and Dunn, *J. Biol. Chem.*, **130**, 341 (1939).

(5) Berg, Rose and Marvel, *ibid.*, **85**, 207 (1929–1930).

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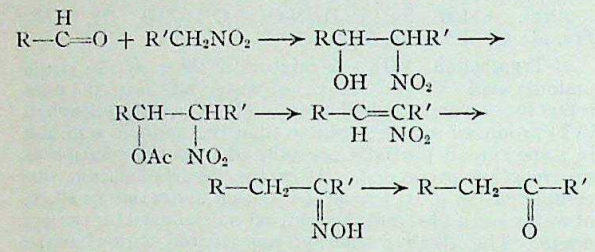
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MISSOURI]

The Preparation of Ketones from Nitroölefins

BY DOROTHY NIGHTINGALE AND J. R. JANES[1]

The purpose of the investigation was to develop a method of preparation of aliphatic ketones from nitroparaffins by the following series of reactions



where R and R′ are aliphatic. It was first necessary to develop a satisfactory method for the preparation of nitroölefins.

The method of Schmidt and Rutz[2] as modified by Hass and co-workers[3,4] has been found suitable for the preparation of nitroölefins. We found that it improved the yield to add methanol to the aqueous sodium bicarbonate solution. The procedure is generally reliable and yields of nitroolefin are usually 90–95% with the best yields from esters of nitroalcohols with nine or more carbon atoms. The yield from nitroalcohol to nitroölefin via the ester is usually around 80–84%.

Bouveault and Wahl[5] have shown that nitroolefins of the structure $R-\underset{H}{C}=\underset{H}{C}-NO_2$ could be reduced to the aldoxime with zinc powder and acetic acid. Hass and Susie[3] have reported that subsequent workers have been unable to repeat the work of Bouveault and Wahl, but we have found that the reduction of nitroölefins of the structure $R-\underset{H}{C}=\underset{NO_2}{C}-R'$ to the ketoxime proceeded smoothly with a 50–60% yield in most cases.

The ketoximes were hydrolyzed to ketones by refluxing with 4 *N* sulfuric acid and a hydroxylamine acceptor (40% formaldehyde). Yields of ketone are around 80%, with an over-all yield from the nitroölefin of 40–48%. Syntheses of

TABLE I

NITROALCOHOLS

Nitroalcohol	$n^{25}D$	d^{25}	B. p. °C.	B. p. Mm.	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1-Nitro-2-butanol	1.4425	1.1303	75	2	40.34	7.56	40.35	7.29
3-Nitro-2-butanol	1.4405	1.1264	78	17			40.34	7.65
1-Nitro-2-pentanol	1.4439	1.0810	85	2	45.11	8.27	44.83	8.52
2-Nitro-3-pentanol	1.4428	1.0915	79	2			44.99	8.51
3-Nitro-2-pentanol	1.4410	1.0839	78	2			45.23	8.05
3-Nitro-3-Me-2-butanol	1.4457	1.1042	64	2			45.32	8.53
1-Nitro-3-Me-2-butanol	1.4455	1.0900	66	1			44.83	8.15
1-Nitro-2-hexanol	1.4458	1.0564	80	1	48.98	8.84	48.65	8.93
2-Nitro-3-hexanol	1.4450	1.0547	82	2			48.66	8.83
3-Nitro-4-hexanol	1.4441	1.0603	89	2			48.75	8.75
2-Nitro-4-Me-3-pentanol	1.4473	1.0682	89	2			49.15	8.81
2-Nitro-2-Me-3-pentanol	1.4478	1.0803	75	4			49.23	8.98
1-Nitro-2-heptanol	1.4452	1.0237	105	2	52.17	9.32	52.33	9.27
2-Nitro-3-heptanol	1.4469	1.0362	92	2			52.00	9.56
3-Nitro-4-heptanol	1.4448	1.0273	92	2			52.24	9.56
1-Nitro-3-Et-2-pentanol	1.4520	1.0422	93	2	52.17	9.32	51.99	9.50
3-Nitro-5-Me-4-hexanol	1.4466	1.0405	78	2			52.30	9.56
2-Nitro-2-Me-3-hexanol	1.4488	1.0398	81	2			52.06	9.56
2-Nitro-3-octanol	1.4498	1.0227	85	2	54.86	9.72	55.01	9.71
3-Nitro-4-octanol	1.4467	1.0113	94	2			54.99	9.93
2-Nitro-4-Et-3-hexanol	1.4580	1.0277	92	2			54.93	9.94
3-Nitro-4-nonanol	1.4500	1.0087	108	2	57.10	10.05	56.85	9.74
3-Nitro-5-Et-4-heptanol	1.4516	1.0058	87	2			57.29	10.24
1-Nitro-3-Et-2-heptanol	1.4539	1.0068	110	2			57.01	10.12
3-Nitro-4-decanol	1.4470	0.9757	108	2	59.11	10.34	59.14	10.64
2-Nitro-4-Et-3-octanol	1.4542	.9965	102	2			58.81	10.53
3-Nitro-5-Et-4-nonanol	1.4530	.9831	100	2	60.83	10.60	60.59	10.82

(1) Abstract of a portion of the dissertation by John Robert Janes in partial fulfillment of the requirements for the degree of Doctor of Philosophy, September, 1943. Present address, Hercules Powder Company, Wilmington, Delaware.

(2) Schmidt and Rutz, *Ber.*, **61**, 472 (1928).

(3) Hass and Riley, *Chem. Rev.*, **32**, 411 (1943).

(4) Hass, Hodge and Vanderbilt, *Ind. Eng. Chem.*, **28**, 339 (1936); **32**, 34 (1940).

(5) Bouveault and Wahl, *Bull. soc. chim.*, [3] **29**, 517 (1903).

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some of these branched chain ketones such as 4-ethyl-2-octanone and 5-ethyl-3-nonanone by any other method would be long and tedious.

All efforts to condense nitroölefins such as 2-nitro-4-ethyl-2-hexene, 2-nitro-4-ethyl-2-pentene, 3-nitro-3-hexene and 1-nitro-1-heptene with butadiene and with cyclopentadiene under a variety of experimental conditions were negative, even using the experimental conditions of Alder, Rickert and Windemuth.[6]

Experimental

The nitroölefins are greenish-yellow liquids when freshly prepared and pure. The 1-nitro-1-ene olefins are unstable and gradually decompose, the 2-nitro-2-enes are somewhat more stable and the 3-nitro-3-enes are quite stable. Branched chain nitroölefins except 1-nitro-1-enes are very stable. The lower members of the series up to the nitroheptenes have sharp biting odors and are strong lachrymators, while the higher members beginning with the nitrononenes have a pleasant odor somewhat similar to camphor.

If the nitroölefins are distilled under pressures at or near atmospheric pressure, they decompose rapidly and exothermically to form a tar, sometimes with explosive violence. Distillation near 1 mm. is desirable.

TABLE II

α-NAPHTHYLURETHANS OF THE NITROALCOHOLS

Nitroalcohol	M. p., °C.	Calcd., % C	Calcd., % H	Found, % C	Found, % H
1-Nitro-2-butanol	118–119	62.50	5.60	62.38	5.61
3-Nitro-2-butanol	122–123			62.40	5.77
1-Nitro-2-pentanol	99–100	63.57	5.97	63.32	6.23
2-Nitro-3-pentanol	126			63.62	6.21
3-Nitro-2-pentanol	100–101			63.51	5.97
3-Nitro-3-methyl-2-butanol	137			63.59	6.09
1-Nitro-3-methyl-2-butanol	97.5–98			63.66	6.05
1-Nitro-2-hexanol	103	64.56	6.34	64.39	6.64
2-Nitro-3-hexanol	136–137			64.55	6.49
3-Nitro-4-hexanol	113–114			64.50	6.27
2-Nitro-4-methyl-3-pentanol	112–113			64.50	6.38
2-Nitro-2-methyl-3-pentanol	97–98			64.30	6.37

TABLE III

ALIPHATIC NITROÖLEFINS

Compound	$n^{25}D$	d^{25}	B. p., °C. (1 mm.)	Calcd., % C	Calcd., % H	Found, % C	Found, % H
2-Nitro-2-hexene	1.4513	0.9883	53	55.81	8.53	55.67	8.65
3-Nitro-3-hexene	1.4521	.9785	53			55.52	8.69
2-Nitro-4-methyl-2-pentene	1.4520	.9780	57			55.48	8.91
1-Nitro-1-heptene	1.4524	.9743	57	58.04	9.09	57.86	9.07
3-Nitro-5-methyl-3-hexene	1.4528	.9741	53			58.18	9.29
2-Nitro-4-ethyl-2-hexene	1.4602	.9551	84	61.16	9.55	61.13	9.81
3-Nitro-5-ethyl-3-heptene	1.4598	.9427	65	63.16	9.94	62.99	10.06
3-Nitro-3-decene	1.4540	.9235	97	64.84	10.27	64.57	10.41
3-Nitro-4-ethyl-2-octene	1.4616	.9343	84			64.81	10.56
3-Nitro-5-ethyl-3-nonene	1.4616	.9273	94	66.30	10.55	66.24	10.73

Preparation of Nitroalcohols and their Derivatives.—The nitroalcohols were prepared by the method of Sprang and Degering.[7] Yields were consistently 70–80%. The properties of the nitroalcohols and the solid α-naphthylurethans, not previously reported in the literature, are summarized in Tables I and II. The urethans were prepared by warming 2 cc. of the nitroalcohol and 1.5 cc. of α-naphthyl isocyanate on a water-bath until the mixture became solid. The urethans were extracted with petroleum ether (86–100°). The higher molecular weight nitroalcohols gave uncrystallizable oils. The melting points were determined in a capillary tube heated in a copper block at one degree rise per minute. The urethans precipitate from petroleum ether as fine needles or small leaflets.

The esters of the nitroalcohols were prepared by the method of Tindall.[8] The acetic anhydride was removed in a partial vacuum and the esters distilled at 1 mm. Some nitroölefin was formed during distillation. The esters were used without further purification.

Preparation of Nitroölefins.—The preparation of 3-nitro-5-ethyl-3-nonene is typical. 3-Nitro-5-ethyl-4-nonanol acetate (83 g.) was placed in a one-liter round-bottom flask with 100 cc. of a 0.5 *N* solution of sodium bicarbonate and 200 cc. of methanol and refluxed eight hours. The mixture formed a fine emulsion at reflux temperature and, as cleavage proceeded, the nitroölefin gradually separated out as the emulsion disappeared and the water layer became clear. The nitroölefin formed a thick greenish globule which came to the top of the reaction mixture on cooling. With nitroölefins below the nitroöctenes the globule settled to the bottom of the flask.

The nitroölefin was extracted with two 100-cc. portions of ether. The ether extract was washed, and dried over anhydrous sodium carbonate and distilled; b. p. 94° (1 mm.); yield, 58 g. (90%). The lower nitroölefins were distilled through a three-foot column packed with glass helices and fitted with a still-head with a total condensation and variable take-off. Yields were usually 90–95%. The higher nitroölefins were pure enough to use without fractionation. The physical properties of the nitroölefins are given in Table III. The molecular refractivities showed exaltation.

The use of solid dehydrating agents led to more or less tar formation.

Ozonolysis of 3-nitro-3-hexene followed by reductive cleavage of the ozonide yielded propionaldehyde which was identified by conversion to propional dimethone, m. p. and mixed m. p. 149–150°.

Preparation of Oximes: 5-Ethyl-3-nonanone Oxime.—Zinc dust (50 g.) was placed in a 500-cc. three-necked conical flask equipped with a motor stirrer, dropping funnel and reflux condenser. An ether solution (200 cc.) of the above nitroölefin (43 g.) was added and stirred vigorously while a solution of 25% acetic acid (110 g.) was added through the dropping funnel over a two-hour period (four hours in some cases) at such a rate that the ether refluxed gently. After all the acid had been added, the reaction mixture was heated gently until it became colorless and bubbles of hydrogen ceased to form, usually four to six hours. The zinc acetate was separated by filtration and

(6) Alder, Rickert and Windemuth, *Ber.*, **71**, 2451 (1938).

(7) Sprang and Degering, THIS JOURNAL, **64**, 1063 (1942).

(8) Tindall, *Ind. Eng. Chem.*, **33**, 65 (1941).

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TABLE IV

KETOXIMES

Oxime of	$n^{25}D$	B. p. °C.	Mm.	Calcd., % C	H	Found, % C	H
5-Ethyl-3-heptanone	1.4547	75–79	1	68.79	12.10	68.48	12.26
3-Decanone	1.4532	81	1	70.18	12.28	69.94	12.46
5-Ethyl-3-nonanone	1.4560	89–92	1	71.35	12.43	71.05	12.47
4-Ethyl-2-hexanone	1.4522	69	1	67.18	11.89	67.13	12.06
5-Methyl-3-hexanone	1.4428	55	1	65.12	11.63	65.32	11.89
3-Heptanone[a]	1.4522	56	1	65.12	11.63	65.45	11.87
3-Nonanone	1.4552	70	1	68.79	12.10	69.14	12.38
4-Ethyl-2-octanone	1.4534	81	1	70.18	12.28	70.31	12.41

[a] Timmermans, *Bull. soc. chim. Belg.*, **36**, 502 (1927).

extracted with ether in a Soxhlet extractor to recover absorbed oxime. The ether extract was added to the filtrate and the ether removed on a water-bath. The acetic acid was removed in a low vacuum and the residue, a greenish oil, distilled at 89–92° (1 mm.); yield 21 g. (52%). The yields of oxime were consistently 50–60%. They are viscous, strong-smelling liquids. Their properties are given in Table IV.

Preparation of Ketones: 5-Ethyl-3-nonanone.—The above oxime (17.5 g.) was refluxed one-half hour with 50 cc. of 4 *N* sulfuric acid and 22 cc. of formalin solution. The ketone was extracted with two 50-cc. portions of ether and the ether solution dried over anhydrous copper sulfate or Drierite. The ether was removed on a water-bath and the ketone distilled; b. p. 53° (1 mm.); yield 12 g. (80%).

Anal. Calcd. for $C_{11}H_{22}O$: C, 76.92; H, 12.82. Found: C, 76.62; H, 12.97.

This ketone, not described in the literature, was the only one of the ketones which would not form a solid derivative. The melting points of the semicarbazones of the other ketones agreed with those reported in the literature.

The reduction of 35 g. of 2-nitro-4-ethyl-3-hexene with hydrogen and Raney nickel at 45 lb. yielded 10 g. of 4-ethyl-2-hexanone as the principal product. A large amount of tar remained in the distilling flask.

Summary

A variety of aliphatic nitroölefins have been prepared in good yield by refluxing the acetates of nitroalcohols with an aqueous methanol solution of sodium bicarbonate.

Nitroölefins of suitable structure were reduced to the corresponding ketoximes in 50–60% yield by means of zinc and acetic acid.

The ketoximes were converted to ketones by hydrolysis with dilute sulfuric acid in the presence of formalin.

The α-naphthyl urethans of a number of nitroalcohols have been described.

COLUMBIA, MISSOURI RECEIVED SEPTEMBER 18, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

The Reaction of Citronellal with Benzylmagnesium Chloride[1]

BY WILLIAM G. YOUNG AND SAMUEL SIEGEL

In attempting to prepare α-benzylcitronellol by the addition of citronellal to benzylmagnesium chloride, Rupe[1a] isolated an almost colorless, viscous liquid, distilling at 243–244°(9 mm.). After determining the elementary analysis for carbon and hydrogen, and the value of the molecular weight of the substance in benzene, he suggested that this material was formed by the addition of two moles of benzylmagnesium chloride to one mole of citronellal, the second mole of the Grignard reagent adding to the ethylenic double bond of the aldehyde. Later Gilman and Schulz[2] sought to disprove this contention by an indirect method. They added the aldehyde to a large excess of benzylmagnesium chloride. The mixture was then treated with carbon dioxide and the resulting acids were isolated. Since the product of the addition of a Grignard reagent to an ethylenic double bond would contain a carbon to magnesium linkage, it should react with carbon dioxide to form the salt of a carboxylic acid. Gilman and Schulz isolated phenylacetic acid but found no indication of the presence of any other acid. They concluded that the Grignard reagent had not added to the ethylenic double bond. Although these workers also isolated a liquid having the same properties as that reported by Rupe, they did not further investigate it. Since this indirect proof is not conclusive[3,4] and because certain evidence obtained in this Laboratory pointed to the possibility of the addition of Grignard reagents to the ethylenic double bond, a more thorough investigation of the above reaction was carried out.

Although Rupe was unable to obtain better than a 25% yield of α-benzylcitronellol, we have

(1) Presented before the Division of Organic Chemistry at the Pittsburgh meeting of the American Chemical Society, Sept., 1943.

(1a) Rupe, *Ann.*, **402**, 161 (1913).

(2) H. Gilman and W. F. Schulz, THIS JOURNAL, **52**, 3588–3590 (1930).

(3) Kharasch, *Ann. Survey of Am. Chem.*, **5**, 193 (1930).

(4) Gilman and Schulz, THIS JOURNAL, **53**, 2799–2801 (1931).

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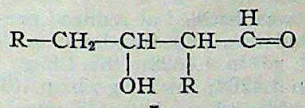
been able to increase the yield to 80% by using an excess of the Grignard reagent. An excess of aldehyde gives 70–80% of the more complex product.

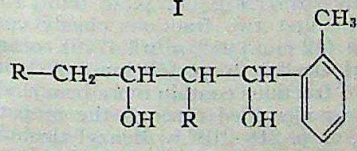
The complex material (which will hereafter be designated substance A) appeared to be homogeneous after several distillations. The elementary analysis and molecular weight indicated the formula $C_{27}H_{44}O_2$ (molecular weight, 400). There are two ethylenic double bonds and two active hydrogen atoms per molecule. Quantitative acetylation with acetic anhydride leads to the same value for the number of hydroxyl groups per molecule. There are also two citronellyl radicals per molecule. This was determined by comparing the amount of acetic acid obtained from A upon oxidation with chromic acid with that obtained upon identical treatment of α-benzylcitronellol.[5] Oxidation of A with alkaline potassium permanganate led to the formation of phthalic acid, which was recovered in good yields. No benzoic acid was isolated.

When A was heated with potassium acid sulfate, one molecule of water was lost. The resulting substance (B) contained one oxygen atom per molecule but neither an active hydrogen atom nor a carbonyl group. It was therefore a cyclic ether (IV).

It is conceivable that A could have been formed in one of the following ways. (1) Two molecules of the aldehyde, under the influence of the Grignard reagent, might condense to form an aldol (I). This aldol would then react with a molecule of benzylmagnesium chloride at the ortho position (to satisfy the condition that phthalic acid be obtained after oxidation) to give, after hydrolysis, the glycol (II).



I



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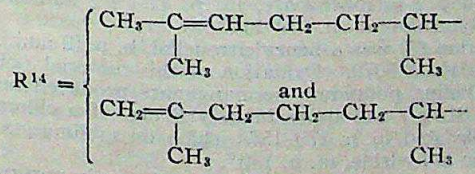
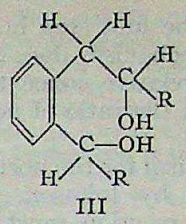
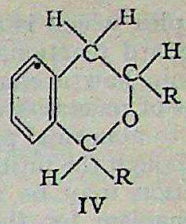


(2) Two molecules of the aldehyde and one molecule of benzylmagnesium chloride might react in such a way that one molecule of the aldehyde would become attached to the ortho position, the other to the methylene group of the benzyl radical as in III.

(5) Karrer, Helfenstein, Wehrli and Wellstein, *Helv. Chim. Acta*, **13**, 1084–1098 (1930).



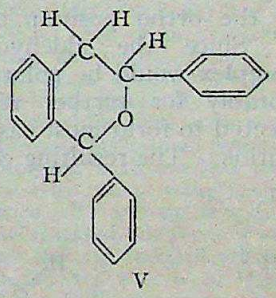
III



IV

The first path for the formation of A was disproved when it was shown that the product isolated from the reaction of the aldol of citronellal with benzylmagnesium chloride was the "normal" addition product (*i. e.*, it was oxidized to benzoic acid and not phthalic acid) and furthermore it readily lost two molecules of water to form a hydrocarbon.

The second path is in complete agreement with all observations. The glycol III should be dehydrated easily to form the cyclic ether IV. Indeed Schmidlin and Garcia-Banûs[6] have shown that benzaldehyde reacts with benzylmagnesium chloride to form a compound, analogous to III, which dehydrated during distillation and formed diphenylisochromane V.



V

The above results prove the correctness of the statement of Gilman and Schultz that benzylmagnesium chloride does not add to the ethylenic double bond of citronellal.

Discussion

In the reaction of benzylmagnesium chloride with citronellal, the concentration and order of addition of reactants play an important role in determining the character of the reaction products. If a large excess of Grignard reagent is used, a good yield of α-benzylcitronellol is obtained. In the formation of this compound, one mole of Grignard reagent and one mole of aldehyde have combined and no abnormal reaction has occurred. On the other hand, if equal amounts of the aldehyde and benzylmagnesium chloride are used, the product is largely one in which two moles of aldehyde and one mole of Grignard reagent have united. In this case the Grignard reagent has reacted abnormally since phthalic acid is obtained upon oxidation of the product.

Johnson[7] has suggested that "the normal and abnormal reactions are to be regarded as two possible transpositions within the initial coördination

(6) Schmidlin and Garcia-Banûs, *Ber.*, **45**, 3193 (1912).

(7) Gilman, "Organic Chemistry," second ed., John Wiley and Sons, Inc., New York, N. Y., 1943, Chap. XXV, p. 1880.

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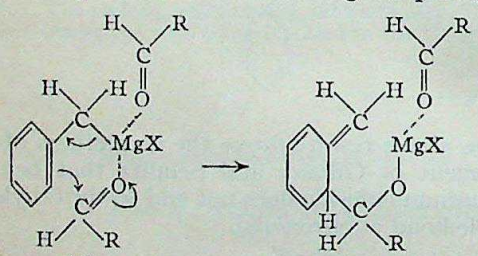
complex which is formed as the first step in all Grignard reactions." This mechanism does not explain how a change in the relative concentrations of reactants can influence the ratio of normal to abnormal products.

Though the intimate mechanism for the normal reaction may be as described by Johnson, the mechanism for the abnormal reaction must be modified.

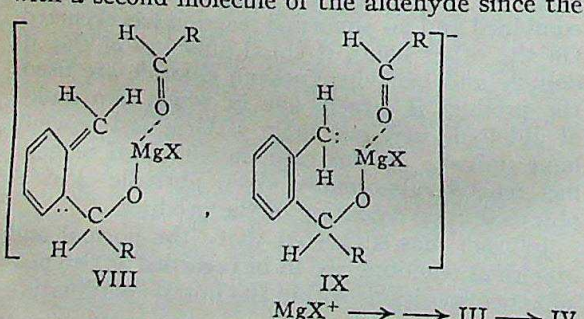
The relationship of concentration of reactants to the kind of product formed suggests that different intermediates are required for the normal and abnormal reaction paths. Since the abnormal reaction is favored by high concentrations of aldehyde, it is reasonable to suppose that the reaction complex for the abnormal reaction contains a larger number of aldehyde molecules than in the case for the normal reaction. Each complex may then react in a manner peculiar to itself and give rise to different products.

The coördination of several aldehyde molecules with one molecule of Grignard reagent may increase the tendency toward ionization of the carbon to magnesium bond and thus permit the activation of the ortho position through resonance (VI). Since the aldehyde molecules within the complex would be polarized and also situated favorably for further reaction, they would be expected to form most easily a bond at the ortho position. The resulting complex (VII)



VI VII

has an active hydrogen atom at the substituted ortho position, since by its removal, the benzenoid system is restored. This proton could be removed readily by another molecule of the Grignard reagent forming toluene and the intermediate VIII. In turn, this intermediate would be expected to react at the methylene position with a second molecule of the aldehyde since the

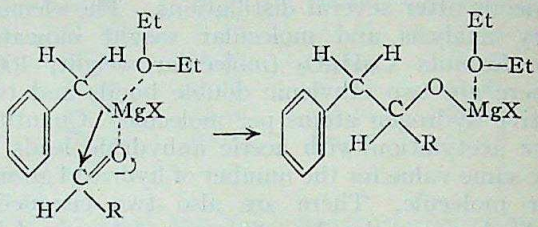


VIII IX

$MgX^+ \longrightarrow \longrightarrow$ III $\longrightarrow$ IV

resonance structure IX would contribute more to the stability of the ion than the non-benzenoid structure with the electron pair at the ortho or para position.

The coördination of only one aldehyde molecule with the Grignard reagent apparently does not allow for activation of the ortho position but leads to a normal reaction as follows



Experimental

Benzylmagnesium chloride was prepared in excellent yields (99%) by adding a solution of freshly distilled benzyl chloride (0.663 mole) in ether (200 ml.) to an excess of magnesium turnings (0.830 mole) covered with ether (100 ml). The Grignard reagent was filtered through glass wool before it was used.

To this vigorously stirred solution, cooled in an ice-bath, freshly distilled citronellal (52.0 g., 0.338 mole) was added dropwise. After the aldehyde had been added, the reaction mixture was allowed to warm up to room temperature (about two hours). It was hydrolyzed by pouring it over a mixture of cracked ice and ammonium chloride. The heat of the reaction melted the ice, leaving two phases. These were separated. The aqueous phase was extracted again with ether (100 ml.). The ether extracts were combined, washed with a little water, and dried over potassium carbonate. After the solvent was removed, the ethereal concentrate was transferred to a 250-ml. Claisen flask and distilled at reduced pressure.

Four fractions were obtained: (1) 27.0 g., distilling below 30°(4 mm.) (trapped in dry-ice); (2)12.0 g., b. p. (4 mm.) 75–100°; (3) 40.5 g., b. p. (3 mm.) 153–175°; (4) 21.5 g., b. p. (3 mm.) 200–235°. The boiler residue showed little or no decomposition.

When redistilled at atmospheric pressure, fraction (1) yielded 20 g. of toluene (b. p. 100–110°), the forerun being ether.

Fraction (2) was distilled at reduced pressure and arbitrarily separated into four fractions: (a) 1.1 g., b. p. (3 mm.) 60–62.5°, $n^{24.5}D$ 1.4622; (b) 4.8 g., b. p. (3 mm.) 62.5–65°, $n^{24.5}D$ 1.4762; (c) 1.6 g., b. p. (3 mm.) 65–70°, $n^{24.5}D$ 1.4948; (d) 1.4 g., b. p. (3 mm.) 75–116° $n^{24.5}D$ 1.4878. The first two fractions chiefly consist of isopulegol (b. p. (12 mm.) 91°, $n^{17}D$ 1.4729) contaminated by some benzyl alcohol (b. p. (10 mm.) 93°, $n^{20}D$ 1.5396). The last two fractions contain more benzyl alcohol. The isopulegol was identified through the preparation of its allophanate, m. p. 218–219°.[8] Benzyl alcohol was identified through the preparation of the acid phthalate, m. p. 103–105°; *p*-nitrobenzoate, m. p. 77–79°; and the 3,5-dinitrobenzoate, m. p. 110–111°.

Fraction (3) was α-benzylcitronellol, b. p. (3 mm.) 153–156°, $n^{24.5}D$ 1.5079. Oxidation of this material (2.01 g.) with alkaline potassium permanganate produced benzoic acid (0.815 g.) and approximately 3 mg. of a chloroform insoluble acid m. p. 170–185° which on sublimation gave phthalic anhydride, m. p. 130°.

When fraction (4) was redistilled, the main portion had the properties: b. p. (3 mm.) 234–235°, $n^{24.5}D$ 1.5120. According to the experimental procedure this fraction should correspond to the substance, which was claimed by Rupe to be the product formed by the addition of a molecule of the Grignard reagent to the ethylenic double bond in citronellal. However, it will be shown later that his material was apparently a dehydration product of the one we isolated.

(8) Béhal, *Bull. soc. chim.*, [4] **25**, 477 (1919).

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The material, substance A, contained only carbon, hydrogen, and oxygen. It appeared to be homogeneous.

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.93; H, 11.08. Found: C, 80.82; H, 11.07.

Identification of Substance A.—The molecular weight was determined cryoscopically in camphor[9] and also in benzene. In the first solvent the values were 360–370 and in the second 484–490 compared with the calculated value, 400. The high value for the molecular weight in benzene indicates association of the solute in that solvent. This phenomenon indicates that Rupe had isolated substance B, an ether, rather than substance A, a glycol. The analysis, he reported (C, 85.10; H, 10.28), is also in fair agreement with the values calculated for the cyclic ether (B) (see below).

Because of the difficulty of identifying the substance by simple degradations, a number of quantitative and semi-quantitative measurements for the various structural units in the substance were carried out.

The number of double bonds per molecule was estimated by means of quantitative bromination[10] and by hydrogenation with a barium sulfate-supported palladium catalyst.[11] The first method indicated 2.04 double bonds, the second 1.84 double bonds per molecule.

The Zerewitinoff method for estimating active hydrogen[12] showed 1.9–2.2 active hydrogens per molecule. No carbonyl groups were present.

A quantitative acetylation showed 1.90 hydroxyl groups per molecule.[13]

The number of citronellyl radicals in the molecule was determined by finding the amount of acetic acid which could be obtained by oxidation of the substance with chromic acid.[5] Since citronellal consists of a mixture of the isomeric limonene and terpinolene forms,[14] it was necessary to compare the amount obtainable from a compound prepared from the same sample of aldehyde. α-Benzylcitronellol, which was formed in the same reaction mixture as A, was used for this purpose.

Karrer's procedure[5] was modified, in order to separate the acetic from the benzoic acid, by following the suggestions of Young, Ballou and Nozaki.[15] In this way, α-benzylcitronellol forms 1.14–1.16 moles of acetic acid per mole of compound while A forms 2.61–2.66 moles of acetic acid per mole of A. This is in fair agreement with the presence of two citronellyl radicals per molecule of A.

Pyridine proved to be far superior to water as a solvent for the oxidation of A with potassium permanganate.[16] In this solvent, 1.09 g. of A yielded 0.325 g. of crude phthalic acid. This was identified by its melting point and the melting point and mixed melting point of the anhydride. No benzoic acid was isolated. This shows that substance A is the "abnormal" reaction product of benzylmagnesium chloride.

Dehydration of A.—Four grams of A was placed in a 10-ml. distilling flask. Potassium acid sulfate (1.0 g.) was added. The mixture was heated to 160° under reduced pressure (thirty minutes) until no more water was evolved. Another gram of the acid salt was then added and the heating continued. After one hour of this treatment, the contents of the flask were cooled and the oil which remained was separated from the acid with the aid of a little ether. This ethereal solution was washed with water and dried with magnesium sulfate. The product was then distilled at reduced pressure. A faintly yellow oil was obtained, b. p. (3 mm.) 215–217°, $n^{25.5}D$ 1.5090.

Anal. Calcd. for $C_{27}H_{42}O$; C, 84.77; H, 11.07. Found: C, 85.12; H, 10.83.

(9) Smith and Young, *J. Biol. Chem.*, **75**, 289 (1927).
(10) A. W. Francis, *Ind. Eng. Chem.*, **18**, 821 (1926).
(11) E. Schmidt, *Ber.*, **52**, 409 (1919).
(12) Kohler, Stone and Fuson, THIS JOURNAL, **49**, 3181 (1927).
(13) Porter, Stewart and Branch, "Methods of Organic Chemistry," Ginn and Co., 1927, p. 182.
(14) J. L. Simonsen, "The Terpenes," Vol. I, Cambridge University Press, London, 1931, p. 60.
(15) Young, Ballou and Nozaki, THIS JOURNAL, **61**, 12 (1939).
(16) Gilman and Kirby, *ibid.*, **54**, 345 (1932).

The analysis above shows the presence of one oxygen atom per molecule. This was shown to be neither a part of a hydroxyl group nor a carbonyl group by the Zerewitinoff method.[17] Bromination led to the value of 182 g. per double bond. Therefore, the dehydration product (B) must be a cyclic ether.

Preparation of the Aldol of Citronellal.—Citronellal (50 g., $n^{23}D$ 1.4479) was added slowly to a solution of potassium hydroxide (2 g.) in 50 ml. of 95% ethanol. The mixture was cooled in ice during the addition. A single phase resulted. The reaction mixture was allowed to stand overnight in a refrigerator. In the morning the solution had become slightly yellow. It was shaken at intervals and kept cold for eleven hours longer. The solution was poured into 200 ml. of water and 50 ml. of ether was added to aid in the separation of the reaction product. This ether phase was washed with sodium bicarbonate solution, then with water and finally dried over sodium sulfate. After the solvent was removed, the product was distilled rapidly under reduced pressure. A colorless liquid (b. p. (5 mm.) 170.5–173.0°; $n^{21.5}D$ 1.4850) was obtained (34 g. or 64% yield). Nine grams of lower boiling material (unreacted aldehyde) also was obtained. The aldol appeared to have become dehydrated to the extent of about 10%. This is indicated by the unsaturation to bromine. Calcd.: 165 g. per double bond; found, 142 g. per double bond.

To check upon the amount of Canizzaro reaction taking place, the aqueous phase from the preparation was acidified and extracted with ether. A small amount of a colorless oil was obtained (less than 1 g.).

Reaction of the Aldol with Benzylmagnesium Chloride.—A solution of 0.241 mole of benzylmagnesium chloride in 180 ml. of ether was cooled in an ice-bath. The aldol (25.0 g., 0.0815 mole) dissolved in 30 ml. of ether was added dropwise to the vigorously stirred Grignard reagent. After the addition of the aldol was completed, the mixture was allowed to warm up to room temperature. The product was hydrolyzed with cracked ice and ammonium chloride. The ether phase was separated, washed with water, and dried with anhydrous sodium sulfate. After the solvent was removed, the product was distilled rapidly from a Claisen flask at reduced pressure. The product (23.8 g.) was collected over a 10° range, b. p. (4 mm.) 226–236°; $n^{28.5}D$ 1.5157; unsaturation to bromine: calcd., 200 g. per double bond; found, 148 g. per double bond. The product was more fluid than substance A. This is probably due to the partial dehydration of the former.

Oxidation of the Product of the Grignard Reaction with the Aldol.—The product (1.42 g.) of the above Grignard reaction was oxidized by potassium permanganate in pyridine under conditions identical with those employed for substance A. There was isolated, in purified form, 0.256 g. of benzoic acid and six milligrams of phthalic acid. The latter was characterized by the melting point of the anhydride and by the brilliant fluorescein test.[18]

Dehydration of the Product of the Grignard Reaction with the Aldol.—The product (17.0 g.) of the reaction of the Grignard reagent with the aldol was dehydrated under conditions identical with those described previously for the dehydration of substance A. The crude distillate was collected over a twelve degree range, 203–215° (3 mm.). The middle fraction was redistilled and used for the analysis reported. Properties: b. p. (3 mm.) 204–206°, $n^{24.5}D$ 1.5278.

Anal. Calcd. for $C_{27}H_{40}$; C, 88.95; H, 11.06. Found: C, 88.81; H, 11.10; unsaturation to bromine, 134 g. per double bond.

The dehydration product is therefore a hydrocarbon. The value for the amount of unsaturation indicates that the product had partially cyclized during the treatment with acid. This was not unexpected.[14] If the material had not cyclized the weight per double bond would have been 91 g.

(17) This analysis was supplied by Dr. Haagen-Smit of the California Institute of Technology, Microchemical Laboratories.
(18) Huntress and Mulliken, "Identification of Pure Organic Compounds, Order I," John Wiley and Sons, Inc., New York, N. Y., 1941.

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Summary

Benzylmagnesium chloride reacts with citronellal to give α-benzyl-citronellol and substance A, a glycol formed from one mole of Grignard reagent and 2 moles of aldehyde.

The structure of A has been determined and it has been shown that the Grignard reagent does not add to the ethylenic double bond as postulated by Rupe.[1a]

A mechanism is suggested to account for the abnormal reaction of benzylmagnesium chloride during the formation of substance A.

LOS ANGELES, CALIF. RECEIVED SEPTEMBER 7, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OREGON STATE COLLEGE]

Reaction of Acetaldehyde with Ethyl Bromide at 400°[1]

BY JACK G. ROOF

The kinetics of the pyrolysis of ethyl bromide has been studied extensively by Daniels and coworkers.[2] The primary step is thought to be the formation of an ethyl free radical and a bromine atom. As an independent method of checking on this primary step a series of experiments was carried out on the liberation of free radicals in ethyl bromide by the photolysis of acetaldehyde and ethyl bromide mixtures[3] at temperatures somewhat below that required to decompose the bromide at an appreciable rate. The experimental facts obtained supported the view that free ethyl radicals are formed in the thermal decomposition of ethyl bromide. In these latter experiments it was found that mixtures of acetaldehyde and ethyl bromide reacted rather rapidly in the dark at 357°, at which temperature acetaldehyde is stable and ethyl bromide decomposes at a very slow rate.

The purpose of the present paper is to describe the results of a further series of experiments on the dark reaction of these two compounds at temperatures near 400° in an apparatus better adapted to thermal reactions than was used previously for this mixture.

Experimental

Chemicals.—Acetaldehyde by Eastman Kodak Co. and ethyl bromide by Merck were used throughout. Each of these was dried over anhydrous cupric sulfate and distilled and sealed off in glass ampules under reduced pressure after the manner previously described.[3]

Apparatus.—A molten lead bath, modeled after that of Daniels,[2] was used as a thermostat. Reactions were carried out in Pyrex vessels. Pressures were measured by means of a thin glass diaphragm[4] used as a null-point instrument in an electrical circuit.

A two-liter glass reservoir, painted black to prevent any light reaction, was attached to the reaction system by means of capillary gates, designed after those of Veltman.[2a] The reservoir was evacuated to a pressure of *ca.* 10^{-4} mm. and warmed by a glow-coil to 60° or higher to aid in outgassing. The sealed reservoir was then cooled and bulblets of the reactants were broken in the reservoir by means of magnetic hammers. This storage vessel was so designed that samples of gas came into contact only with glass while in storage or while being transferred to the reaction vessel. By means of magnetically-operated hammers and tractors one could open the reservoir and let a gas sample into the reaction flask. Momentary heating of two thin-walled capillary goose-necks then sealed off both reservoir and reaction flask independently. The chief advantage of the reservoir was that one could maintain constant composition of reactants while studying the other variables of temperature and pressure over a series of experiments.

A micro-analysis apparatus, essentially that of Blacet and Leighton,[5] was available for analysis of products of the last few experiments. The gaseous products passed through a stopcock and through a trap cooled in dry-ice and were collected in the analytical apparatus by means of a Toepler pump. A lower temperature in the trap would have been desirable, in order to decrease the amount of unchanged reactants being introduced into the analytical apparatus.

Results

A few preliminary experiments were carried out on the pyrolysis of pure ethyl bromide. The plots of pressure *vs.* time were similar to those of Daniels. There were indications of an induction period in the reaction, but the pressures used were higher than those at which this phenomenon is pronounced.[2a]

Twenty-one experiments were then performed on acetaldehyde–ethyl bromide mixtures. A summary of the data is shown in Tables I and II. Pressure–time curves for three typical runs at 404° are shown in Fig. 1. Certain facts are immediately noticeable about these plots. There was a definite induction period of comparatively long duration, with the inflection point not being reached for a matter of minutes. This induction period was quite different from the "time lag" reported for the pyrolysis of ethyl bromide. In this latter case the pressure remained constant for several minutes and then started upward at a continuously decreasing rate as required for a first-order reaction.

For the mixtures there was an abrupt drop-off in the rate of pressure increase after a certain time. This "knee" was followed by a slow pressure rise which decreased in rate over a period of another hour or more, much after the fashion of ethyl bromide alone.

(1) Published with approval of the Monographs Publications Committee, Oregon State College, Research Paper No. 78, School of Science, Department of Chemistry.

(2) (a) P. Fugassi and F. Daniels, THIS JOURNAL, **60**, 771 (1938); (b) F. Daniels and P. Veltman, *J. Chem. Phys.*, **7**, 756 (1939).

(3) J. Roof and F. Daniels, THIS JOURNAL, **62**, 2912 (1940).

(4) F. Daniels, *ibid.*, **50**, 1115 (1928).

(5) F. Blacet and P. Leighton, *Ind. Eng. Chem., Anal. Ed.*, **3**, 266 (1931), *et seq.*

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The rate of pressure increase for the mixture was many times as fast as that of ethyl bromide alone at the same pressure and temperature.

The higher the temperature (over the range studied, 372 to 408°) the more rapid was the rate of reaction. However, the general shape of the curve was not changed by temperature.

The first run in a "cleaned" flask[2a] was more rapid than succeeding ones made under similar conditions without introduction of air into the flask between runs. An increasingly darkening film was observed to deposit upon the walls of the flask during consecutive runs, as is the case in the ethyl bromide decomposition.

TABLE I

SUMMARY OF DATA OBTAINED

Run	Temp., °C.	N_a[b]	P_0, mm.	P_b, mm.	R	t_b, min.	P_∞/P_0
1	372	0.629	132	222	1.08	15.8	1.75 (0.9 hr.)
2	373	.629	117	186	0.94	17.3	1.82 (2.5 hr.)
3	383	.629	93	151	.99	18.3	1.69 (1.0 hr.)
4	408	.562	159	251	1.03	3.0	2.01 (2.9 hr.)
5	405	.562	120	192	1.07	8.3	2.01 (6.1 hr.)
6	404	.562	99	164	1.17	9.5	..
7	407	.562	70	120	1.27	10.3	..
8	407	.562	26	*a*	*a*	*a*	..
9	405	.0496	72	*a*	*a*	*a*	..
10	405	.0496	25	*a*	*a*	*a*	..
11	405	.0496	37	*a*	*a*	*a*	..
12	404	.604	44	78	1.28	12.5	..
13	404	.604	85	143	1.13	11.0	..
14	400	.604	73	120	1.07	18.3	..
15	385	.604	56	92	1.06	35	..
16	400	.378	125	181	1.18	3.0	..
17	404	.378	103	148	1.15	3.5	..

[a] Indicates data not observable. [b] N_a, mole fraction of acetaldehyde; P_0, initial pressure of mixture; P_b, pressure at "knee" in curve; P_∞, pressure at time indicated; $R = (P_b - P_0)/N_aP_0$; t_b, time at "knee" (estimated to nearest one-quarter minute).

Let P_0 designate the initial pressure, P_b the pressure at the knee in the curve, N_a the mole fraction of acetaldehyde, and t_b the time of occurrence of the knee. Define $R = (P_b - P_0)/N_aP_0$, the ratio of (the pressure increase before the break)/(the original partial pressure of the acetaldehyde). All values of R observed are given in Table I. This quantity had an average value of 1.11 ± 0.08 mean deviation. There was no consistent correlation between the value of R and the order of the runs after a flask was cleaned. Also there was no significant correlation between the observed value of R and the temperature of the reaction.

Under the same conditions of temperature and total pressure, the lower the partial pressure of acetaldehyde, the smaller the time interval until the break was reached. Also the pressure increases were less. Hence for low pressure of acetaldehyde ($N_a \sim 0.05$) the results were inconclusive. With the exception of the low pressure run 8, none of the other experiments, ranging from $N_a = 0.38$ to 0.63, offered such difficulty.

The inflection point in the rate curve was difficult to locate accurately, but it usually occurred after a pressure increase of about one-half to two-thirds of the value of $P_b - P_0$.

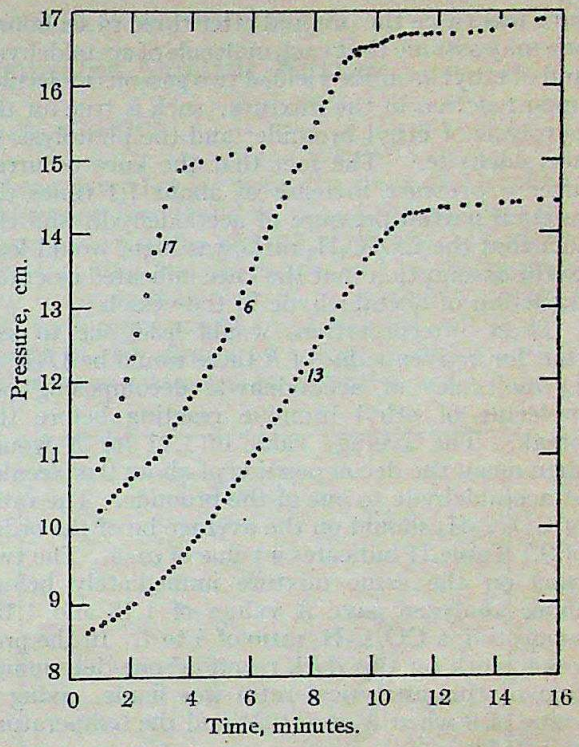

Fig. 1.—Pressure *vs.* time curves for three typical runs (404°): No. 17—$N_a = 0.378$; No. 6—$N_a = 0.562$; No. 13—$N_a = 0.604$.

In the first five runs the reaction was allowed to continue for a relatively long period of time. The ratio P_∞/P_0 seemed to approach the value of 2 as a limit.

In Table II are shown results on the analysis for carbon monoxide and ethylene in the last three runs with a mole fraction of acetaldehyde of 0.378. The break time, t_b, is estimated to have been of the order of five minutes. The R values on two preceding runs on this same mixture were 1.18 and 1.15.

TABLE II

DETERMINATION OF CO AND C_2H_4 IN THE REACTION PRODUCTS

Run	Temp., °C.	Time of reaction, minutes	Ratio CO/C_2H_4
20	404	2	4.30
19	405	5	2.77
21	402	192	1.48

Discussion

The presence of both ethylene and carbon monoxide in the products and the fact that the ratio R is greater than unity indicate that the pressure increase was due to decomposition of both reactants. Although the choice of both P_0 and P_b was subject to some doubt in each experiment, the fair consistency in the values of R indicates something of the mechanism of the reaction in the early stages. From the fact that the final pres-

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sure was twice the original after three to six hours, one may assume that each molecule of acetaldehyde and of ethyl bromide yielded two gaseous molecules upon reaction in the mixture; such is true for the pyrolysis of ethyl bromide[2] and the photolysis of acetaldehyde.[6] The fact that the knee occurred after a pressure increase of about 1.1 times the original partial pressure of acetaldehyde, and the fact that the CO/C_2H_4 ratio was high, would lead to the assumption that the knee indicated essential depletion of acetaldehyde in the vessel.

These interpretations would lead one to say that for a given value of R there would be $1/(R - 1)$ molecules of acetaldehyde decomposing per molecule of ethyl bromide reacting before the break. The average value of 1.11 for R would then mean the decomposition of about 9 molecules of acetaldehyde to one of the bromide. The ratio of CO/C_2H_4 should on the average be of the order of 9. Table II indicates a value of *ca.* 4. The two runs on the same mixture immediately before those analyzed gave R values of 1.18 and 1.15, suggesting a CO/C_2H_4 ratio of 5 to 7. In the previous work on this dark reaction[3] one determination of this analytical ratio was made, giving a value of 9 when N_a was 0.21 and the temperature was 355°.

If the decomposition of ethyl bromide proceeds by a chain mechanism, the chain length is short.[2a] At these temperatures acetaldehyde is itself stable, but the photolysis in the ultraviolet at temperatures above 300° occurs with quantum yields[6,7] of the order of 10^2 to 10^3. It is evident that in the present studies on mixtures the chain length of the acetaldehyde decomposition is of the magnitude of ten times that of the bromide.

The data presented herewith are considered to be in harmony with the postulated[3] decomposition of ethyl bromide into an ethyl free radical and a bromine atom, followed by reaction of the ethyl radical with CH_3CHO to form ethane, carbon monoxide and a methyl radical; this methyl radical then carries on the chain in the aldehyde decomposition. The presence of the ethyl bromide permits the acetaldehyde to decompose at this lower temperature, but it also shortens the chain length that would be possible in its absence.

(6) Mitchell and Hinshelwood, *Proc. Roy. Soc.* (London), **A159**, 32 (1937).

(7) J. A. Leermakers, THIS JOURNAL, **56**, 1537 (1934).

The induction curve obtained in this reaction is quite different from the time-lag curves obtained at low pressures of pure ethyl bromide. The "auto-catalytic" initial part of each of the present curves indicates a progressive destruction of an inhibitor or the building up of a positive catalyst until the rate begins to drop off due to the decreasing amount of aldehyde left for reaction. Since this type of curve was observed in each case and not alone in the first run in a "cleaned" flask, it is not associated with the condition of the surface of the vessel. If it is due to destruction of an inhibitor, that inhibitor must have been introduced with each new sample of the mixture into the reaction chamber. The phenomenon may be due to building up of a positive catalyst. If there is a thermal reaction of acetaldehyde and ethyl bromide together to form a complex of long life, a curve of the type obtained might be expected. If such type of activated complex is involved, it must not dissociate into ultimate molecules but must of necessity give rise to free radicals to propagate the aldehyde chain.

When conditions permit resumption of this work, it is planned to study in detail the factors influencing the induction period of this reaction.

The author is indebted to Professors Farrington Daniels and Francis E. Blacet for suggestions concerning the interpretation and presentation of these data.

Summary

1. The dark reaction of mixtures of acetaldehyde and ethyl bromide at 400° has been studied from pressure measurements and analysis of the products.

2. A pronounced induction period of an autocatalytic type is obtained in the early stages of the reaction. A sharp decrease in the rate of pressure rise occurs after an increase of approximately 1.1 times the original partial pressure of acetaldehyde.

3 It is indicated that on the average the order of ten molecules of the aldehyde are decomposed per molecule of the bromide.

4. Correlations with previous work on the separate decomposition of these two substances is made.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

Refractive Indices of the Normal Saturated Aliphatic Nitriles

BY A. DORINSON AND A. W. RALSTON

The aliphatic nitriles constitute an excellent series of compounds with which to test the hypothesis regarding the temperature dependence of the refractive indices of polar organic molecules advanced in a previous communication from this Laboratory.[1] There it was found that the refractive index of a straight chain fatty acid in the liquid state, plotted as a function of temperature, exhibited a sharp change of slope in the vicinity of 40°. This was ascribed to the influence of temperature on the orientation of the dipoles in the body of the liquid: at temperatures sufficiently elevated the thermal agitation of the molecules overcomes the restraint imposed by dipole interaction. A more extensive study of this effect is possible with the normal aliphatic nitriles because the members of this series up to pentadecylonitrile are liquids throughout the range necessary to demonstrate the effect.

The even carbon numbered nitriles used in this study were prepared by the catalyzed action of ammonia on the corresponding highly purified acids; the odd nitriles were prepared from the next lower fatty acids by the well-known sequence: ester → alcohol → halide → nitrile. The final purification consisted of a careful fractional distillation. Some of the nitriles, available from a previous investigation,[2] were treated with a few pellets of potassium hydroxide to remove fatty acids and water before distillation. Judged by the observation that the refractive indices of the entire series at 25°, from capronitrile to stearonitrile, fell on a smooth curve, the nitriles used were quite pure. Butyronitrile and valeronitrile were slightly less pure by this criterion. The freezing points[3] of several of the nitriles are: caprinitrile, −14.46°; lauronitrile +4.02°; myristonitrile 19.25°; palmitonitrile 31.40°; stearonitrile 40.88°.

The refractive indices were read on an Abbe type refractometer with jacketed prisms through which water from a thermostat was circulated. Temperatures were read on a calibrated thermometer.

The refractive indices of the nitriles are listed in Table I. These are the data as read directly on the refractometer, uncorrected for the effect of temperature on the prism of the instrument. A graphical representation is given in Fig. 1; here a correction whose magnitude amounts to 0.000006 $(t - 20)$ has been added to the original data for temperatures above 20°. The range of the graph has been extended by using the data of Merckx, Verhulst and Bruylants[4] at 15°. A definite change of slope occurs in the vicinity of 40–45°. In view of the fact that the dipole moment of the nitrile group is larger than that of the carboxyl group, some significance might be attributed to the occurrence of this change at a slightly higher temperature than was noted for the fatty acids.

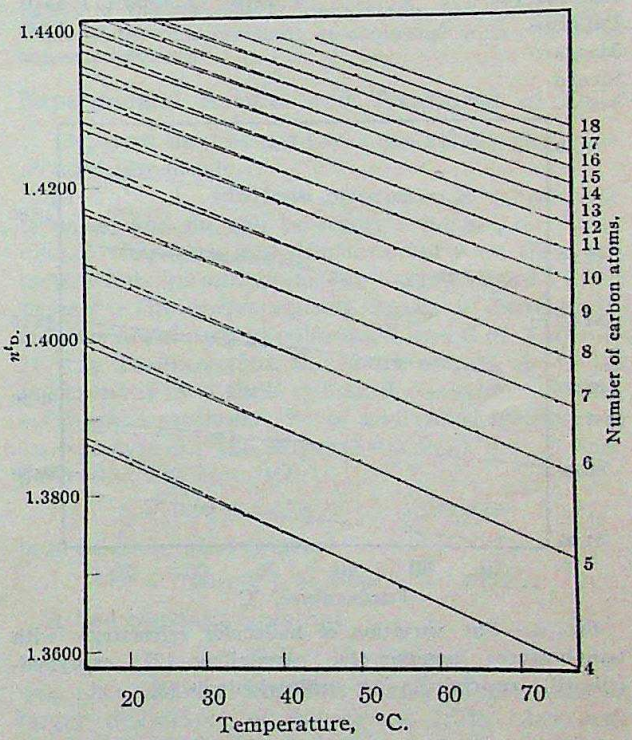

Fig. 1.—The variation of refractive index with temperature. Extrapolation is represented by the dotted line. The points at 15° are from the data of Merckx, Verhulst and Bruylants.[4]

The availability of reliable data on the densities of the nitriles[4,5] makes it possible to calculate their molecular refractivities. Several of these are plotted as a function of temperature in Fig. 2. Change of slope is more pronounced for the molecular refractivities than for the refractive indices themselves. The value of the molecular refractivity does not become constant above the inflection point, which indicates that other factors besides orientation of the dipoles affect its magnitude. It is also seen that the slope of molecular refractivity *vs.* temperature becomes steeper for higher members in the series. Careful examina-

(1) Dorinson, McCorkle and Ralston, THIS JOURNAL, **64**, 2739 (1942).

(2) Ralston, Selby and Pool, *Ind. Eng. Chem.*, **33**, 682 (1941).

(3) These freezing points were determined by Mr. C. W. Hoerr of his Laboratory.

(4) Merckx, Verhulst and Bruylants, *Bull. soc. chim. Belg.*, **42**, 177 (1933).

(5) Dasagan, *ibid.*, **44**, 602 (1935).

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TABLE I

REFRACTIVE INDICES (n'D) OF NORMAL ALIPHATIC NITRILES (UNCOR.)

Nitrile	20.0°	25.0°	30.0°	35.0°	40.0°	45.0°	50.0°	55.0°	65.0°	75.0°
Butyro-	1.3842	1.3820	1.3798	1.3773	1.3754	1.3729	1.3706	1.3862	1.3636	1.3590
Valero-	1.3972	1.3950	1.3929	1.3908	1.3887	1.3864	1.3843	1.3820	1.3774	1.3727
Capro-	1.4069	1.4049	1.4028	1.4008	1.3986	1.3966	1.3944	1.3921	1.3878	1.3834
Enantho-	1.4144	1.4124	1.4104	1.4083	1.4064	1.4044	1.4022	1.4000	1.3960	1.3917
Caprylo-	1.4204	1.4183	1.4164	1.4145	1.4124	1.4104	1.4085	1.4063	1.4021	1.3980
Pelargono-	1.4254	1.4235	1.4216	1.4197	1.4176	1.4157	1.4137	1.4115	1.4075	1.4035
Capri-	1.4296	1.4276	1.4256	1.4237	1.4218	1.4199	1.4180	1.4159	1.4119	1.4080
Undecylo-	1.4330	1.4312	1.4293	1.4273	1.4254	1.4236	1.4217	1.4197	1.4156	1.4118
Lauro-	1.4360	1.4341	1.4322	1.4304	1.4286	1.4267	1.4248	1.4227	1.4188	1.4149
Tridecylo-	1.4387	1.4368	1.4349	1.4330	1.4312	1.4294	1.4275	1.4254	1.4216	1.4177
Myristo-	1.4410	1.4392	1.4373	1.4354	1.4335	1.4317	1.4298	1.4279	1.4240	1.4202
Pentadecylo-		1.4413	1.4395	1.4376	1.4356	1.4338	1.4320	1.4300	1.4261	1.4224
Palmito-				1.4396	1.4377	1.4358	1.4340	1.4319	1.4281	1.4244
Margaro-					1.4392	1.4373	1.4355	1.4336	1.4298	1.4260
Stearo-						1.4389	1.4370	1.4351	1.4313	1.4276

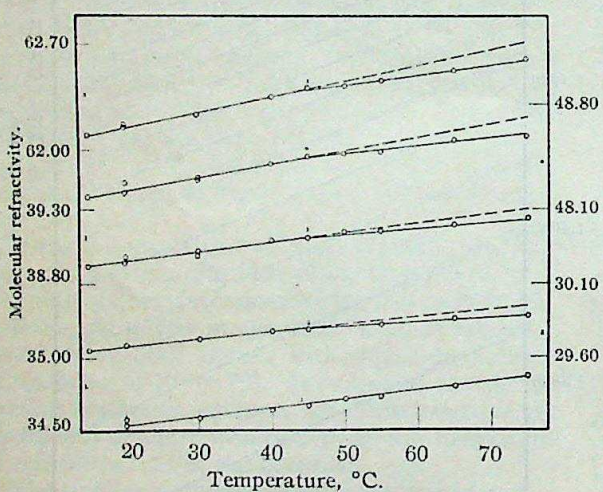

Fig. 2.—The variation of molecular refractivity with temperature: heptane (1); capronitrile (2); caprylonitrile (3); caprinitrile (4); tridecylonitrile (5).

tion of the graphs of the densities and of the refractive indices showed a distinct convergence of these curves at lower temperatures.

Highly purified specimens of *n*-heptane and *n*-octane were run as control substances. The refractive indices and the molecular refractivities of these compounds were found to be straight-line functions of temperature.

Summary

1. The refractive indices of the normal aliphatic nitriles from butyronitrile to stearonitrile inclusive were determined at a number of temperatures between 20 and 75°.

2. For each nitrile an abrupt change of slope in the refractive index *vs.* temperature curve occurs at 40–45°.

3. Corresponding graphs of the molecular refractivities also show a change of slope.

CHICAGO, ILL. RECEIVED NOVEMBER 19, 1943

[CONTRIBUTION NO. 508 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Heats of Dilution of Sodium Chloride in Ethylene Glycol at 25°[1]

BY W. E. WALLACE, L. S. MASON AND A. L. ROBINSON

The heats of dilution of electrolytes of nearly all the common valence types have been extensively studied in aqueous solution. These heats of dilution, when extrapolated to infinite dilution, have provided ample opportunity for comparison with the Debye–Hückel limiting law. Further comparison of experiment with theory could be provided by a comparable body of data in non-aqueous media. Theory requires that, in the limit, ΦL_2, the relative apparent molal heat content of the solute, be linear with respect to the square root of the concentration, regardless of the solvent medium, but that for a salt of a given valence type ΦL_2 be dependent on certain characteristics of the solvent, namely, the dielectric constant, the temperature derivative of the dielectric constant, and the volume–temperature relationships for the particular solvent.

Probably the only significant study of heats of dilution of electrolytes in strictly non-aqueous solvents is the work of Jackson, Smith, Gatty and Wolfenden[2] who determined these properties for

(1) This investigation was supported by a grant from the Buhl Foundation. This paper was presented to the Division of Physical and Inorganic Chemistry at the Pittsburgh meeting of the American Chemical Society, September, 1943.

(2) N. S. Jackson, A. E. C. Smith, O. Gatty and J. H. Wolfenden, *J. Chem. Soc.*, 1376–1379 (1934).

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a number of electrolytes in several solvents, including methanol, nitrobenzene, nitromethane and water.

Chord-area plots[3] of their data for sodium chloride, sodium iodide, sodium perchlorate and tetraethylammonium bromide in methyl alcohol indicate extrapolated slopes of the order of 5000 to 7000, as compared to their theoretically calculated limiting slope of 2610. A single measurement for the lowest concentration of sodium perchlorate studied suggests a reversal in the direction of the theoretical slope, although here as in the other cases insufficient data are available at low concentration to permit a significant comparison with theory.[4,5]

Ethylene glycol was selected as the solvent in the present work because the Debye–Hückel theoretical limiting slope for electrolytes in this liquid is appreciably different from the value in water. The glycol is of relatively low volatility and exhibits satisfactory solubility behavior toward electrolytes.

Experimental

Heats of dilution were measured with a Lange-type differential adiabatic calorimeter, the design and operation of which have been completely described elsewhere.[6a,b,c,d]

The sodium chloride used was a C. P. product, which was dried thoroughly and used without further purification.

The ethylene glycol was obtained by fractionation of the best grade material supplied by the Carbide and Carbon Chemicals Corporation and the Coleman and Bell Company. Using a 12-plate column, the fraction whose boiling range was 197.7 to 197.8° at 760 mm. pressure was selected. After a set of dilution experiments the solvent was recovered from the salt by distillation using a Yoe still. The physical properties of the material agreed well with published values. The material had a freezing point of −12.8°, a boiling point of 197.7–197.8°, and a refractive index, n_D 1.4336 at 15°. Values from the literature are: −12.6°[7] and −13.2°[8] for the freezing point; 197.85° at 760 mm.[7] for the boiling point; and 1.43312 at 15°[7] and 1.4314 at 20°[8] for refractive index.

The purified product exhibited a strong tendency to take on atmospheric moisture. This was prevented by handling the glycol in a closed container under a carefully dried atmosphere. In spite of these precautions, a slight increase in water content was noted during the course of the investigation. Titration of the solvent using Karl Fischer reagent[9] showed a water content of about 0.1% at the beginning of the study and about 0.4% at the conclusion.

One of the chief experimental difficulties appeared to lie in the relatively high viscosity of the glycol. The time of mixing of the solutions was materially longer than in the case of aqueous solutions, stirring heats were greater, and attainment of thermal equilibrium conditions was slower. Greater opportunity for heat exchanges between the two halves of the calorimeter undoubtedly reduced the precision of the measurements as compared with studies of aqueous solutions.

Experimental Results and Treatment of Data

The treatment of data was essentially the same as used previously.[10]

In Table I, dilutions between the concentrations m_1 and m_2 will be referred to as the "long chord" dilutions, and dilutions between the concentrations m_3 and m_2 as the "short chord" dilutions.[10] The corresponding heats of dilution in calories are shown in columns 4 and 6 of Table I. It was assumed that the short chords could be represented by a three constant equation. Using established methods[3,11a,b] of analytical treatment, an equation for the slope, $S = d(\Phi L_2)/dm^{1/2}$, was derived. The equation

$$S = 1580 + 63{,}720m^{1/2} - 1{,}193{,}000m \qquad (1)$$

may be integrated to give

$$\Phi L_2 = 1580m^{1/2} + 31{,}860m - 397{,}700m^{3/2} \qquad (2)$$

A two constant equation

$$S = 3170 - 29{,}050m^{1/2} \qquad (3)$$

was also derived, but was found to give much larger deviations of calculated from observed heat effects. A plot of the short chords together with the curves obtained from equations (1) and (3) is shown in Fig. 1. A three constant equation using the theoretically calculated limiting slope was also derived.

$$S = 1970 + 43{,}750m^{1/2} - 889{,}900m \qquad (4)$$

It was found that this equation fitted the experimental values almost as well as equation (1).

Comparison of a plot of equation (2) with a "point-to-point"[4,12] plot indicates that the error of extrapolation to infinite dilution was not greater than ± 5 calories. By combination of

(3) T. F. Young and O. G. Vogel, THIS JOURNAL, **54**, 3030 (1932).

(4) E. Lange and A. L. Robinson, *ibid.*, **52**, 4218 (1930), reported heats of dilution of potassium chloride in 15% sucrose solutions and in 5% urea solutions as solvents. Measurements were made to sufficiently low concentrations so that extrapolations to infinite dilution could be made. A linear relationship between ΦL_2 and $\sqrt{c}$ at the lower concentrations was observed. The values of the limiting slopes were about the same as for pure water, although the theoretical limiting slope (using the dielectric constant data of Kockel, *Ann. Physik*, **77**, 417 (1926)) had a sign opposite to the experimental slope in the case of the urea solutions. This discrepancy suggested a redetermination of the dielectric constants of the urea solutions. Calculations using later measurements of the dielectric constants (J. Wyman, Jr., THIS JOURNAL, **55**, 4116 (1933)) of the urea solutions provided reasonably good agreement between the experimental and theoretical limiting slopes.

(5) H. S. Harned, J. O. Morrison, F. Walker, J. G. Donelson and C. Calmon, *ibid.*, **61**, 49 (1939), have made a comprehensive study of the thermodynamic properties of HCl as a function of its concentration, the temperature and dielectric constant, by means of electromotive force measurements of the cell: H_2/HCl (m) dioxane (X), H_2O (Y)/AgCl − Ag in dioxane-water solutions having a dielectric constant range from 80 to 10 from 0 to 50°. It was found that observed values of $\bar{L}_2$ in dilute solutions at 25° displayed an increasing tendency to be higher than the limiting values as the dielectric constant decreased.

(6) (a) E. Lange and A. L. Robinson, *Chem. Rev.*, **9**, 89 (1930); (b) E. A. Gulbransen and A. L. Robinson, THIS JOURNAL, **56**, 2637 (1934); (c) T. H. Dunkelberger and A. L. Robinson, *ibid.*, **60**, 1301 (1938); (d) W. E. Wallace and A. L. Robinson, *ibid.*, **63**, 958 (1941).

(7) Timmermans and Hennaut-Roland, *J. chim. phys.*, **32**, 589 (1935).

(8) A. F. Gallaugher and H. Hibbert, THIS JOURNAL, **58**, 813 (1936).

(9) D. M. Smith, W. M. D. Bryant and J. Mitchell, Jr., *ibid.*, **61**, 2407 (1939).

(10) A. L. Robinson and W. E. Wallace, *Chem. Rev.*, **30**, 195 (1942).

(11) (a) T. F. Young and W. L. Groenier, THIS JOURNAL, **58**, 187 (1936); (b) T. F. Young and P. Seligman, *ibid.*, **60**, 2370 (1938).

(12) E. Lange, J. Monheim, and A. L. Robinson, *ibid.*, **55**, 4785 (1933).

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TABLE I

INTERMEDIATE HEATS OF DILUTION OF SODIUM CHLORIDE IN ETHYLENE GLYCOL

Moles/1000 g. of glycol			Calories					Cal./mole salt	
$10^5 m_1$	$10^5 m_2$	$10^5 m_3$	$-q_{1\to 2}$	$\Delta q_{1\to 2}$	$-q_{3\to 2}$	Eqn. (5) $\Delta q_{3\to 2}$	Eqn. (2) $\Delta q_{3\to 2}$	$-\Delta H_{1\to 2}$	$-\Delta H_{3\to 2}$
17,400	187.0	372.2	0.951	+0.031	0.134	−0.019	+0.015		
17,400	187.0	372.2	.899	− .021	.101	− .052	− .017	451 ± 4	29 ± 2
17,400	187.0	372.2	.928	+ .008	.127	− .026	+ .009		
8,967	93.95	187.0	.391	− .013	.052	− .006	− .007		
8,967	93.95	187.0	.407	+ .003	.077	+ .019	+ .018	396 ± 7	38 ± 3
8,967	93.95	187.0	.439	+ .035	.076	+ .018	+ .017		
8,967	93.95	187.0	.401	− .003	.032	− .026	− .027		
4,536	47.21	93.95	.1714	+ .0020	.0385	+ .0173	+ .0161		
4,536	47.21	93.95	.1547	− .0147	.0113	− .0099	− .0111	318 ± 7	26 ± 5
4,536	47.21	93.95	.1769	+ .0075	.0401	+ .0189	+ .0177		
4,536	47.21	93.95	.1592	− .0102	.0185	− .0027	− .0039		
2,277	23.71	47.21	.0774	+ .0101	.0117	+ .0040	+ .0040		
2,277	23.71	47.21	.0768	+ .0095	.0009	− .0068	− .0068	289 ± 4	13 ± 4
2,277	23.71	47.21	.0712	+ .0039	.0085	+ .0008	+ .0008		
2,277	23.71	47.21	.0770	+ .0097					
1,144	10.92	23.71	.0332	+ .0071	.0038	+ .0007	+ .0009		
1,144	10.92	23.71	.0202	− .0059	.0006	− .0025	− .0023	181 ± 23	11 ± 3
1,144	10.92	23.71	.0187	− .0074	.0042	+ .0011	+ .0013		

the long chord heats of dilution with those calculated from equation (2), a series of values of ΦL_2 for the entire concentration range studied was obtained. A least squares treatment of the values yielded the following equation for ΦL_2

$$\Phi L_2 = 2502m^{1/2} - 4036m + 2837m^{3/2} \quad (5)$$

The plot of equation (5) is shown in Fig. 2. Circles represent the experimental values.

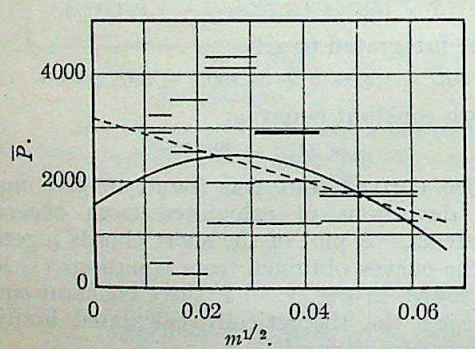

Fig. 1.—Plot of short chords ($\bar{P} = -\Delta H_{3\to 2}/\Delta m^{1/2}$) *vs.* $m^{1/2}$ and equations 1 and 3 for sodium chloride in ethylene glycol.

q-Values for the long chord dilutions were calculated from equation (5) and q-values for the short chord dilutions were calculated from equations (5) and (2). The deviations of calculated from observed values are shown in columns 5, 7 and 8, respectively, in Table I. Examination of these deviations shows that equation (2) is somewhat better than equation (5) for the short chord dilution range. This is perhaps to be expected considering that equation (2) was derived from the short chord range.

Relative Partial Molal Heat Contents.—Equations for $\bar{L}_1$ and $\bar{L}_2$ may be obtained directly from equation (5) by Rossini's method.[13]

$$\bar{L}_1 = -22.54m^{3/2} + 72.71m^2 - 76.68m^{5/2} \quad (6)$$

$$\bar{L}_2 = 3753m^{1/2} - 8072m + 7093m^{3/2} \quad (7)$$

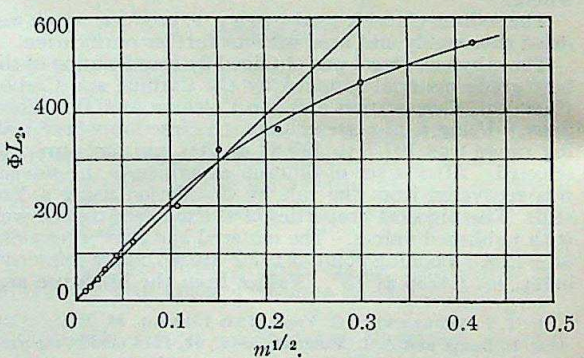

Fig. 2.—ΦL_2 (calories per mole of salt) *vs.* $m^{1/2}$. Curve is equation 5. The straight line is the theoretical limiting slope. Circles are experimental values.

Values of $\bar{L}_1$ and $\bar{L}_2$ at several rounded concentrations calculated from equations (6) and (7) are given in Table II.

TABLE II

m	$-\bar{L}_1$, cal./mole solvent	$\bar{L}_2$, cal./mole NaCl
0.0001	2.18×10^{-5}	37
.0005	2.34×10^{-4}	80
.001	6.42×10^{-4}	111
.01	1.60×10^{-2}	302
.05	1.13×10^{-1}	514
.1	2.28×10^{-1}	602
.2	4.79×10^{-1}	698

Comparison of Theory and Experiment

The volume–temperature relationships for

(13) F. D. Rossini, *Bur. Standards J. Research*, **4**, 313 (1930); **6**, 791 (1931).

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ethylene glycol as determined by Gibson and Loeffler[14] together with the dielectric constant data of Akerlof[15] were used for the computation of the theoretical limiting slope for a uni-univalent electrolyte in this solvent. The value is 1970 cal.-kg.solvent-moles.$^{-3/2}$ The presence of 0.4% of moisture reduces the limiting slope by about 1%. The experimental limiting slopes are 1580 from equation (1) and 2502 from equation (5). The former value is to be recommended since it was obtained by a method specifically developed for the evaluation of such quantities. The probable error of the limiting slope of equation (1) has been calculated to be ±1188.[16] This value, although relatively large, indicates that the experimentally determined limiting slope is essentially in agreement with the theoretical slope.

A comparison of ΦL_2 values for sodium chloride in glycol with those in water[11b] in the concentration range studied shows that the heat effects in general are greater in glycol than in water by a factor of 5 or 6. This might have been anticipated from the theoretical limiting slopes (477 for water). The ΦL_2 curve for water shows a maximum in the neighborhood of $m^{1/2} = 0.4$. A maximum was not realized in glycol in the concentration range studied, although the shape of the curve (Fig. 2) indicates that a maximum might occur at $m^{1/2} = 0.6$ to 0.7.

It may be noted also that the ΦL_2 curve for aqueous solutions is below the limiting law curve over the complete concentration range, but that the curve for glycol is slightly above the limiting law in the lower concentrations (Fig. 2). The same is true for $\bar{L}_2$ values in the two solvents. This behavior with decreasing dielectric constant is in qualitative agreement with the behavior of hydrochloric acid in dioxane–water mixtures.[5]

(14) R. E. Gibson and O. H. Loeffler, THIS JOURNAL, **63**, 898 (1941).

(15) G. Akerlof, *ibid.*, **54**, 4125 (1932).

(16) A. G. Worthing and Joseph Geffner, "Treatment of Experimental Data," John Wiley and Sons, Inc., New York, N. Y., 1943.

Summary

Heats of dilution of sodium chloride in ethylene glycol have been measured from 0.17m to 0.0001m at 25°. Equations for the relative apparent molal heat content of the solute and for the relative partial molal heat contents of the solute and solvent have been derived.

The experimental limiting slope is in agreement with the theoretically calculated limiting slope.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

Factors Determining the Course and Mechanisms of Grignard Reactions. XII. The Effect of Cobaltous Chloride on the Reaction of Methylmagnesium Bromide with Alicyclic Chlorides

BY M. S. KHARASCH, FRANCES ENGELMANN AND W. H. URRY

Introduction.—It was recently shown[1] that, in the presence of cobaltous chloride, phenylmagnesium bromide reacts with aliphatic halides (methyl, ethyl, propyl, *n*-butyl bromides and *t*-butyl chloride) to yield biphenyl and the saturated and unsaturated hydrocarbons derived from the alkyl halide used. A free radical mechanism was postulated to explain these results. In order to study the behavior of alicyclic free radicals in solution, the reactions of a number of alicyclic chlorides with methylmagnesium bromide in the presence and in the absence of cobaltous chloride have now been investigated.

Procedure.—The Grignard reactions were carried out according to the directions of Kharasch, Lewis and Reynolds,[1] with two modifications: a trap cooled in dry-ice was placed between the reaction flask and the gas collector, and a 10% excess of Grignard reagent was used. Twenty-gram samples were used in reactions with bornyl and isobornyl chlorides. With *cis*- and *trans*-2-methylcyclohexyl chlorides and cyclohexyl chloride, 50-g. samples were used in the cobaltous chloride catalyzed reactions, and 25-g. samples in the control experiments. In the reactions catalyzed by cobaltous chloride, the mixtures were refluxed for five hours and allowed to stand overnight. In the control experiments where no cobaltous chloride was used, refluxing was continued for twenty-eight hours.

The reaction products were analyzed by procedures described in detail in the experimental part.

Results.—The results of the reactions between the alicyclic halides and methylmagnesium bromide (shown in Table I) indicate that the normal condensations are extremely slow, and that, consequently, the secondary reaction (elimination of hydrogen chloride and formation of the unsaturated compounds) predominates.

The reaction of methylmagnesium bromide and the alicylic halides takes an entirely different course when about 5 mole per cent. of cobaltous chloride is first added to the Grignard reagent. The results are summarized in Table II.

The column headed "Unsaturated Compound" refers to cyclohexene and bornylene in experiments

(1) Kharasch, Lewis and Reynolds, THIS JOURNAL, **60**, 1605 (1938).

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TABLE I

REACTION OF METHYLMAGNESIUM BROMIDE WITH ALICYCLIC CHLORIDES

Alicyclic chloride	Reaction,[a] %	Addition product	Unsaturated compound	Gas evolved
2-Methylcyclohexyl-(*trans*)	46	10	33	Pure methane
2-Methylcyclohexyl-(*cis*)	49	10	34	Pure methane
Bornyl	5			
Isobornyl	90		90	Pure methane

[a] The extent of the reaction was determined by halogen titration (Kharasch and Fields, THIS JOURNAL, **63**, 2316 (1941)).

cobaltous chloride is particularly striking in the case of bornyl chloride which, in the absence of cobaltous chloride, reacts only to the extent of 5%, even if the reaction mixture is heated for twenty-eight hours. These results are, in our estimation, best explained by a free radical chain reaction.

(1) $CH_3MgBr + CoCl_2 \longrightarrow CH_3CoCl + CoClBr$
(2) $CH_3CoCl \longrightarrow CH_3\cdot + CoCl\cdot$
(3) $RCl\ (Alicyclic) + CoCl\cdot \longrightarrow R\cdot + CoCl_2$
(4) $R\cdot \longrightarrow R_{-H} + R_{+H}$
(5) $R\cdot \longrightarrow R{:}R^4$
(6) $CH_3\cdot + C_2H_5OC_2H_5 \longrightarrow CH_4 + C_2H_6 + C_2H_4$

However, the alicyclic free radicals differ significantly from the lower aliphatic free radicals (up to butyl) in that the reaction (5), the dimerization of the free radicals, does not occur with free aliphatic radicals, but takes place to the extent of 26% with the free cyclohexyl and 2-methylcyclohexyl radicals, and to the extent of 63% with the free bornyl radical. Since the free radicals derived from bornyl or isobornyl chloride are the same, the formation of 32% less dimer from the isobornyl chloride can be ascribed only to the greater ease of elimination of hydrogen chloride from that molecule. The formation of equal quantities of the saturated and unsaturated hydrocarbons in the reaction with bornyl chloride, and the preponderance of the unsaturated over the saturated compound (44 to 19%) in the reaction with isobornyl chloride is in full agreement with this view.

TABLE II

REACTION OF METHYLMAGNESIUM BROMIDE WITH ALICYCLIC CHLORIDES IN THE PRESENCE OF COBALTOUS CHLORIDE[a]

Alicyclic chloride	Reaction, %	Dimer, %	Unsatd. compound, %	Satd. compound, %	Gaseous products, % Methane	Ethane	Ethene
Cyclohexyl	86	26	29	27	85	9	6
2-Methylcyclohexyl-(*trans*)	87	27[b]	23	28	77	15	8
2-Methylcyclohexyl-(*cis*)	89	22	31	34	83	9	8
Bornyl	98	63	20	15	72	19	9
Isobornyl	94	31	44	19	77	15	8

[a] Cobaltous chloride (5 mole per cent.) was used in all experiments. [b] About 6% of an unidentified higher polymer was also isolated.

with bornyl and isobornyl chlorides, and to methylcyclohexene or cyclohexene in the experiments with the cyclohexyl chlorides. The "unsaturated compound" resulting from the reactions of bornyl and isobornyl chlorides is believed to be a mixture of camphene and bornylene because a 10% increase in unsaturation was observed when esterification was carried out under more drastic conditions.[2] Control samples of camphene gave the same unsaturation value when either method of esterification was used. The column headed "Saturated compound" refers to camphane in the bornyl and isobornyl chloride experiments, and to methylcyclohexane or cyclohexane, respectively, in the experiments with 2-methylcyclohexyl or cyclohexyl chloride.

Discussion

It is of considerable theoretical interest to note that in the uncatalyzed experiments the *cis*- and *trans*-forms of 2-methylcyclohexyl chloride react alike, while bornyl and isobornyl chlorides differ considerably in their stability. Isobornyl chloride reacts by elimination of hydrogen chloride to the extent of 90% in about one hour. Bornyl chloride is surprisingly stable in this respect.

In general, the catalyzed reactions are very much faster than the uncatalyzed ones. The reaction probably comes to an end while the reaction mixtures are allowed to warm from +5° to room temperature; they are certainly complete before the end of the first hour during which the mixture is kept at the boiling point of ether.[3]

This enhanced reactivity in the presence of

The non-dimerization of the simple free alkyl radicals which do not possess sufficient energy to react with the solvent, and the dimerization of the free alicyclic, benzyl and substituted benzyl radicals, supports the hypothesis previously submitted.[5b] In this connection, it is important to note that, although resonance stability in the free radical is important insofar as the tendency to dimerize is concerned, the dimerization of free alicyclic radicals and other radicals in which resonance (as currently interpreted) plays only a minor part must have a different origin. The facts cited are compatible, however, with the view that only free radicals derived from weakly electro-

(2) Bredt and Hibbing, *J. prakt. Chem.*, **84**, 783 (1911).
(3) Kharasch and Fields, THIS JOURNAL, **63**, 2316 (1941).
(4) A detailed mechanism for the dimerization of free radicals in solution will be discussed in a future publication.
(5) For previous references see (a) Kharasch, Reinmuth and Mayo, *J. Chem. Ed.*, **13**, 7 (1936); (b) Kharasch and Kleiman, THIS JOURNAL, **65**, 491 (1943).

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negative radicals dimerize, and that the free benzyl or substituted benzyl radicals, which stabilize themselves through resonance, are members of a larger class of free radicals derived from weakly electronegative radicals, in many of which resonance plays only a very minor part. In other words, other things being equal, resonance is a sufficient but not a necessary condition for dimerization.

Experimental

Reagents.—Dow methyl bromide and Mallinckrodt magnesium turnings were used in the preparation of the Grignard reagent. The Grignard reagent was made by the method of Kharasch and Kleiman,[5b] filtered through a sintered glass disk, and titrated for basicity and halogen content immediately before use.

Anhydrous cobaltous chloride was prepared by heating the hydrated salt at 150° *in vacuo*.

The bornyl chloride was prepared according to the directions of Fisher.[6] The pinene used was first distilled over sodium; the fraction boiling between 153° and 156° was used in the preparation.

Isobornyl chloride was prepared from camphene (m. p. 41.2–41.6°) according to the directions of Meerwein and Van Emster.[7] Cyclohexyl and 2-methylcyclohexyl chloride (*cis*) were prepared according to the directions of Zelinski.[8] *trans*-2-Methylcyclohexyl chloride was prepared according to the method given for menthyl chloride by Cumming, Hopper and Wheeler.[9]

Analysis.—The reaction products from the bornyl and isobornyl chloride experiments were analyzed by the method of Hesse.[10] The amount of bibornyl was determined by distilling the ether from an aliquot portion of the ether extracts. The residue was heated on a steam-bath. A stream of air was blown over the warm material until the loss in weight per hour came to a small constant value. The weight of the remaining residue corrected for the known loss was taken as the weight of the bibornyl. In the analysis for camphene, ether from another aliquot portion was removed by fractional distillation through a 37-centimeter column filled with single-turn glass helices. The last of the ether was removed *in vacuo* while the residue was maintained at −18°. The camphene was converted to the ester according to the directions of Bertram and Walbaum.[11] The ester and mixed terpenes were dissolved in ether; the solution was washed with water and with sodium carbonate. The ether was removed as before. The saponification equivalent of the mixture was determined by the method of Shriner and Fuson.[12] The formation of the ester and the saponification were conducted in a closed flask to avoid loss of the highly volatile camphene and ester. Corrections, determined by blank runs, were made for hydrogen chloride removed from the bornyl and isobornyl chlorides during the saponification, and for losses due to the volatility of camphene. The amount of camphane was determined by difference.

Bibornyl and camphane were identified by their melting points (88–90° and 150°, respectively). Camphene was identified by conversion to the *p*-nitrobenzoyl ester of isoborneol (long needles, m. p. 133°). The melting point of this material was not lowered by admixture with a known sample of isobornyl *p*-nitrobenzoate.

In the reaction with cyclohexyl chloride and the 2-methylcyclohexyl chlorides, the products were separated by fractional distillation in a 12-plate concentric tube column.

The product of the reaction between cyclohexyl chloride and methylmagnesium bromide in the presence of cobaltous chloride was distilled and three fractions collected: (1) b. p. 81–84°, a mixture of cyclohexene and cyclohexane; (2) b. p. 83° at 110 mm., unreacted cyclohexyl chloride; and (3) b. p. 68° at 2 mm., bicyclohexyl. The product of the reaction between 2-methylcyclohexyl chloride and methylmagnesium bromide in the presence of cobaltous chloride was distilled and three fractions collected: (1) b. p. 63.5 to 67.5° at 140 mm.; b. p. 101–104° at 760 mm. (a mixture of methylcyclohexene and methylcyclohexane); (2) b. p. 101–102° at 133 mm. (unreacted 2-methylcyclohexyl chloride); (3) b. p. 104–106° at 3 mm. (2,2′-dimethylbicyclohexyl). The amounts of unsaturation in the cyclohexene–cyclohexane and methylcyclohexane–methylcyclohexene fractions were determined by bromide–bromate titration.[13]

The gas analyses were made according to the procedure of Kharasch, Lewis and Reynolds.[1] The gas collected was in all cases approximately 70% of the amount calculated from the amount of reaction determined by Volhard titration.

Summary

1. The reactions of some alicyclic chlorides with methylmagnesium bromide in the presence and in the absence of cobaltous chloride have been studied.

2. The significance of the formation of the dimers in the presence of cobaltous chloride is discussed.

CHICAGO, ILLINOIS RECEIVED SEPTEMBER 17, 1943

(6) Fisher, "Laboratory Manual of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1920, p. 198.

(7) Meerwein and Van Emster, *Ber.* **55**, 2526 (1922).

(8) Zelinski, *ibid.*, **41**, 2679 (1908).

(9) Cumming, Hopper and Wheeler, "Systematic Organic Chemistry," Arnold Constable, London, 1937, p. 335.

(10) Hesse, *Ber.*, **39**, 1132 (1906).

(11) Bertram and Walbaum, *J. prakt. Chem.*, **49**, 8 (1894).

(12) Shriner and Fuson, "Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, 1941, p. 117.

(13) "Scott's Standard Methods of Analysis," N. H. Furman, Ed., Vol. II, D. Van Nostrand Co., New York, N. Y., 1939, p. 2253.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

Factors Determining the Course and Mechanisms of Grignard Reactions. XIII. The Effect of Metallic Halides on the Reaction of Sterically Hindered Acid Halides with Methylmagnesium Iodide

BY M. S. KHARASCH, R. MORRISON AND W. H. URRY

Introduction

The usual products of the reaction between acid halides and Grignard reagents are ketones and tertiary alcohols. However, highly significant observations on the reaction of tri-substituted benzoyl halides and Grignard reagents show that the reaction may take a different course. Thus, Fuson and Corse[1] found that, when 2,4,6-trimethyl- or triethylbenzoyl chloride was added to an ether solution of methylmagnesium iodide, only the monoketone (1) was formed. However, when the order of addition was reversed, the reaction product was a mixture consisting of 35% of the expected ketone (I) and 38% of the substituted benzil (II). Fuson and Corse[1] represent the mechanism of these reactions as follows

$$R_3C_6H_2COCl + CH_3MgI \longrightarrow \underset{(I)}{R_3C_6H_2COCH_3} + MgICl \quad (A)$$

$$2R_3C_6H_2COCl + 2CH_3MgI \longrightarrow \underset{(II)}{(R_3C_6H_2CO-)_2} + C_2H_6[2] + 2MgICl \quad (B)$$

Because of the uniqueness of the reaction (B), and because of our finding that methylmagnesium bromide does not undergo this reaction, a thorough investigation of the reaction of 2,4,6-trimethylbenzoyl (mesitoyl (β-isodurylyl)) chloride with Grignard reagents was undertaken.

Factors Influencing the Reaction of Mesitoyl Chloride with Grignard Reagents.—The effects of the following experimental conditions on the products formed in the reaction of mesitoyl chloride with Grignard reagents were thoroughly investigated: (a) the order of addition of the reagents; (b) the purity of the magnesium, and the age of the Grignard reagent; (c) the effect of the halides of iron, copper and manganese; (d) the effect of the halogen atom in CH_3MgX; (e) the effect of cobaltous chloride.

(a) As already demonstrated by Fuson and Corse,[1] the order of addition of the reagents plays an extremely important part in the reaction between methylmagnesium iodide and mesitoyl chloride. Our results (K, M and U), as well as those of Fuson and Corse (F and C) are given in Table I. The somewhat larger yield of the substituted benzil (II) obtained by us is readily accounted for by the findings presented under headings (c) and (d) (*q. v.*). The 50% yield of the substituted benzil (II) is a mean of sixteen experiments carried out in the dark and in the light; in the presence and in the absence of air. The average deviation in these experiments was about ±2%.

TABLE I

EFFECT OF THE ORDER OF ADDITION OF REAGENTS ON THE REACTION OF MESITOYL CHLORIDE AND METHYLMAGNESIUM IODIDE

Conditions	% Yield based on acid chloride used: Ketone F and C	Ketone K, M and U	Substituted benzil F and C	Substituted benzil K, M and U
Grignard added to acid chloride	35	25	39	50
Acid chloride added to Grignard	86	83	0	0

(b) Because of the known effects of traces of metallic halides on the course of Grignard reactions,[3] the reaction of mesitoyl chloride with methylmagnesium iodide prepared both from Dow sublimed magnesium and from Mallinckrodt magnesium was investigated. Considerable variations in the yield of the substituted benzil (II) were at once apparent; it also became equally clear that the difference tended to disappear when the Grignard reagent prepared from the Mallinckrodt magnesium was aged by allowing it to stand before use. No such aging effect was noted with Grignard reagent prepared from Dow magnesium. It is significant that the highest yield of (II) prepared from Mallinckrodt magnesium is about equal to the yield of this substance obtained from Grignard reagent of any age prepared from Dow magnesium. The observations are summarized in Table II.

TABLE II

EFFECT OF AGE OF GRIGNARD REAGENT AND PURITY OF MAGNESIUM ON THE REACTION BETWEEN MESITOYL CHLORIDE AND METHYLMAGNESIUM IODIDE

Magnesium used	Age of Grignard	% Yield based on acid chloride: Ketone	Benzil
Mallinckrodt	1 hour	40	31
Mallinckrodt	1 day	35	38
Mallinckrodt	30 days	18	54
Dow	1 hour	25	50
Dow	14 days	26	52

(c) It was suspected that the differences observed with the various magnesiums might be due to metallic impurities. It has been shown[4] that

(1) Fuson and Corse, THIS JOURNAL, **60**, 2063 (1938).

(2) The formation of ethane in reaction (B) was not demonstrated experimentally by Fuson and Corse. This product was probably assumed because of the similarity of the reaction with that of the benzyl halides on methylmagnesium iodide; in this latter reaction, bibenzyl and ethane are formed in equivalent amounts (Fuson, THIS JOURNAL, **48**, 2681 (1926)).

(3) For previous references, see Kharasch and Fuchs, THIS JOURNAL, **65**, 504 (1943).

(4) Kharasch, Kleiger, Martin and Mayo, *ibid.*, **63**, 2305 (1941).

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Dow sublimed magnesium is practically free of all heavy metals, except for 0.01% of lead; Mallinckrodt magnesium, on the other hand, contains 0.05–0.10% Mn, 0.01% Cu, 0.01% Sn and 0.01% Fe. In support of this hypothesis, we find that the addition of a little copper, manganese or iron halide to the Grignard reagent tends to increase the amount of the ketone (I) at the expense of the substituted benzil (II). The observations are summarized in Table III.

TABLE III

EFFECT OF METALLIC HALIDES ON THE REACTION BETWEEN MESITOYL CHLORIDE AND METHYLMAGNESIUM IODIDE

Metallic halide 1 mole %	% Yield based on acid chloride Ketone	Benzil
None	26	52
$MnCl_2$	88	1
$MnCl_2$ (0.1 mole %)	75	5
$FeCl_3$	85	7
Cu_2Cl_2	85	2
Cu[a]	45	30

[a] Grignard reagent prepared from a mixture of Dow magnesium and copper–magnesium alloy.

(d) and (e): in an attempt to find an explanation for the observations recorded in (a), (b) and (c), we examined the reaction of methylmagnesium bromide with mesitoyl chloride. Here, even under the optimum conditions (use of Dow magnesium, etc.), only traces of the substituted benzil (II) were obtained. Methylmagnesium chloride would doubtless act like the bromide. The formation of substituted benzil (II) from mesitoyl chloride is, therefore, specific for the iodide Grignard reagent. However, in the presence of a little cobaltous chloride, methylmagnesium bromide gives a fair (but probably not the optimum) yield of (II). These results are given in Table IV.

TABLE IV

EFFECT OF THE HALIDE OF THE GRIGNARD IN THE REACTION WITH MESITOYL CHLORIDE

Grignard reagent[a]	% Yield based on acid chloride Ketone	Substituted benzil
CH_3MgI	25	50
CH_3MgBr	87	1
$CH_3MgBr + CoCl_2$	35	31[b]
$CH_3MgI + CoCl_2$	17	63

[a] In each of these reactions, the Grignard was added to the acid chloride. [b] The lower total yield of known products is accounted for by the formation of an unidentified tarry material.

The fact that mesitoyl chloride forms a substituted benzil (II) when treated with (1) methylmagnesium iodide or with (2) methylmagnesium bromide and cobaltous chloride[5] but does not form such a benzil when treated with (3) methylmagnesium bromide alone suggests a common mechanism for the reactions with (1) and (2).

(5) Phenylmagnesium bromide reacts with mesitoyl chloride in the presence of cobaltous chloride to give 4% of the substituted benzil (II), 41% of phenyl mesityl ketone and 21% of *sym*-diphenyldimesitylpinacol.

In the reaction with (2), there is abundant evidence that the Grignard reagent exercises its reducing action on the acid chloride by first forming the cobalt subhalide (CoCl), which acts as a chain carrier. The essential features of the postulated mechanism are as follows

(1) $CH_3MgBr + CoCl_2 \longrightarrow CH_3CoCl + MgBrCl$
(2) $CH_3CoCl \longrightarrow CH_3\cdot + \cdot COCl$
(3) $RCOCl + CoCl\cdot \longrightarrow RCO\cdot + COCl_2$
(4) $2RCO\cdot \longrightarrow RCOCOR$
(5) $CH_3\cdot + C_2H_5O\text{-}C_2H_5 \xrightarrow{\text{gas}} CH_4\ (80\%) + C_2H_6\ (10\%) + C_2H_4\ (10\%)$

It seems probable, therefore, that, where methylmagnesium iodide is used, a similar free radical must operate, although no chain reaction is required to account for the result. It is assumed that methylmagnesium iodide can react in two ways

(6) $CH_3MgI \longrightarrow CH_3^- + (MgI)^+$
(7) $CH_3MgI \longrightarrow CH_3\cdot + MgI\cdot$

The active reagents, insofar as the reaction with mesitoyl chloride is concerned, are, therefore, similar; where methylmagnesium bromide and cobaltous chloride are used, cobaltous subhalide is the reducing agent; where methylmagnesium iodide is used, the reducer is magnesious iodide.[6] This assumption, however, requires similarity in gaseous products of the reaction. Here there appeared at first to be a disagreement with experiment, for Fuson and Corse[1] (see Introduction) in writing the over-all reaction indicated that ethane is the exclusive gaseous product of the reaction (B). However, our experience has shown that whenever methyl radicals are formed in ether solution, the gas evolved consists, within ±5%, of about 80% methane,[7] 10% ethane and 10% ethylene. The latter gases are presumably formed in the cleavage of the ether molecule by the free methyl radicals. The gas evolved during the addition of the mixture of methylmagnesium bromide plus cobaltous chloride (5 mole per cent.) to the mesitoyl chloride is a mixture of methane (74%), ethane (16%) and ethylene (10%).[8] The molecular weight of the gas resulting from the interaction of methylmagnesium iodide with mesitoyl chloride is 18.0. This figure corresponds to a mixture containing 85% of methane and 15% of the heavier gases (ethane and ethylene).

(6) The observation of Fuson and Corse (THIS JOURNAL, 61, 975 (1939)) that a mixture of magnesium and magnesium iodide reduces diortho-substituted acid halides as well as diortho-substituted diketones to enediols may be looked upon as further support of this hypothesis.

(7) The somewhat lower figure given for methane (62%) and higher figures for ethane (18%) and ethylene (20%) given by Kharasch, Lewis and Reynolds (THIS JOURNAL, 65, 493 (1943)) were probably due to small losses of methane during the evacuation of the vessel. Our recent improved technique eliminates this slight error in the analyses.

(8) The gas evolved, when addition of the Grignard reagent has been completed and the reaction vessel is allowed to warm to room temperature, is almost pure methane. This gas is probably formed in the reaction between the ketone (I) and the Grignard reagent, a reaction known to take place slowly in the cold (Kohler, Stone and Fuson, THIS JOURNAL, 49, 3181 (1927)).

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Evidently, if the reaction proceeds as outlined by Fuson and Corse,[1]

$$2RCOCl + 2CH_3MgI \longrightarrow RCOCOR + C_2H_6 + 2MgClI$$

the amount of ethane is too small and the amount of methane is too large to be strictly accounted for by enolization of the ketone. The amount of methane, however, is compatible with the hypothesis that free methyl radicals are formed (*cf.* equations (1) to (5)). On the other hand, another difficulty presents itself. The 15% of the heavier gas is not a mixture of equal parts of ethane and ethylene, but is almost pure ethane. Two explanations for this fact suggest themselves. In the first place, if 12% of the reaction proceeds according to the mechanism of Fuson and Corse[1] and 88% according to the mechanism suggested in reaction (7) and reactions (1) to (5), then the gas should contain only about 3% of ethylene, a quantity which we may have overlooked because of difficulties in the analytical procedure. Secondly, free methyl radicals in the presence of such reactive molecules as methylmagnesium iodide may react in a manner different from that indicated in equation (5). Thus, although removal of the hydrogen atom from the ether molecule may still be the dominant reaction (80–85%), the secondary cleavage of the ether molecule (15%), because of the stability of the magnesious iodide, may be outstripped by the faster reaction with the Grignard reagent.

$$CH_3\cdot + CH_3{:}MgI \longrightarrow C_2H_6 + MgI\cdot$$

Of the two alternative explanations, we prefer the latter, since it not only reconciles the facts recorded in this paper, but also explains observations which we hope to report in the near future.

Methylmagnesium iodide thus can react by either an ionic or a free-radical mechanism. The former is apparently much the faster of the two. The free-radical mechanism comes into play only where substances which can be reduced by magnesious iodide are present, and where the normal reaction of the Grignard reagent with the organic molecule is comparatively slow. High dilution of both components, and particularly of the Grignard reagent should, therefore, favor the free-radical reactions of the alkyl magnesium iodides.[9]

Experimental Details

Materials.—Mallinckrodt magnesium turnings or Dow sublimed magnesium was used. Methyl bromide was obtained from the Dow Chemical Company; bromobenzene from the Eastman Kodak Company. The bromobenzene was carefully fractionated before use. The methyl iodide was Mallinckrodt reagent grade. It was carefully distilled before use and was free from traces of iodine. The cuprous chloride was the usual anhydrous reagent. Anhydrous cobaltous and manganous chlorides were prepared from the hydrates by heating *in vacuo:* the former was heated to 150°, and the latter to 200°. Anhydrous ferric chloride was prepared from pure iron wire and chlorine.

Preparation of Grignard Reagents.—The Grignard reagents were prepared in a three-neck flask equipped with a mercury-sealed stirrer, reflux condenser, dropping funnel, and (in the case of the methylmagnesium bromide) an inlet tube extending nearly to the bottom of the flask. The apparatus was flushed with dry nitrogen and flamed before use.

Bromobenzene, diluted with enough dry ether to give a two-molar solution, was added to an excess of magnesium covered with a small amount of ether; the rate of addition was such that refluxing was maintained. After all the halide had been added, the mixture was refluxed for about an hour to insure completion of the reaction, and then filtered under nitrogen pressure through a coarse sintered glass filter. The reagent was stored under nitrogen in a brown bottle, and was titrated just before use.

Methylmagnesium iodide was prepared in a similar manner. The filtered Grignard reagent was always clear; where Dow magnesium was used, the liquid was water white.

The methyl bromide gas was bubbled into the flask containing excess magnesium and part of the ether at such a rate as to maintain refluxing. Portions of ether were added from time to time so that the final concentration was about two-molar. The Grignard reagent was refluxed, filtered, and stored as indicated previously.

Reaction of Phenylmagnesium Bromide with Mesitoyl Chloride.—The mesitoyl chloride (b. p. 86–88° at 4 mm.) was prepared from mesitoic acid according to the directions of Fuson, Corse and McKeever.[10]

Cobaltous chloride (0.01 mole) was added to phenylmagnesium bromide (0.28 mole in 330 ml. of ether) contained in a three-neck flask equipped with a mercury-sealed stirrer, reflux condenser, and dropping funnel. The flask was cooled in an ice-bath. The resulting black mixture was siphoned under nitrogen pressure into the dropping funnel and added slowly to a second three-neck flask equipped like the first, and containing 0.10 mole of mesitoyl chloride and 0.01 mole of $CoCl_2$ in 330 ml. of dry ether; the second flask was kept cool in an ice-bath. The addition was complete in ninety minutes. The mixture was stirred for thirty minutes longer at room temperature, and then allowed to stand overnight.

The product was decomposed with ice and hydrochloric acid, the ether layer separated, and the water layer extracted twice with ether. The combined ether layers were washed first with sodium bicarbonate, then with water, and finally dried over sodium sulfate. The ether was removed and the residue was steam distilled. From the distillate there was obtained a solid (4.3 g.) which, after crystallization from alcohol, melted at 66–68°. This substance was identified as biphenyl by its melting point and by the fact that it did not depress the melting point of an authentic sample of biphenyl.

After the steam distillation, the residue remaining in the flask was poured into ethyl alcohol; a light yellow solid separated (wt. 4.7 g., m. p. 228–232°). This substance, After several crystallizations from benzene and sublimation under high vacuum, yielded a white solid (m. p. 237–238°).

Anal. Calcd. for $C_{32}H_{34}O_2$: C, 85.33; H, 7.55. Found: C, 84 97; H, 7.37.

This material did not depress the melting point of *sym* diphenyldimesitylpinacol prepared by another method The yield of pure material was 21% based on the acid chloride used.

The alcohol was removed from the filtrate and the residue distilled at 1 mm. pressure. A colorless liquid which boiled at 130–140° was collected. This substance was identified as 2,4,6-trimethylbenzophenone; the yield was 41% based on the acid chloride used.

The residue remaining in the flask was a black tar. From this tar, a yellow solid (0.5 g., m. p. 119–120°) was obtained by sublimation in high vacuum. This substance was identical with the hexamethylbenzil obtained by re-

(9) The tendency of the Grignard reagent to dissociate into magnesious iodide and an organic free radical should increase with the decreasing electronegativity of the organic radical (*cf.* Kharasch and Weinhouse, *J. Org. Chem.*, 1, 209 (1936)).

(10) Fuson, Corse and McKeever, THIS JOURNAL, 61, 2010 (1939).

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action of methylmagnesium iodide with mesitoyl chloride. The yield of this material was 4% based on the acid chloride used. The material which could not be sublimed weighed 3 g.

When phenylmagnesium bromide was added to mesitoyl chloride (in the absence of cobaltous chloride), only 2,4,6-trimethylbenzophenone was isolated. The yield was 90%, based on the acid chloride used.

Reactions of Methylmagnesium Bromide and Mesitoyl Chloride in the Presence of Cobaltous Chloride.—The procedure was similar to that previously described, except that the Grignard reagent was mixed with the catalyst in a flask cooled in an ice-salt bath, and the dropping funnel into which the mixture was siphoned was equipped with a cold-finger filled with a mixture of ice and salt. Mesitoyl chloride (0.06 mole), methylmagnesium bromide (0.15 mole) and cobaltous chloride (0.0075 mole) were used. The reaction mixture was worked up in the usual manner. The quantities of the products formed are recorded in Table IV.

A total of 1700 cc. (corrected to standard) of gas was collected. The first 500 cc. of this gas was rejected. The molecular weight of the gas contained in the second 500 cc. was 19.4, and the unsaturation amounted to 10%. The gas analyses were made by the method of Kharasch, Lewis and Reynolds.[7]

When methylmagnesium bromide was added to mesitoyl chloride in the absence of cobaltous chloride, an 87% yield of 2,4,6-methylmesityl ketone was obtained; there was only a trace of the substituted benzil.

Reaction of Methylmagnesium Iodide and Mesitoyl Chloride.—In all experiments with these reagents, the concentrations and proportions of reactants, as well as the rate of addition and the manner of working up the products, were the same as previously described. The isolation procedure was similar to that of Fuson and Corse. The results of the experiments are given in Tables I, II, III and IV.

In the experiments in which metallic halides were used, the metal halide was usually added to the Grignard reagent; the resulting mixture was added to the mesitoyl chloride dissolved in ether. In the cobaltous, copper and iron chloride experiments, the Grignard reagent turned almost black; when manganous chloride was used, the solution remained clear and colorless.

Summary

1. In the reaction between mesitoyl chloride and methylmagnesium iodide it has been shown that: (a) the order of addition of the reactants is important; (b) light and small amounts of oxygen have no effect upon the reaction; (c) the use of pure magnesium in making the Grignard reagent and aging of the reagent made from ordinary magnesium give higher yields of 2,4,6,2′,4′,6′-hexamethylbenzil; (d) traces of the halides of iron, copper, and manganese limit the reaction to the normal addition; (e) small amounts of cobaltous chloride increase the yield of the substituted benzil, as is also the case when methylmagnesium bromide is used.

2. A mechanism has been proposed to account for the products of the reaction of mesitoyl chloride with Grignard reagents.

CHICAGO, ILLINOIS RECEIVED SEPTEMBER 17, 1943

[CONTRIBUTION FROM THE CENTRAL RESEARCH LABORATORIES OF THE MONSANTO CHEMICAL COMPANY]

Unsaturated Esters of Glycolonitrile

BY DAVID T. MOWRY

In aqueous solution a mixture of formaldehyde and sodium cyanide reacts like glycolonitrile and sodium hydroxide.

$$CH_2O + NaCN + H_2O \rightleftharpoons HOCH_2CN + NaOH$$

With benzoyl chloride a typical Schotten–Baumann reaction occurs to give cyanomethyl benzoate[1] in 45% yields.

$$C_6H_5COCl + HOCH_2CN + NaOH \longrightarrow C_6H_5COOCH_2CN + NaCl + H_2O$$

In extending this reaction we have found that good yields (53–73%) of cyanomethyl esters of α,β-unsaturated acids can be obtained from the corresponding acid chlorides. Acrylyl chloride, however, gives poor yields because of a side reaction leading to the formation of an ester, $C_6H_9O_3N$, the structure of which has not yet been established. Furthermore, dibasic acid chlorides, such as fumaryl chloride, give only insignificant yields of diesters by the aqueous method. These esters are satisfactorily prepared by the method of Hechenbleikner[2] in which the acid chloride is treated with glycolonitrile in anhydrous ether in the presence of a tertiary amine.

Inasmuch as it has been observed[3] that acetyl chloride gives low yields in the Schotten–Baumann reaction, it is not surprising that the method is of little value for the preparation of cyanomethyl esters of saturated aliphatic acids. A better procedure appears to be the reaction of the sodium salt of the acid with chloroacetonitrile.[4] The properties of the unsaturated esters are reported in Table I.

Experimental

Reagents.—The methacrylyl, crotonyl, cinnamoyl and α-methylcinnamoyl chlorides were prepared by the action of thionyl chloride on the acids. Acrylyl chloride was prepared in 27% yields by the action of phosphorus oxychloride on sodium acrylate[5] and in 35% yield by dehydrohalogenation[6] of β-chloropropionyl chloride over alumina at 250°. β-Chlorocrotonyl chloride was obtained from ethyl acetoacetate and phosphorus pentachloride.[7] Fu-

(1) Aloy and Rabaut, *Bull. soc. chim.*, [4] **13**, 457 (1913).

(2) Hechenbleikner, U. S. Patents 2,266,199 (1941), 2,307,649 (1943).

(3) Menalda, *Rec. trav. chim.*, **49**, 967 (1930).

(4) Henry, *Bull. soc. chim.*, [2] **46**, 42 (1886); *Rec. trav. chim.*, **24**, 170 (1905).

(5) Moureu, *Ann. chim.*, [7] **2**, 145 (1894).

(6) Fikentsher, U. S. Patent 2,050,752 (1936).

(7) Shringer and Keyser, THIS JOURNAL, **60**, 286 (1938).

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Table I

Cyanomethyl ester of	Method	Yield, %	B. p. °C.	B. p. Mm.	M. p., °C.	$n^{25}D$	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Acrylic acid	A	17	60	4	..	1.4331	54.05	53.75	4.54	4.87	12.62	12.57
Methacrylic acid	A	58	90–91	10	..	1.4390	57.60	57.66	5.64	5.66	11.20	11.38
Crotonic acid	A	60	103–104	17	..	1.4482	57.60	57.81	5.64	5.90	11.20	11.38
β-Chlorocrotonic acid	A	53	116	16	..	1.4797	45.15	45.37	3.78	3.87	8.98	8.64
Cinnamic acid	A	73	164–165	4	63	....	70.57	70.69	4.84	4.75	7.48	7.63
	B	75										
α-Methylcinnamic acid	A	63	162–163	3	..	1.5669	71.62	72.36	5.52	5.73	6.96	6.87
Fumaric acid	B	45	.....	..	83	....	49.50	49.68	3.11	3.02	14.43	14.38
Mesaconic acid[a]	B	43	192–193	3	..	1.4815	51.92	52.50	3.87	3.98	13.46	13.42

[a] Prepared by Dr. W. Frederick Huber.

maryl and mesaconyl chlorides were made from maleic anhydride and phthalyl chloride.[8]

Glycolonitrile.—A modification of the cyanohydrin interchange method[9] was used for the preparation of glycolonitrile.

To a concentrated aqueous solution of 1040 g. of sodium bisulfite was added 720 g. (10.0 moles) of methyl ethyl ketone with stirring and cooling by addition of ice. A solution of 520 g. of 95% sodium cyanide was then added in a similar manner. The resultant supernatant oil was separated and mixed with 871 g. of 37% formalin, to which 5 g. of sodium cyanide had been added. After this solution had been stirred at 35° for two hours, 30 g. of phthalic anhydride was added and the material distilled. The regenerated ketone and water were removed at 100 mm. The product was then rapidly distilled at 20–30 mm. (slight decomposition), b. p. 100–120°. When the distillation was about two-thirds completed, the residue became very viscous. The flame had to be removed and the flask cooled immediately to avoid violent dissociation and polymerization caused by superheating. The crude product was refractionated without decomposition over 5 g. of phthalic anhydride, giving 228 g. (40% yield) of glycolonitrile, b. p. 99–100° (17 mm.), $n^{25}D$ 1.4090.

Cyanomethyl Acrylate (Method A).—Acrylyl chloride (233 g., 2.6 moles) was added dropwise to a briskly stirred solution of 236 cc. (2.7 moles) of 37% formalin and 154 g. (2.9 moles) of 95% sodium cyanide in 300 cc. of water at 10°.

Stirring was continued for one hour after addition was complete, while the solution was allowed to rise to room temperature. The supernatant oil was taken up in several volumes of ether, washed with dilute solutions of sodium carbonate and hydrochloric acid. Distillation over hydroquinone of the dried ether solution gave 46 g. (17%) of cyanomethyl acrylate, b. p. 42–43° (1 mm.), and 50 g. of a compound, $C_6H_9O_3N$, b. p. 82–83° (1 mm.), $n^{25}D$ 1.4248, which did not decolorize a carbon tetrachloride solution of bromine.

Anal. Calcd. for $C_6H_9O_3N$: C, 50.36; H, 6.34; N, 9.79. Found: C, 50.74; H, 6.27; N, 9.94.

Solid acid chlorides such as cinnamoyl chloride were dissolved in dioxane to facilitate dropwise addition to the aqeuous solution.

Cyanomethyl Cinnamate (Method B).—Glycolonitrile (28.5 g., 0.5 mole) was added slowly with stirring to a solution of 86 g. of cinnamoyl chloride (0.5 mole) and 60 g. of dimethylaniline (0.5 mole) in 100 cc. of anhydrous ether at 5–10°. The solution was allowed to warm to room temperature and stirred for two hours before dilution with two volumes of ether and washing with dilute solutions of sodium carbonate and hydrochloric acid. Evaporation of the ether gave 72 g. (75%) of crude cyanomethyl cinnamate, m. p. 57–60°. Three recrystallizations from dilute ethanol gave large colorless plates, m. p. 62.7–63.0°.

(8) Kyrides, This Journal, **59**, 207 (1937).

(9) Kung, U. S. Patent 2,259,167 (1941).

Summary

The reaction of an aqueous solution of sodium cyanide and formaldehyde with benzoyl chloride has been extended to the acid chlorides of monobasic α,β-unsaturated acids. The cyanomethyl esters of acrylic, methacrylic, crotonic, β-chlorocrotonic, cinnamic, α-methylcinnamic, fumaric and mesaconic acids are reported.

Dayton, Ohio Received November 26, 1943

[Contribution from the Department of Chemistry, University of Washington]

The Condensation of Isobutyraldehyde with Aliphatic Ketones

By S. G. Powell and French Hagemann[1]

It has been shown that certain straight chain aliphatic aldehydes condense with methyl ethyl ketone through the methylene group of the ketone,[2] whereas homologous methyl ketones which contain six or more carbon atoms appear to condense through the methyl group.[3] On the other hand, the condensation of α-methylbutyraldehyde, α-ethylbutyraldehyde and α-ethylcaproaldehyde with various methyl ketones has been found to take place through the methyl group.[4]

The same alkaline condensing agents which bring about the above-mentioned reactions with aliphatic aldehydes cause aromatic aldehydes to react with the methyl group of the ketone, while acids bring about condensation with the methyl-

(1) From the Ph.D. dissertation of French Hagemann.

(2) (a) Powell, *et al.*, This Journal, **46**, 2514 (1924); **55**, 1153 (1933); (b) Salkind, *J. Russ. Phys.-Chem. Soc.*, **37**, 484 (1905); (c) Merling and Köhler, U. S. Patent 981,668 (1901).

(3) Wickert and Freure, U. S. Patent 2,088,018 (1937), British Patent 461,662 (1937).

(4) (a) Powell and Baldwin, This Journal, **58**, 1871 (1936); (b) Wickert and Carter, U. S. Patent 2,088,017 (1937); (c) Carbide and Carbon Chemicals Corp., French Patent 782,835 (1935); (d) Ref. (3).

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ene group.[5] No similar behavior seems to have been observed in the case of aliphatic aldehydes.

The course of the reaction between the simplest *alpha*-branched chain aldehyde, isobutyraldehyde and unsymmetrical methyl ketones has been established only in the case of methyl ethyl ketone, which Thoms and Kahre[6] found to condense through the methyl group. Therefore, it seemed desirable to investigate the reaction of isobutyraldehyde with other ketones.

Isobutyraldehyde was condensed with methyl *n*-propyl, methyl *n*-butyl, methyl isobutyl, methyl *n*-amyl and methyl *n*-hexyl ketones in the presence of dilute potassium hydroxide and the resulting ketol was dehydrated to the unsaturated ketone. The structure of the unsaturated ketone was determined by ozonolysis, and in each case the condensation was found to take place upon the methyl carbon atom. By repeated fractionation of the crude unsaturated ketone resulting from the reaction between isobutyraldehyde and methyl *n*-amyl ketone there was obtained a small fraction which consisted chiefly of the compound formed by methylene condensation. It is possible that similar small quantities of the methylene isomer may have formed in the other condensations.

When the ozonides were decomposed, the expected 1,2-dicarbonyl compounds were oxidized by the hydrogen peroxide to mixtures of acids which were identified.

$$(CH_3)_2CHCH{=}CHCOCH_2R = (CH_3)_2CHCHO + RCH_2COCHO + H_2O_2$$
$$RCH_2COCHO + H_2O_2 = RCH_2COOH + HCOOH$$

In the neutral fraction of the decomposition products, in addition to isobutyraldehyde, appreciable amounts of acetone and acetone peroxide were identified. The last two substances must have been formed by oxidation of the isobutyraldehyde by the hydrogen peroxide.

Further proof of the structure of the unsaturated ketones in the case of methyl *n*-amyl and methyl *n*-hexyl ketones was obtained by reducing them to the corresponding saturated ketones and oxidizing the latter to a mixture of acids which were identified. Also, the saturated ketone from the methyl *n*-amyl ketone condensation was found to be identical with *n*-amyl isoamyl ketone prepared by another method.

Thoms and Kahre gave the structure of the condensation product of di-ethyl ketone and isobutyraldehyde as $(CH_3)_2CHCH{=}CHCH_2COCH_2CH_3$, whereas Franke and Köhler[7] gave the structure as $(CH_3)_2CHCH{=}C(CH_3)COCH_2CH_3$. As no proof of structure was given in either case, this work was repeated. The unsaturated ketone was ozonized and the ozonide decomposed in the presence of hydroxylamine. Since methylethylglyoxime was identified as a product, the correct structure is that given by Franke and Köhler.

It was not possible to reduce completely some of the unsaturated ketones to the saturated alcohols with sodium and alcohol or moist ether, even though a large excess of sodium was used. 2-Methyl-3-decen-5-one, 2-methyl-3-undecen-5-one and 2,7-dimethyl-5-octen-4-one yielded products which were still unsaturated, but which gave the saturated alcohols upon hydrogenation with platinum oxide catalyst.

In order to explain this behavior, 2-methyl-3-decen-5-one was treated with sodium and ethyl alcohol. The analysis and the molar refraction of the product agreed closely with that calculated for an unsaturated alcohol, $C_{11}H_{22}O$. Ozonolysis established its formula as $(CH_3)_2C{=}CHCH_2CHOHCH_2CH_2CH_2CH_2CH_3$. Acetone, but no isobutyraldehyde, and an aldehyde which appeared to be unsaturated were found as ozonolysis products. The semicarbazone of the latter compound was prepared and found to melt at 169–170° (cor.); van Romburgh[8] reported the melting point of the semicarbazone of α-octenaldehyde as 163°. Analysis of the compound corresponded to octenaldehyde semicarbazone. α-Octenaldehyde would result from the dehydration of β-hydroxycaprylaldehyde which would be the primary ozonolysis product of this alcohol. Apparently in the presence of the alkaline reduction medium the double bond shifts from the α-β to the β-γ position. In the latter position the ethylenic bond is very resistant to reduction by sodium and alcohol or water.

Experimental Part

The physical properties and analyses of the ketones and alcohols prepared in the course of this investigation are collected in Table I. The melting points and analyses of the new derivatives prepared are listed in Table II.

Condensations.—All of the condensations were carried out by the addition of a mixture of one mole proportion of aldehyde and one-half mole of ketone to two and one-half moles of ketone and excess alcoholic potassium hydroxide as previously described.[2a] The rate of addition was regulated so as to keep the temperature below 35°.

Dehydrations.—The ketols were dehydrated by slow distillation at atmospheric pressure in the presence of a small amount of iodine.[9] The distillate was separated from water and the distillation repeated with fresh iodine. Drying over anhydrous magnesium sulfate and fractionation gave the desired unsaturated ketone.

The crude unsaturated ketone from the methyl *n*-amyl ketone condensation was put through a 28-plate fractionating column at atmospheric pressure. From 246 g. were obtained the following fractions: up to 205°, 15 g.; 205–223°, 45 g.; 223–224°, 85 g. A large viscous residue of about 100 g. remained in the pot, due to decomposition and resinification during the long-continued heating at high temperature. Refractionation of the 205–223° portion gave 28 g. of material boiling from 208–218°, which upon redistillation at reduced pressure yielded 14.2 g. boiling at 103–105° (24.5 mm.). This material gave a very strong positive iodoform reaction,[10] whereas the 223–224° fraction gave a negative reaction.

(5) (a) Harries and Mueller, *Ber.*, **35**, 966, 3088 (1902); (b) Ryan and Cahill, *Proc. Roy. Irish Acad.*, **36B**, 334 (1924).

(6) Thoms and Kahre, *Arch. Pharm.*, **263**, 241 (1925).

(7) Franke and Köhler, *Ann.*, **433**, 314 (1923).

(8) Van Romburgh, *Rec. trav. chim.*, **57**, 494 (1938).

(9) Hibbert, THIS JOURNAL, **37**, 1748 (1915).

(10) Shriner and Fuson, "Identification of Organic Compound 2d ed., John Wiley and Sons, Inc., New York, N. Y., 1940, p. 53

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TABLE I

Compound	Yield, %	B. p. °C.; cor.	Mm.	d^{20}_4	$n^{20}D$	MD (obs.)	MD (calcd.)	Analyses, % Calcd. C	Calcd. H	Found C	Found H
7-Methyl-5-octen-4-one[a]	45	85–86	25	0.8520	1.4413	43.49	43.32[f]	77.08	11.50	76.96	11.73
2-Methyl-3-nonen-5-one	50	103–105	25	.8485	1.4438	48.27	47.94[f]	77.87	11.76	77.89	12.08
2,7-Dimethyl-5-octen-4-one	65	199–200	760	.8412	1.4399	48.31	47.94[f]	77.87	11.76	78.02	12.02
2-Methyl-3-decen-5-one	61	223–224	760	.8487	1.4457	52.84	52.58[f]	78.52	11.98	78.28	12.22
2-Methyl-3-undecen-5-one	35	135–136	28	.8502	1.4480	57.40	57.18[f]	79.06	12.16	78.77	12.44
4,6-Dimethyl-4-hepten-3-one[b]	49	176–178	760	.8499	1.4432	43.76	43.32[f]	77.08	11.50	76.77	11.68
7-Methyl-4-octanone[c]	62	177–179	760	.8239	1.4210	43.77	43.79	76.00	12.75	75.75	12.82
2-Methyl-5-nonanone	54	203–204	760	.8213	1.4239	48.54	48.41	76.86	12.90	76.78	13.14
2,7-Dimethyl-4-octanone	64	196–198	760	.8305	1.4280	48.41	48.41	76.86	12.90	76.76	12.65
2-Methyl-5-decanone	50	119–121	28	.8235	1.4279	53.19	53.03	77.58	13.02	77.48	13.25
2-Methyl-5-undecanone	47	126–128	23.5	.8268	1.4307	57.67	57.65	78.19	13.12	78.19	13.24
4,6-Dimethyl-3-heptanone[d]	57	170–173	760	.8208	1.4197	44.26	43.79	76.00	12.75	75.80	12.97
2-Methyl-5-nonanol	78	111.5–113	28.5	.8215	1.4310	49.89	49.92	75.88	14.01	75.98	14.09
2,7-Dimethyl-4-octanol[e]	68	107–108	29.5	.8183	1.4297	49.94	49.92	75.88	14.01	75.91	14.02
2-Methyl-5-decanol	42	122.5–123	24	.8266	1.4351	54.40	54.54	76.67	14.04	76.55	13.87
2-Methyl-5-undecanol	50	132–133	24	.8266	1.4346	58.76	59.16	77.35	14.07	77.65	13.77

[a] Thoms and Kahre, ref. (5), gave b. p. 68–78° (24 mm.); d^{12} 0.9011; n_D 1.47477. [b] Thoms and Kahre, ref. (6) gave b. p. 171–184° (760 mm.), 73–77° (19 mm.); d^{19} 0.8628; n_D 1.44533 for the unsaturated ketone which they considered to be 7-methyl-5-octen-3-one. Franke and Köhler, ref. (7), gave b. p., 178–183° (760 mm.), 66–69° (16 mm.) for the unsaturated ketone which they reported to be 4,6-dimethyl-4-hepten-3-one. [c] Blaise, *Compt. rend.*, **133**, 1217 (19 1), reported the b. p. as 176–178°, and Douris, *ibid.*, **157**, 55 (1913), gave b. p. 177–179°, d^{21}_4 0.8205; semicarbazone, m. p. 144.5–145.5°. *Anal.* Calcd. for $C_{10}H_{21}N_3O$: N, 21.08. Found: N, 21.05. Blaise gave 102° and Douris, 107° as the m. p. of the semicarbazone. [d] Thoms and Kahre, ref. (6), gave for the corresponding saturated ketone considered to be 7-methyl-3-octanone, b. p. 180–185°; d^{20}_{20} 0.8353; n_D 1.43479. [e] Tuot, *Compt. rend.*, **202**, 1339 (1936), gave b. p. 96° (18 mm.); d^{20}_{20} 0.8154; $n^{20}D$ 1.4280. [f] Calculated without exaltation for conjugation.

TABLE II

Hydantoin[a] of	M. p., °C. (cor.)	Analyses, % N Calcd.	Found
2-Methyl-3-nonen-5-one	149.5–150	12.49	12.65
2,7-Dimethyl-5-octen-4-one	176.5–177	12.49	12.52
2-Methyl-3-decen-5-one[f]	135–136	11.76	11.83
3-*n*-Butyl-5-methyl-3-hexen-2-one	175–176	11.76	11.65
2-Methyl-3-undecen-5-one	118.5–119	11.10	11.07
7-Methyl-4-octanone	175–175.5	13.20	13.14
2-Methyl-5-nonanone	192–192.5	12.38	12.39
2,7-Dimethyl-4-octanone	216–217	12.38	12.44
2-Methyl-5-decanone	192–192.5	11.66	11.70
2-Methyl-5-undecanone	175–175.5	11.02	11.02
4,6-Dimethyl-3-heptanone	186–186.5	13.20	13.23
Nitroguanylhydrazone[b] of			
2-Methyl-5-decanone	78–79.5 (d.)	25.81	25.97
2-Methyl-5-undecanone	84.5–86 (d.)	24.54	24.49
Semicarbazone[c] of			
2,7-Dimethyl-4-octanone	78–79	19.70	19.86
2,4-Dinitrophenylhydrazone[d] of			
4,6-Dimethyl-4-hepten-3-one	174–175	17.49	17.56
3,5-Dinitrobenzoate[e] of			
2-Methyl-5-nonanol	63.5–64.5	7.95	7.94
2,7-Dimethyl-4-octanol	81–82	7.95	8.10

[a] Ref. (11). [b] Whitmore, Revukas and Smith, THIS JOURNAL, 57, 706 (1935). [c] Ref. (10), p. 142. [d] Ref. (10), p. 143. [e] Reichstein, *Helv. Chim. Acta*, 9, 800 (1926). [f] This compound showed no depression in melting point when mixed with the hydantoin of *n*-amyl isoamyl ketone obtained by oxidation of *n*-amylisoamylcarbinol prepared by the Grignard method.

The 5,5-disubstituted hydantoin derivative[11] of the 223–224° fraction melted at 135–136° while that of the 103–105° (24.5 mm.) fraction melted at 175–176°. Ozonolysis showed that the latter fraction consisted chiefly of 2-*n*-butyl-5-methyl-3-hexen-2-one.

Reduction of Unsaturated to Saturated Ketones.—The unsaturated ketones were converted to the corresponding saturated ketones by vapor phase hydrogenation over supported nickel catalyst maintained at 200°.

Reduction of Saturated Ketones to Alcohols.—2-Methyl-5-nonanone and 2,7-dimethyl-4-octanone were reduced to the corresponding alcohols by dissolving 0.1-mole proportion in 100 ml. of absolute ethyl alcohol and adding 0.4 mole of sodium. After initial cooling, the reaction was completed upon the steam-bath. The solution was then diluted with 400 ml. of water, the insoluble layer separated, washed with water and steam distilled. Extraction of the distillate with ether, drying over potassium carbonate and removal of the ether yielded the desired alcohol.

Reduction of Unsaturated Ketones to Alcohols: (1) Preparation of 2-Methyl-5-decanol.—Four-tenths mole (67 g.) of 2-methyl-3-decen-5-one was dissolved in 500 ml. of ether and placed in a flask containing a suspension of 250 g. of sodium bicarbonate in 500 ml. of water. Sixty grams (2.6 moles) of sodium metal cut in narrow strips was added piece by piece. After completion of the addition, the ether layer was separated and dried over anhydrous sodium sulfate. There was obtained 34.5 g. of material boiling from 120–128° (24 mm.). Redistillation yielded a sample boiling at 124–126° (24 mm.) which upon analysis gave C, 76.75 and H, 13.61. Calcd. for $C_{11}H_{24}O$: C, 76.67; H, 14.04.

As the material was apparently still partially unsaturated, the reduction was completed by catalytic hydrogenation. Twenty-nine grams of the substance was dissolved in 150 ml. of 95% ethyl alcohol and treated with hydrogen at about three atmospheres pressure using 0.3 g. of platinum oxide as catalyst.[12] Upon redistillation the pure compound boiled at 122.5–123° (24 mm.).

(2) Preparation of 2-Methyl-5-undecanol.—Four-tenths mole (74 g.) of 2-methyl-3-undecen-5-one was reduced with moist ether as above yielding 50 g. of material of b. p. 135–140° (27 mm.). A sample boiling at 135° (24 mm.) obtained by redistillation gave the following analysis: C, 77.84; H, 12.92. Calcd. for $C_{12}H_{26}O$: 77.35; H, 14.07.

Thirty grams of this material was reduced catalytically

(11) Henze and Speer, THIS JOURNAL, 64, 522 (1942).

(12) Gilman, "Organic Syntheses," Coll. Vol. I, 1932, p. 452.

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as above. Distillation of the alcohol gave 22 g. of material boiling from 129–134° (24 mm.). Upon redistillation the compound boiled at 132–133° (24 mm.).

(3) **Preparation of 2-Methyl-2-decen-5-ol.**—Twenty grams (0.12 mole) of 2-methyl-3-decen-5-one was dissolved in 200 ml. of absolute ethyl alcohol and 71 g. (0.75 mole) of metallic sodium added. After completion of the reaction the solution was diluted with water, the oily layer separated, washed with water and steam distilled. The distillate was extracted with ether and dried over potassium carbonate. Distillation gave 8.6 g. (42%) of colorless, rather viscous liquid, b. p. 129.5–131° (30 mm.); d^{20}_4 0.8422; $n^{20}D$ 1.4473; M_D (obs.), 54.05; M_D (calcd.), 54.07.

Anal. Calcd. for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.34; H, 13.27.

The 3,5-dinitrobenzoate was an oil which could not be made to crystallize.

Ozonolysis.—For production of ozone, a generator similar in design to that described by Henne[13] was used. The ozone content of the issuing gas was about 8% by weight at a flow of about 3 liters per hour.

(1) **Unsaturated Ketones Obtained from Methyl Ketones.**—Ozone was passed through the sample (0.1 to 0.15 mole), cooled by an ice–salt mixture, until the sudden liberation of iodine in a solution of potassium iodide serving as a trap for the exit gases indicated completion of the reaction. All of the ozonides were viscous yellow liquids possessing reeking odors. Decomposition was immediately carried out by adding the ozonide dropwise, with stirring, to a boiling mixture of 200 ml. of water, an excess of zinc, and a trace of hydroquinone and silver nitrate.[14] The volatile decomposition products were allowed to distill over during the addition of the ozonide, and, after addition was complete, distillation was continued until all steam-volatile products were removed, more water being added if necessary. The residue was then acidified with an amount of sulfuric acid equivalent to the zinc used and the mixture distilled with repeated additions of water until no more acid material came over. In each case an appreciable amount of white solid deposited on the walls of the condenser. This was identified as acetone peroxide by its melting point of 131.5–132.5°, both alone and when mixed with a known sample prepared by oxidation of acetone with Caro's acid.[15]

The distillate was neutralized with sodium hydroxide and the neutral material removed by distillation. In each case this was found to consist of isobutyraldehyde, identified as the 2,4-dinitrophenylhydrazone, acetone, identified by conversion to dibenzalacetone, and a high boiling fraction which was not investigated further.

The remaining solution was evaporated to dryness, an equivalent amount of dilute sulfuric acid added and the liberated acids distilled off by repeated additions of water. The distillate was extracted with ether, the ether solution was dried over calcium chloride, the ether was removed and the acids fractionated. The aqueous layer was neutralized with sodium hydroxide and evaporated to dryness. The sodium salts were treated with *p*-bromophenacyl bromide,[10] and in all but one case the product was the formic acid ester, m. p. 140–141°, alone and when mixed with an authentic sample. In the case of the small lower boiling fraction of the unsaturated ketone from the methyl *n*-amyl ketone condensation, the formic acid ester was found and in addition a larger quantity of the acetic acid ester, m. p. 84.5–85.5°, alone and mixed with a known sample.

Table III lists the acids which were found in the ether soluble fractions. In each case mixed melting point determinations with known samples of the derivatives were made to confirm the identity of the compounds.

(2) **Unsaturated Ketone Obtained from Diethyl Ketone.**—Three-hundredths mole of 4,6-dimethyl-4-hepten-3-one was dissolved in 25 ml. of ethyl acetate and ozonized as above. The solution of ozonide was poured into 100 ml. of water containing 0.12 mole each of hydroxylamine hydrochloride and sodium acetate. The mixture was stirred for two hours, then distilled to remove ethyl acetate and other volatile material. To the residue was added 1 g. of ammonium chloride and ammonium hydroxide until alkaline to litmus. A solution of 3.7 g. of nickel acetate was then added and the mixture allowed to stand overnight. The orange-brown precipitate of nickel salt was filtered and dried; yield, 1.0 g. (18%).

The dry salt was shaken with 5% sulfuric acid and the solution extracted with ether. Evaporation of the ether left a white solid residue, which, after recrystallization from water, melted at 172–173°. A sample of methylethylglyoxime was prepared by treating isonitrosodiethyl ketone (prepared from diethyl ketone by treating with ethyl nitrite) with hydroxylamine hydrochloride and sodium acetate. The melting point was 172–173° and a mixed melting point with the above material was also 172–173°.

(3) **2-Methyl-2-decen-5-ol.**—Four and two-tenths grams of the alcohol was dissolved in 10 ml. of glacial acetic acid and ozonized as above. The colorless ozonide solution was diluted with 50 ml. of ether and decomposed by addition of 5 g. of zinc dust followed by dropwise addition of 5 ml. of water. The mixture was stirred and refluxed until a drop of the solution no longer gave a blue color when shaken with starch–iodide solution, then the sludge of zinc and zinc acetate was filtered off and washed with ether. The filtrate and washings was almost neutralized with powdered sodium bicarbonate, then shaken with sodium carbonate solution, washed with water and dried over anhydrous magnesium sulfate.

After removing the ether, about 3 g. of yellow liquid remained. The material appeared to decompose, splitting out water when distillation was attempted, so it was purified by means of steam distillation. A colorless liquid possessing a penetrating aromatic odor somewhat similar to that of *n*-heptaldehyde was obtained which readily gave a purple color with fuchsin-aldehyde reagent, and rapidly absorbed bromine in carbon tetrachloride solution without evolution of hydrobromic acid. The semicarbazone of this material melted, after two recrystallizations from dilute methanol, at 169–170°. The melting point of α-octenaldehyde semicarbazone was reported by van Romburgh[8] as 163°.

Anal. Calcd. for $C_9H_{17}N_3O$: C, 58.99; H, 9.35; N, 22.93. Found: C, 58.72; H, 9.14; N, 22.73.

TABLE III

Methyl ketone	Unsaturated ketone	Acid
	$(CH_3)_2CHCH{=}CHCO$-*n*-propyl	
n-Propyl	$(CH_3)_2CHCH{=}CHCO$-*n*-propyl	*n*-Butyric[a]
n-Butyl	$(CH_3)_2CHCH{=}CHCO$-*n*-butyl	*n*-Valeric[b]
Isobutyl	$(CH_3)_2CHCH{=}CHCO$-isobutyl	Isovaleric[c]
n-Amyl	$(CH_3)_2CHCH{=}CHCO$-*n*-amyl	*n*-Caproic[d]
n-Amyl	$(CH_3)_2CHCH{=}C(n\text{-butyl})COCH_3$	*n*-Valeric[e]
		n-Caproic[f]
n-Hexyl	$(CH_3)_2CHCH{=}CHCO$-*n*-hexyl	*n*-Heptoic[g]

[a] Identified as the piperazonium salt, m. p. 119–120°; ref. (18). [b] Identified as the anilide, m. p. 62–63°; ref. (10), p. 132. [c] Identified as the piperazonium salt, m. p. 140.5–141.5°, and as the anilide, m. p. 110.5–111.5°. [d] Identified as the piperazonium salt, m. p. 112–113° and as the anilide, m. p. 96–97°. [e] Identified as the anilide, m. p. 61–62°, and the piperazonium salt, m. p. 109–110°. [f] By fractional crystallization from dilute methanol a small amount of anilide, m. p. 91–92.5°, was obtained from the least soluble portion. A mixed melting point determination with known *n*-caproanilide, m. p. 96–97°, gave m. p. 93–95°. With known *n*-valeranilide, m. p. 62–63°, the mixed melting point was 60–75°. [g] Identified as the piperazonium salt, m. p. 96–97°.

(13) Henne, THIS JOURNAL, **51**, 2676 (1929).
(14) Church, Whitmore and McGrew, *ibid.*, **56**, 176 (1934).
(15) Baeyer and Villiger, *Ber.*, **32**, 3625 (1899).

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The ether which had been removed by distillation was found to contain acetone, identified by conversion to dibenzalacetone, mf. p. 111.5–112.5°, both alone and when mixed with an authentic sample.

Oxidation of Saturated Ketones to Acids: (1) **Methyl *n*-Amyl Ketone Condensation.**—Five-hundredths mole of 2-methyl-5-decanone was oxidized with 0.15 mole of sodium dichromate, 0.6 mole of sulfuric acid and 250 ml. of water as previously described.[2a,16] Considerable carbon dioxide was evolved at the start and throughout the course of the oxidation. A total of 0.09 mole of acid was obtained. *n*-Caproic acid was identified in the water-insoluble acid fraction by conversion to the 2-alkyl benzimidazole,[17] m. p. 157–158°, which showed no depression when mixed with the known *n*-caproic acid derivative, m. p. 158–158.5°. Acetic acid was shown to be present in the water-soluble fraction by preparing the *p*-toluide, m. p. 146.5–147.5°, alone and when mixed with known aceto-*p*-toluide.

(2) **Methyl *n*-Hexyl Ketone Condensation.**—Five-hundredths mole of 2-methyl-5-undecanone, oxidized as above, gave 1.1 moles of total acids. *n*-Heptoic acid was identified in the water-insoluble fraction by conversion to the piperazonium salt,[18] m. p. 97–98°, which showed no depression when mixed with authentic piperazonium di-*n*-heptoate, m. p. 96–97°. Isovaleric acid was also shown to be present by preparing the piperazonium salt, m. p. 140–141°, alone and mixed with known piperazonium di-isovalerate, m. p. 140–141°. The presence of acetic acid in the water-soluble fraction was shown by preparing the *p*-toluide, m. p. 146.5–147.5°, which exhibited no depression when mixed with known aceto-*p*-toluide.

Preparation of 2-Methyl-5-decanone.—From 0.6 mole of isoamyl bromide, 0.6 mole of *n*-hexaldehyde and 0.6 mole of magnesium there was obtained 38 g. (37%) of 2-methyl-5-decanol boiling at 122–126° (28.5 mm.). Twenty-nine grams (0.17 mole) of the alcohol was oxidized to the ketone by adding dropwise, with stirring, to a mixture of 0.057 mole of sodium dichromate, 0.226 mole of sulfuric acid and 100 ml. of water. Rate of addition was controlled so that the temperature did not rise above 50°. The mixture was stirred for one hour longer, then the insoluble layer was separated, washed with sodium carbonate solution and water and dried over potassium carbonate. Distillation gave 21.5 g. (75%) of *n*-amyl isoamyl ketone, b. p. 113–118° (28.5 mm.); hydantoin, m. p. 193–194°.

(16) Powell and Secoy, THIS JOURNAL, **53**, 765 (1931).
(17) Pool, Harwood and Ralston, *ibid.*, **59**, 178 (1937).
(18) Pollard, Adelson and Bain, *ibid.*, **56**, 1759 (1934).

Summary

1. It has been shown that isobutyraldehyde, in alkaline reaction medium, condenses through the alpha methyl carbon atom of the following methyl ketones: *n*-propyl, *n*-butyl, isobutyl, *n*-amyl and *n*-hexyl. A small fraction consisting chiefly of the unsaturated ketone resulting from methylene condensation was isolated in the methyl *n*-amyl ketone condensation.

2. Isobutyraldehyde condenses through the alpha methylene carbon atom of diethyl ketone.

3. Reduction of 2-methyl-3-decen-5-one with sodium and ethyl alcohol yielded 2-methyl-2-decen-5-ol.

4. The following new compounds have been prepared and characterized: 2-methyl-3-nonen-5-one, 2,7-dimethyl-5-octen-4-one, 2-methyl-3-decen-5-one, 2-methyl-3-undecen-5-one, 2-methyl-5-nonanone, 2,7-dimethyl-4-octanone, 2-methyl-5-decanone, 2-methyl-5-undecanone, 2-methyl-5-nonanol, 2-methyl-5-decanol, 2-methyl-5-undecanol, and 2-methyl-2-decen-5-ol.

5. The 5,5-disubstituted hydantoins of the following ketones have been prepared and characterized: 2-methyl-3-nonen-5-one, 2,7-dimethyl-5-octen-4-one, 2-methyl-3-decen-5-one, 3-*n*-butyl-5-methyl-3-hexen-2-one, 2-methyl-3-undecen-5-one, 7-methyl-4-octanone, 2-methyl-5-nonanone, 2,7-dimethyl-4-octanone, 2-methyl-5-decanone, 2-methyl-4-undecanone, and 4,6-dimethyl-3-heptanone.

6. The following new derivatives have been prepared and characterized: the nitroguanylhydrazones of 2-methyl-5-decanone and 2-methyl-5-undecanone; the 2,4-dinitrophenylhydrazone of 4,6-dimethyl-4-hepten-3-one; the semicarbazone of 2,7-dimethyl-4-octanone; the 3,5-dinitrobenzoates of 2-methyl-5-nonanol and 2,7-dimethyl-4-octanol.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF TEXAS]

Electrolyte Catalysis in the Ammonolysis of 9-Phenyl-9-chlorofluorene by Liquid Ammonia[1]

BY P. M. WILLIAMSON,[2] ROBBIN C. ANDERSON AND GEORGE W. WATT

Studies on the ammonolysis of both esters and organic halogen compounds by liquid ammonia[3] have provided numerous examples of acceleration of the rates of these reactions by ammonium salts. Since ammonium salts behave as acids in liquid ammonia solutions,[4] it has been assumed that the observed catalytic effects are to be attributed to acid catalysis. Earlier work in these Laboratories,[5–7] has led to the suggestion[7] that catalysis by ammonium salts is fundamentally no different from similar effects produced by non-onium type salts. As a result of their studies on both ammonolytic and aminolytic reactions, Audrieth, Scott and Hill[8] have expressed tentatively this same opinion and have suggested the use of the term "electrolyte catalysis."

(1) From the Ph.D. Dissertation of P. M. Williamson, The University of Texas, August, 1943.

(2) Present address: Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana.

(3) For review and primary references see Fernelius and Bowman, *Chem. Revs.*, **26**, 3–48 (1940).

(4) Bergstrom, *J. Phys. Chem.*, **20**, 160 (1925).

(5) Lemons, Anderson and Watt, THIS JOURNAL, **63**, 1953 (1941).

(6) Lemons, Williamson, Anderson and Watt, *ibid.*, **64**, 467 (1942).

(7) Williamson, Anderson and Watt, *ibid.*, **65**, 49 (1943).

(8) Audrieth, Scott and Hill, *ibid.*, **64** 2498 (1942).

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In an earlier paper,[7] data on the autocatalyzed ammonolysis of 9-phenyl-9-chlorofluorene and on the influence of added ammonium chloride have been presented. Work described in the present paper includes the effects produced by another ammonium salt (ammonium nitrate) and two non-onium type salts (sodium chloride and sodium nitrate). These studies provide quantitative proof of the assumption that, at least in one case, effects heretofore attributed to acid catalysis are not uniquely due to the fact that ammonium salts behave as acids in liquid ammonia but rather that these effects are more properly looked upon as typical examples of a more general electrolyte catalysis.

Experimental

Materials.—All materials were prepared and/or purified as described previously[5-7] with the exception of ammonium nitrate, in which case the C. P. reagent grade material was recrystallized three times from water, dried at 150°, and stored under anhydrous conditions.

Procedure.—Experimental data reported in this paper were obtained by procedures identical with those described by Williamson, Anderson and Watt.[7]

Data.—Sample data relating to reactions involving excess liquid ammonia and 0.3000-g. samples of 9-phenyl-9-chlorofluorene in the presence of sodium nitrate are given in Table I, while the experimental data relating to sodium chloride, sodium nitrate, and ammonium nitrate are represented graphically by Figs. 1, 2 and 3. On these graphs, each point represents the average of at least two independent measurements which were reproducible within 2%.

TABLE I

THE AMMONOLYSIS OF 9-PHENYL-9-CHLOROFLUORENE IN THE PRESENCE OF SODIUM NITRATE

$NaNO_3$, g.	Time, hr.	Vol. of soln., ml.	AgCl, g.
	Temperature, 15.08°		
0.0616	6.00	14.46	0.0490
.1229	6.00	14.52	.0600
.2460	6.00	14.67	.0786
.0616	9.00	14.43	.0673
.1229	9.00	14.50	.0811
.2459	9.00	14.70	.1022
.0616	12.00	14.33	.0848
.1230	12.00	14.48	.0988
.2458	12.00	14.48	.1193
	Temperature, 25.08°		
0.0614	3.00	14.70	0.0552
.1230	3.00	14.46	.0678
.2460	3.00	14.65	.0897
.0614	4.50	14.56	.0776
.1230	4.50	14.65	.0925
.2459	4.50	14.65	.1152
.0617	6.00	14.50	.0954
.1229	6.00	14.40	.1124
.2457	6.00	14.64	.1305

Discussion

The essential reaction already has been shown[7] to be the autocatalyzed formation of 9-phenyl-9-aminofluorene and ammonium chloride by the interaction of 9-phenyl-9-chlorofluorene and liquid ammonia. The results summarized in Figs. 1, 2 and 3 show that the reaction is also catalyzed by ammonium nitrate, sodium chloride, and sodium nitrate. Since preliminary calculations indicated that the catalytic effect is directly proportional to the concentration of the catalyst, the rate equation for the catalyzed reaction was concluded to be of the form

$$-dC_{C_{19}H_{13}Cl}/dt = k_1(a - x) + k_2(x)(a - x) + k_3c(a - x)$$

where a = the initial concentration of 9-phenyl-9-chlorofluorene, x = moles/l. of 9-phenyl-9-chlorofluorene ammonolyzed at time t, c = concentration of some added electrolyte other than ammonium chloride, and k_1, k_2 and k_3 are, respectively, reaction velocity constants for the un-

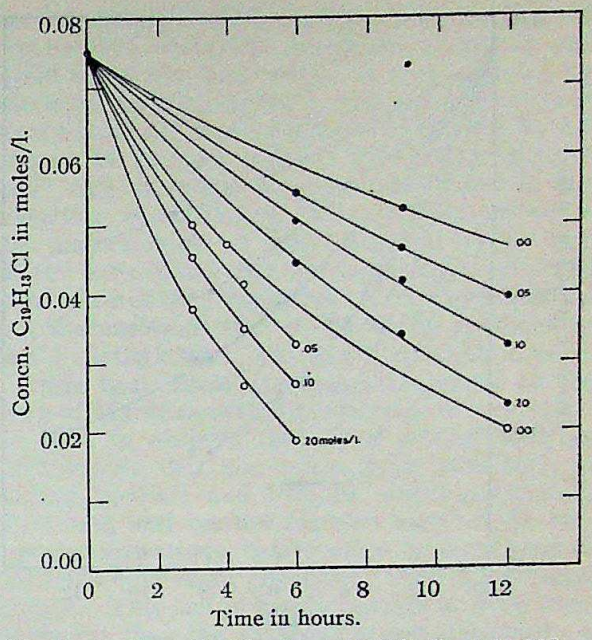

Fig. 1.—Sodium chloride: O, at 25.08°; ●, at 15.08°.

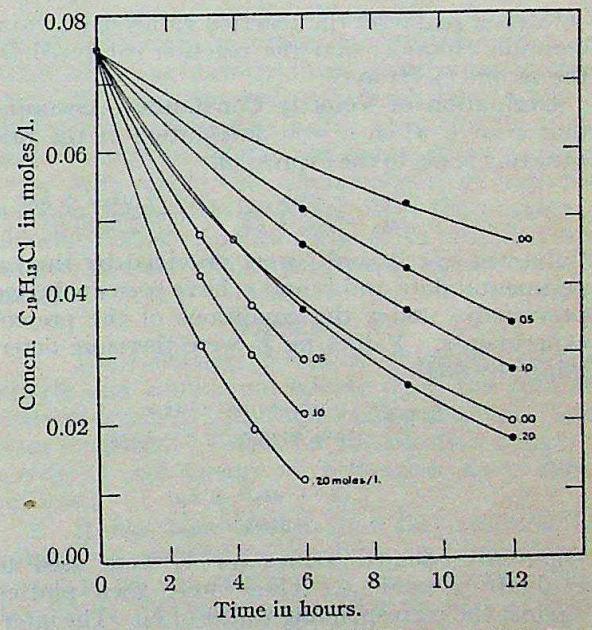

Fig. 2.—Sodium nitrate: O, at 25.08°; ●, at 15.08°.

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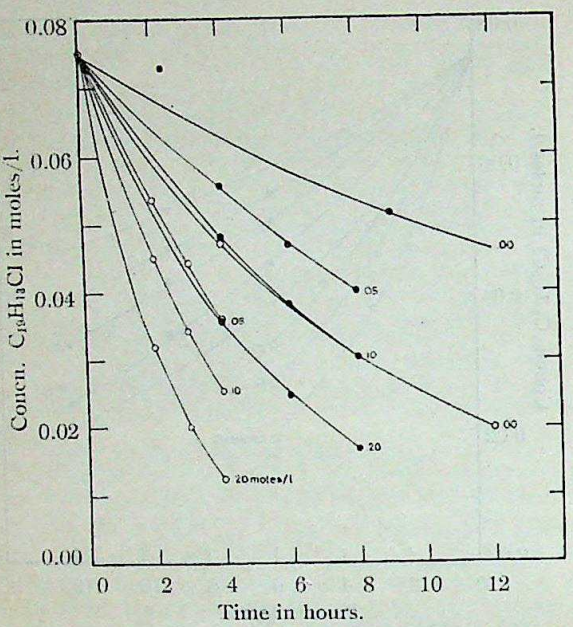

Fig. 3.—Ammonium nitrate: ○, at 25.08°; ●, at 15.08°.

catalyzed reaction, the reaction catalyzed by ammonium chloride, and the reaction catalyzed by the second electrolyte.

Evaluation of Velocity Constants.—Assuming that $x = 0$ when $t = 0$, integration of the rate equation leads to the expression

$$\log \frac{ack_3 + ak_1 + ak_2x}{-cxk_3 + ack_3 - k_1x + ak_1} = \frac{(k_1 + ak_2)t + k_3ct}{2.3026}$$

Values of a, c, x and t were provided by the experimental data and k_1 and k_2 have been evaluated previously[7] under the conditions of the present experiments. Values for k_3 were therefore determined by setting

$$y_1 = \log \frac{ack_3 + ak_1 + ak_2x}{-cxk_3 + ack_3 - k_1x + ak_1}$$

and

$$y_2 = \frac{(k_1 + ak_2)t + k_3ct}{2.3026}$$

Different assumed values for k_3 were used to evaluate y_1 and y_2. These were then plotted against the corresponding values of k_4. The intersection of the two curves determined a value of k_3 for the set of data used. For each added electrolyte at a given temperature, nine such values were determined. These were then averaged by the method of least squares.

The resulting values of the various velocity constants are summarized in Table II. By use of these constants, values for x under different experimental conditions were calculated and, in general, these values agreed with the experimental data within 2–3%. Values of k_3 decrease consistently with increase in the concentration of the electrolyte (*e. g.*, 0.2690 in 0.05 *M* NaCl, 0.2536 in 0.1 *M*, and 0.2302 in 0.2 *M*). This trend is not surprising since the electrolyte is probably not completely dissociated in the liquid ammonia solutions. The value c, used in calculating k_3, should, therefore, be corrected by the use of an activity coefficient. Quantitative data on activities of the various solutes in liquid ammonia are not available but there is good qualitative evidence from conductance data, etc.,[9] that the probable changes in these activities are sufficient to account for both the magnitude and direction of the variations in the calculated values of k_3.

TABLE II

VELOCITY CONSTANTS AND APPARENT ENERGY OF ACTIVATION

Catalyst	Velocity constants (15.08°C.)	Velocity constants (25.08°C.)	Energy of activation, cal./mole
None	0.0349	0.0807	14,300
NH_4Cl	.409	.953	14,400
NaCl	.242	.694	17,900
$NaNO_3$	.405	1.012	15,600
NH_4NO_3	.690	1.638	14,800

Energy of Activation.—Values for the *apparent* energy of activation were calculated from the rate constants at 15.08 and 25.08° using the Arrhenius equation. These results are summarized in Table II. The values given are all reproducible to within ±800 cal./mole.

Because of experimental difficulties, including the high vapor pressure of ammonia at elevated temperatures and the very limited solubility of 9-phenyl-9-chlorofluorene at lower temperatures, it was not feasible to study the influence of variation of temperature over a wide range. Accordingly, values obtained by assuming the applicability of the Arrhenius equation do not provide an adequate basis for definite conclusions as to the mechanism of the catalytic effect. Nevertheless, it is significant that in no case is the energy of activation lower than that for the uncatalyzed reaction. This same effect has been observed previously for a number of other ammonolytic reactions.[6] The results indicate clearly that the ordinary concept that catalysis involves a lower energy of activation is not necessarily applicable to catalysis of ammonolytic reactions in liquid ammonia.

Electrolyte Catalysis.—The results summarized in Figs. 1, 2 and 3 show that the ammonolysis of 9-phenyl-9-chlorofluorene is catalyzed not only by salts which behave as acids in liquid ammonia but also by certain non-onium salts. The rate of reaction in the presence of sodium nitrate is even greater than in the presence of ammonium chloride.

Since, in the experiments involving added non-onium type salts, ammonium chloride must always be present as a product of the ammonolytic reaction, it might be suggested that the observed change in rate of reaction is a result of a change in the activity of the ammonium chloride. Shatenshtein and Markova[10] have attributed the in-

(9) Fuoss and Kraus, THIS JOURNAL, **55**, 476 (1933).

(10) Shatenshtein and Markova, *Acta Physicochim.* (U. S. S. R.), 11, 131 (1939).

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fluence of non-onium type salts upon the "acid-catalyzed ammonolysis" of pilocarpine to the resultant change in the activity of the acid. Such an explanation is certainly not tenable in the present case. The form of the rate equation indicates that there is a second catalytic effect which is additive to that of the ammonium chloride. The quantity of ammonium chloride present varies continuously, but there appears to be no correlation whatever between this variation and the observed catalytic effect. The total electrolyte concentration undoubtedly has some effect on the activity of the acid, but it is not to be expected that the addition of sodium nitrate would change the activity more than would the addition of an equivalent quantity of ammonium chloride.

Comparison of the data for sodium and ammonium salts indicates that the ammonium salts are slightly more effective catalysts than are the corresponding sodium salts. It is possible that the actual catalysts are the ammonium and sodium ions which might distort materially the carbon–chlorine bond. Comparison of the chlorides and nitrates does not, however, show any consistent variation for the different cations. This lack of consistency may arise simply from the fact that the activities of the various salts at the same concentration are different. However, it is also possible that the associated ion-pairs of a salt such as sodium chloride, which should have a large dipole moment, may influence the activation of a carbon–halogen bond in liquid ammonia and thus tend to catalyze the ammonolytic cleavage. Unfortunately, quantitative data on activities are not available and these possibilities cannot be tested at present.

After completion of the present experiments, there became available a publication in which Markova and Shatenshtein[11] describe what might appear to be a rather comprehensive study of the kinetics of the ammonolysis of organic compounds involving carbon–halogen bonds. It is impossible to evaluate their results effectively since no information is given with regard to the experimental methods employed, even though time intervals of less than five minutes were involved in some measurements while in others two liquid phases were present in the reaction mixtures. So far as one can determine from their publication, all rate constants were calculated using the equation for a first order reaction, yet in some experiments equimolar quantities of halide and liquid ammonia were used. It was assumed by Markova and Shatenshtein that the sole reaction involved in each rate measurement was the formation of the primary amine. Fernelius and Bowman[3] call attention to numerous cases of the formation of secondary and tertiary amines in the ammonolysis of alkyl halides. Otto and Watt[12] have found that the ammonolysis of ethyl iodide (one of the compounds studied by Markova and Shatenshtein) at 0° yields 48.8% ethylamine, 31.8% diethylamine, and 18.4% triethylamine.

Aside from these questionable aspects of the work of Markova and Shatenshtein, it is of interest here to observe that their results indicate qualitatively that non-onium type salts such as sodium bromide and lithium, sodium, calcium, strontium, and barium nitrates may all, at certain concentrations, catalyze the ammonolysis of ethyl chloride more effectively than ammonium nitrate. This fact is hardly consistent with their viewpoint that the catalysis is fundamentally a function of the acid present.

In view of the results obtained in the present study, it becomes important to determine whether other salts, particularly those of different charge type, will show catalytic effects similar to those exhibited by the sodium salts. Quantitative data are also needed on the influence of non-onium type salts upon the ammonolysis of organic halogen compounds involving other than carbon–chlorine bonds. Studies designed to provide such information are now in progress in these Laboratories.

Summary

1. The influence of sodium chloride, sodium nitrate and ammonium nitrate upon the rate of ammonolysis of 9-phenyl-9-chlorofluorene has been described. Values for the reaction velocity constants and energy of activation have been recorded.

2. It has been shown that this reaction is subject to electrolyte catalysis by ammonium salts and by non-onium type salts as well. The bearing of this fact upon earlier theories of acid catalysis has been discussed.

3. Attention has been directed to certain questionable aspects of related work described by Markova and Shatenshtein.

AUSTIN, TEXAS RECEIVED AUGUST 9, 1943

(11) Markova and Shatenshtein, *Compt. rend. acad. sci. U. R. S. S.*, **35**, 68–70 (1942); *cf. Chem. Abs.*, **37**, 1321 (1943).

(12) Otto and Watt, forthcoming publication.

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[COMMUNICATION NO. 946 FROM THE KODAK RESEARCH LABORATORIES]

Some Effects of Solvents upon the Absorption Spectra of Dyes. III. Temperature and Organic Solutions of Cyanine Dyes

BY S. E. SHEPPARD AND H. R. BRIGHAM

Some reference to the influence of temperature on solutions of cyanine dyes was made in Part I.[1] The experiments reported there have been extended, particularly to include both polar and non-polar solvents, and both neutral (otherwise dipolar) and ionized cyanine dyes.

Apparatus and Experimental Procedure

Apparatus.—The cell used to measure the spectral absorption of these dyes is shown in Fig. 1. The cooling mixture was contained in a Dewar flask which had plane windows sealed in the bottom of each wall and parallel to each other. The cell in which the sample was placed was a cylindrical glass tube which had a plane window sealed onto one end, and this cell was set on the inside window of the Dewar flask. Then, in order to eliminate trouble caused by frost forming on the surface of the solution being measured, a cylindrical tube with windows sealed on each end parallel to each other was evacuated and placed inside the cell containing the solution. This tube was held in position by a holder so that the bottom was parallel to and at a known distance from the cell window. The distance between these two cell windows, *i. e.*, the thickness of the solution, was obtained by having the holder for the evacuated cell connected to a micrometer screw graduated to 0.1 mm. The plunger is long enough so that the lower end of the liquid to be examined is at the temperature of this liquid, while the upper end is free from external frost, because maintained at room temperature.

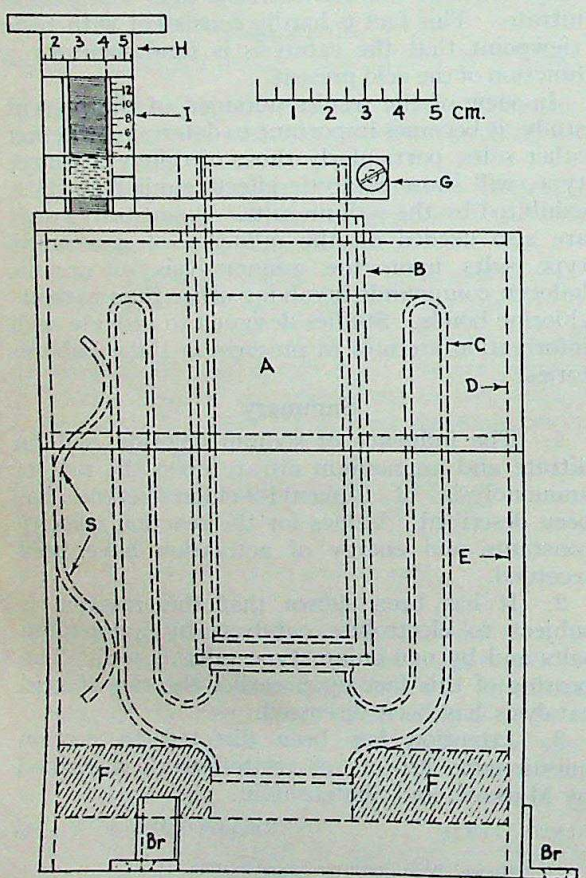
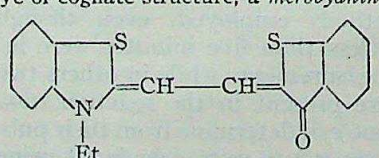


Fig. 1.—A, Cylindrical evacuated plunger; B, absorption tube holding sample; C, Dewar flask, note optical flats sealed in bottom; D and E, top and bottom of container; F, circular positioning block for Dewar flask; G, arm holding plunger; I and H, scale and vernier for plunger; S, positioning spring for Dewar flask; Br, mounting brackets.

A Hilger spectrometer, with a glass prism and calibrated for light in the visible part of the spectrum, was used for most of these measurements. The transmission was measured by the use of two barrier-layer photocells connected in a series-opposing circuit and with a potentiometer in each arm of the bridge. One of the photocells was held beneath the Dewar cell and was illuminated by part of the monochromatic light from a tungsten source after passing through the spectrometer. The second photocell was illuminated directly by the other portion of the same beam of light. The current was balanced out by means of the potentiometer so as to give a null reading instrument. The transmission is inversely proportional to the ratio of the resistance in the circuit when the solvent is in the light beam and when the dye solution is in the beam.

Other data were obtained on an instrument in which the spectrophotometer of the apparatus was replaced by a Bausch and Lomb monochromator. This was used with a photoelectric cell and amplifier. The transmission was measured by the ratio of the galvanometer deflection with the sample to that with the solvent in the beam.

Procedure.—The absorption spectra of dissolved ionized (cyanine) dyes are practically unaffected by the polarity of the solvent,[1] in respect of the position of absorption bands. We used as solvent for these a mixture of ethanol and diethyl ether, 50% each by volume. This solution became more viscous as the temperature was lowered and set to a clear glass at about −145°. This could be cooled somewhat below that temperature without losing transparency. However, at about −180°, the glass suddenly crystallized and shattered into opaque crystals, particularly if the sample was jarred. Most of the measurements were, therefore, made above −180°. As a neutral or non-ionized dye of cognate structure, a *merocyanine* having the structure (I) was employed. Three solvents were used with this, of diminishing polarity, *viz.*, a 50:50 mixture of *ethanol* and *methanol*, *diethyl ether*, and *hexane*.



(Dye XXIII)

In the experiments in which a complete spectral absorption curve in the visible was measured at temperatures above −75°, the desired temperature was obtained by adding "dry-ice" to alcohol in the Dewar flask. For lower temperatures, liquid nitrogen was introduced into the Dewar flask in sufficient quantity to produce the desired temperature and still not have the dye solution immersed in the liquid nitrogen. The evaporation of the liquid nitrogen below the level of the inner window of the Dewar cell held the temperature of the solution constant for a time sufficient to make the measurements. The spectral ab-

(1) S. E. Sheppard, P. T. Newsome and H. R. Brigham, THIS JOURNAL, **64**, 2923 (1942).

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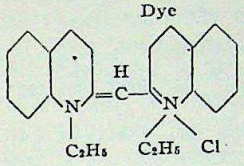
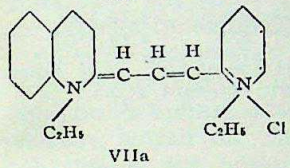
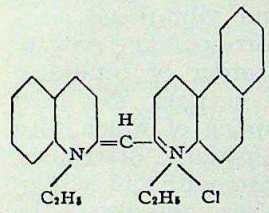
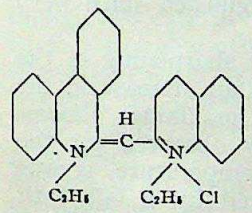
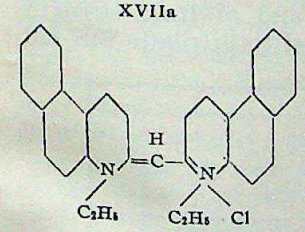
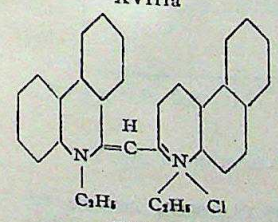
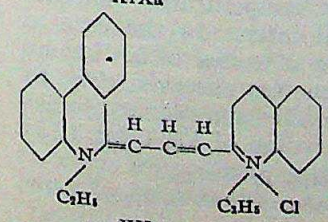
sorption was measured as quickly as possible, beginning at the point of maximum absorption and making readings on each side of the maximum. Thus, errors due to any change in the temperature would least affect the maximum position in the absorption spectrum. The temperature was measured by a calibrated thermocouple immersed in the dye solution.

For temperatures above the lowest, equilibrium was obtained by first cooling the sample slightly below the desired temperature and then letting it warm up. In some cases, readings were made on either side of the point of maximum absorption at various temperatures by allowing the same sample to warm up gradually and taking a series of readings at definite temperatures.

The cyanine dyes studied, the molecular extinction coefficient of the main band, the half-width of this band, and the area under the total absorption curve in the visible which has been defined above as the band strength at the various temperatures, are given in Table I. The extinctions were calculated on a concentration of dye in solution corrected for thermal cubic expansions.

TABLE I

Dye	Temp., °C.	$\epsilon \times 10^{-4}$	Half width in mμ	Relative band strength (area sq. cm.)
 Va	298	7.85	22.0	128.5
	203	7.90	16.0	106.5
	123	7.45	16.0	111.5
 VIIa	298	17.5	18.0	111.6
	202	15.1	16.5	99.3
	108	11.9	15.5	83.3
 XVIa	298	7.65	21.0	116.9
	229	9.0	18.0	127.0
	181	8.90	16.0	124.3
	153	8.4	19.0	124.0
 XVIIa	295	4.9	27.0	82.0
	215	5.4	24.0	84.6
	137	5.90	20.0	98.5
	95	6.7	19.0	101.2
 XVIIIa	298	9.0	20.0	144.0
	266	8.75	19.0	135.5
	222	9.20	16.0	146.0
	90	7.85	15.0	136.6
 XIXa	298	4.90	27.0	85.3
	229	5.10	28.0	84.5
	92	5.55	22.5	95.5
 XXa	298	7.10	21.0	99.5
	214	8.00	16.0	94.6
	105	7.30	17.0	88.7

Experimental Data

To conserve space, only selected typical absorption curves are shown; *e. g.*, in Fig. 2 the full absorption curves of Dye VIIa (pinacyanol chloride) for 298°, 202° and 108°K. The fall in

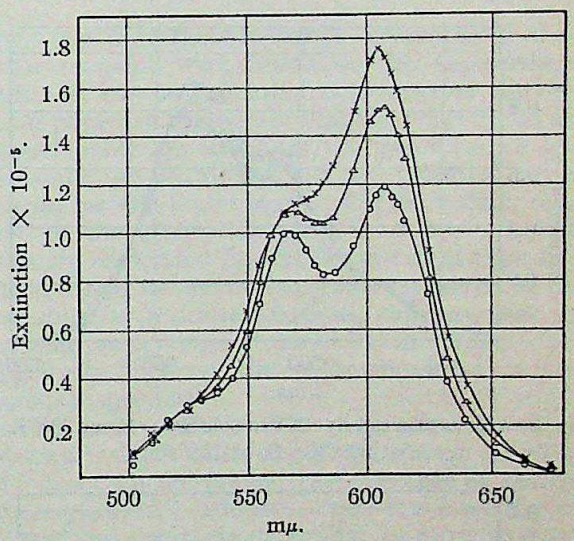


Fig. 2.—Absorption of dye VIIa solution: ×, at 298°K.; Δ, at 202°K.; O, at 108°K.

total absorption is discussed later. More important features are: (i) there is little or no displacement of the absorption peak, (ii) the structure of the (multiple) band becomes better defined, that is, the β and γ auxiliary bands[2] show up more clearly. There is some evidence in this example, but less in other cases examined, that with falling temperature the γ and β bands are actually strengthened relative to the α band. This may indicate some tendency to "dimerization" in the organic mixed solvent at low temperatures, a phenomenon otherwise observed with these dyes only in aqueous solution.[2] However, evidence has been presented recently[3] by G. N. Lewis, *et al.*, for spectral absorption of "dimerization" type of methylene blue in 95% ethanol at low temperature (170°K.). Dimerization and associated spectral changes will be discussed more fully in later papers.

(2) S. E. Sheppard, *Rev. Modern Physics*, **14**, 303 (1942).

(3) G. N. Lewis, O. Goldschmid, T. T. Magel and J. Bigeleisen, THIS JOURNAL, **65**, 1150 (1943).

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If a phenyl group be attached to the quinoline nuclei, producing the isomeric dyes XVIa and XVIIa, the resultant molecules are more soluble in solvents of low or zero polarity. At the same time, the isomers differ in that XVI has a planar, and XVII a non-planar, configuration. These structural differences are reflected in the absorption spectra, and in the influence of temperature on the absorption spectra. The planar dye XVI indicates below 25° (298°K.) no change in band strength (*cf.* Fig. 3), but the band structure becomes sharper. With the corresponding non-planar dye XVIIa (*cf.* Fig. 4), the intensity of absorption, as shown both by the extinction at the maximum and by the band strength, actually increases as the temperature is lowered. Similar behavior, but in less marked degree, is shown by the planar and non-planar isomers XVIIIa and XIXa (*cf.* Table I).

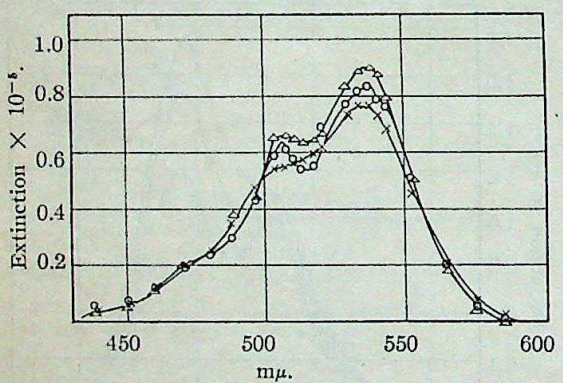


Fig. 3.—Absorption of dye XVIa solution: ×, at 298°K.; Δ, at 229°K.; O, at 153°K.

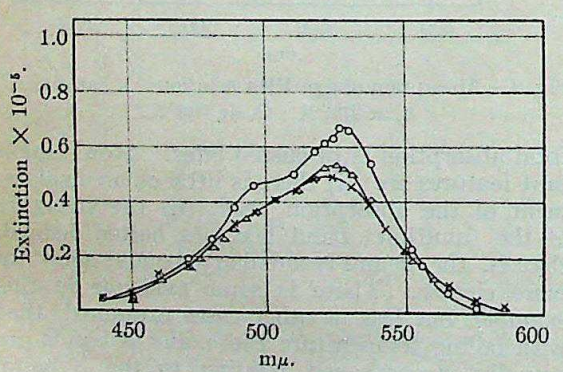


Fig. 4.—Absorption of dye XVIIa solution: ×, at 298°K.; Δ, at 215°K.; O, at 95°K.

The behavior of a neutral cyanine dye (merocyanine, dye XXIII) on change of temperature in three different solvents—different in respect of molecular polar moment—is shown in Table II.

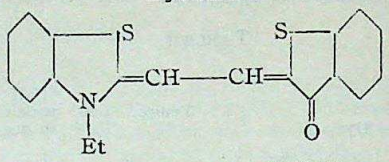
Discussion

The first feature apparent in the effect of temperature on cyanine dye solutions is the sharpening of the band structure with fall of temperature. This is to be attributed to the progressive

TABLE II

EFFECT OF TEMPERATURE CHANGE ON MEROCYANINE DYE SOLUTIONS

Dye XXIII



Solvent	n_D	$\mu \times 10^{18}$	E	$\nu_{max} \times 10^{-12}$ at °K. 298°	195°	123°	log ϵ_{max} at °K. 298°	195°	123°
50:50 Ethanol: Methanol	1.343	1.69	29.8	537	532	530	4.94	5.03	5.11
Ethyl ether	1.351	1.12	4.33	577	558		4.76	4.83	
Hexane	1.375	0	1.87	587	577		4.89	4.72	

n_D = Refractive index for D line at 25°. μ = Polar moment at 25°. E = Dielectric constant at 25°. ν = Frequency in fresnels. log ϵ = Logarithm of extinction coefficient.

elimination of rotational and vibrational energies—the latter, however, corresponding only to low energy values, of the order of rotational quanta. Larger vibrational energies, say from 600 to 2000 cm.$^{-1}$, the coupling of which with fundamental electronic transitions determines the main band structure of aromatic and heterocyclic molecules, of the polyenes,[4] and also of the cyanine dyes,[5] are not extinguished until very low temperatures are reached.

A secondary result of such sharpening of the band structure is liable to be an increase in the extinction at the position of maximum absorption. While this is generally observed for the early stages of lowering of temperature, it was generally found to be followed by a fall both of the extinction at λ_m and of band strength (Fig. 5). We were inclined to attribute this fall

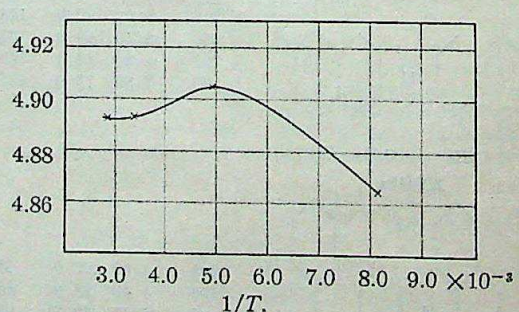


Fig. 5.—Temperature and extinction of dye Va.

to desolution of the dye, in consequence of reduced solubility at lower temperatures; another possibility will be noted later. In the case of dye XVIIa—the non-planar isomer of XVIa—no decrease of the extinction was observed (Fig. 6) and again with XIXa, the non-planar isomer of XVIIIa, a maximum value of log ϵ (at 4.75)

(4) K. W. Hausser, *Z. techn. Physik*, **15**, 10 (1934).

(5) S. E. Sheppard, R. H. Lambert and R. D. Walker, *J. Chem. Phys.*, **9**, 96 (1941).

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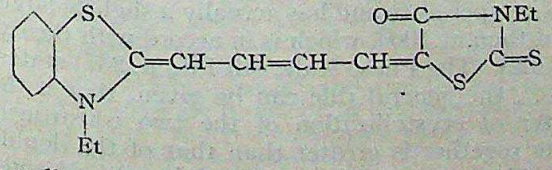
was not reached until a very considerable lowering of temperature had been effected. As noticed elsewhere,[4] these non-planar dyes have a much more diffuse band and lower extinction than their planar isomers. The observations suggest that as lower temperatures are approached, the deviation from planarity tends to become less—possibly because of the lowering of thermal energy and increased capacity of the molecule to remain in a strained configuration. It is also possible that the solubility is less affected by temperature fall, which may be connected with a diminished ease of crystallization of non-planar dyes. It has been indicated elsewhere,[2] that such non-planar cyanines have less tendency to dimerize and do not form spectrally distinguishable mesophases.

Whereas the ionized cyanines dissolved in the diethyl ether–ethanol mixture showed little or no displacement of the absorption maxima in respect of wave length on change of temperature, the behavior of the non-ionized merocyanine (Dye XXIII) in various solvents is very different. In each solvent used, the absorption maxima are shifted toward the longer wave length; the shift or "red displacement" is least in the case of the mixed alcohols solvent of highest polarity, and greatest for the solvent (ethyl ether) of moderate polarity, while hexane, of zero polar moment, shows an intermediate value. These results, though less extensive than is desirable, appear to be in reasonable accord with the observations on solvents of differing polarity discussed in Part I.[1] In that, the alcohols were shown to behave as "superpolar" solvents, in which the "red displacement" approached a saturation value. In the case of solvents of zero polar moment, it may be presumed that lowering the temperature could increase the refractive index, and thereby have some, but not a large, displacement effect. There remains to be explained, therefore, the relatively large effect of lowered temperature with solvents of moderate polarity, such as *ether*.

Before dealing with this problem, and in view of the sparsity of data, it is desirable to note that another type of merocyanine dye synthesized by Dr. L. G. S. Brooker, having the structure



as well as certain related compounds, have been found by Dr. C. West[6] to exhibit qualitatively very similar properties on change of temperature of their solutions. "In non-polar solvents, *e. g.*, hexane, and in strongly polar solvents, the position of the absorption band is not very dependent on temperature. In solvents of intermediate polarity, the position of the band is strongly temperature dependent." A restatement of the effect

(6) Private communication.

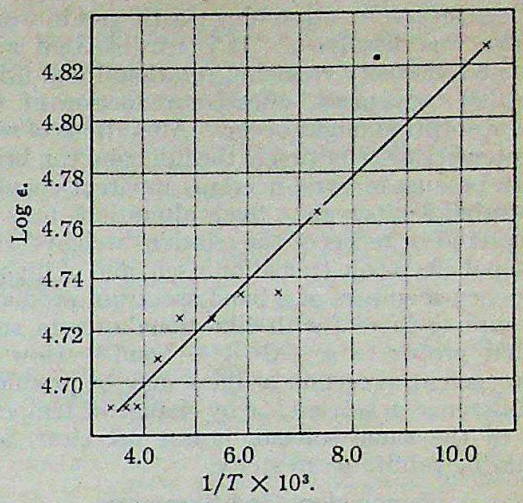


Fig. 6.—Temperature and extinction of dye XVIIa.

is to say that these solvents behave as if their polar moment were raised as the temperature falls. It has been pointed out, however, in previous papers of this series[1] that the polar moments ascertainable are either for the gas state, or less certainly for solutions, and are practically unknown for the liquid state. The fact that, relative to the absorption spectra of dyes, certain strongly associated liquids behave *as if* they had much higher moments than those measured in the gas state or in dilute solutions, suggests that increasing association at lower temperatures does effectively increase the polar moments of the liquids in question.

The total shift of the absorption band of (neutral) dyes with change of polar moment of solvent (in the present case, because of change of temperature) indicates that the coupling of *solvent* and *dye* molecules must be very sharp—practically an "all or none" affair. Otherwise, there would be no sharp or total displacement of the spectrum, but displacement associated with diffusion. This would happen if, for example, there were varying orientation of the same polar solvent molecule to the dye molecule, producing some sort of variable polarization of the latter. Actually, nothing of the sort seems to happen.

A change of capacity factor, *e. g.*, of the number of molecules effective, is observed, however, in the aforementioned changes of band strength and ϵ_{max} (extinction at peak of absorption band). In the case of fall of absorption with drop in temperature, two possibilities suggest themselves. One, already mentioned, is separation of the dye as crystals owing to decreased solubility. Another is reduction of number of (planar) dye molecules per unit time, *e. g.*, 10^{-8} sec.—suitably oriented to the electric vector of the light beam. As the temperature falls, the viscosity of the solvent increases; in fact, the mixed alcohol-ether solvent forms a clear glass at about 128°K. The importance of the orientation of planar dye molecules for the degree of absorption (extinction coefficient)

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has been shown by stretching elastic gels in which the dye was dissolved.[2] It is feasible that with increased viscosity reducing rotational and other brownian movement, effective reduction of the total absorption might occur. Alterations of *relative* intensity distribution in the full band can bring about, because of band-overlap, apparent changes of infraband intervals. Such alterations may be interpreted in terms of the relative "weights" of a principal electronic transition itself, and of higher[7] frequency members of a band spectrum produced by coupling thereof with vibrational quanta, such as that proper to a —C=C— bond.[4] How an enhancement of certain of these may be produced by difference in solvent, or by change of temperature of the same solvent, is not yet clear, and should be profitable to study.

Conclusions and Summary

Some effects of change of temperature on the absorption spectra of cyanine dyes in organic solvents have been measured over a temperature range from *ca.* 300 to 90°K. In this range the ionized cyanine dyes showed no appreciable displacement of the wave lengths of maximum absorption. The spectra became appreciably sharper as the temperature fell, which is attributed to suppression of rotational and low order vibrational energies. Temperatures were not reached sufficiently low to eliminate the vibrational quanta responsible (by coupling with the electronic transition) for the auxiliary absorption bands. The sharpening produced at first an increase in ϵ_{max} (or log ϵ_{max}) but as the temperature was further lowered a reduction in band strength occurred—less or absent in the case of non-planar dyes. Non-ionized merocyanine dyes show a greater or less displacement of the spectrum with change of temperature, depending upon the polarity of the solvent. A notably sharp coupling of solvent and soluble (dye) molecules is indicated by this displacement.

RECEIVED SEPTEMBER 29, 1943

(7) Rarely lower; the lower values $\nu_0 - \Delta\nu$ seem to be generally prohibited in absorption. The "extra" band of merocyanines in the gas state or in non-polar solvents[2] may be an exception.

[CONTRIBUTION FROM THE EASTERN EXPERIMENT STATION, U. S. BUREAU OF MINES]

The System Potassium Carbonate–Sodium Carbonate–Water at 100 and 150°[1]

BY GUY ERVIN, JR., A. L. GIORGI AND C. E. MCCARTHY

Introduction

A study of the solubility relations in aqueous solutions of the carbonates of sodium and potassium was undertaken at this Laboratory in connection with a laboratory and pilot-plant investigation[1a] of a process for the production of potassium carbonate from wyomingite, a leucite-bearing rock found in Wyoming. The process involves a base-exchange step by which a solution containing a mixture of sodium and potassium carbonate is obtained. For the separation of the carbonates it is proposed to evaporate at 100°, producing the monohydrate, $Na_2CO_3 \cdot H_2O$, followed by the anhydrous double salt, $K_2CO_3 \cdot Na_2CO_3$. The resulting solution is cooled to 25°, crystallizing out potassium carbonate sesquihydrate, $K_2CO_3 \cdot 3/2H_2O$. The mother liquor from the crystallization step is recirculated to the double-salt step, and the double salt is recirculated to the original solution, thus effecting a continuous process with no material discarded. An accurate knowledge of solubility is essential to operation of the process.

Two previous studies of this system in the high-temperature range have been made in Russia[2] in connection with a similar technological problem on the treatment of solutions obtained by alkaline leaching of nepheline. At 50° and lower the system has been adequately studied by Hill and Miller.[3] The authors' results at 100° are in essential agreement with those of Makarow and Schulgina. However, those authors present data at 120, 140, and 145° which indicate that the double-salt field becomes smaller with increasing temperature and ceases to exist at 145°; upon the basis of this result they propose evaporation at 145°, thus simplifying the process by eliminating the need for recycling the double salt. In the present study at 150° conclusive evidence was obtained to prove that the double salt exists at this temperature and has actually a slightly larger field than at 100°, which is in accord with theory. Findlay (The Phase Rule, 8th Ed., p. 237) states: " . . . the general rule can be given, that if the water of crystallization of the two constituent salts together is greater than that of the double salt, the latter will be produced from the former on raising the temperature." This is a direct result of van't Hoff's law of mobile equilibrium, which is a particular case of the theorem of Le Chatelier.

Experimental Procedure

The sodium carbonate and potassium carbonate used were Baker C. P. reagents. Qualitative tests showed the absence of impurities. For the majority of the runs the

(1) Published by permission of the Director, Bureau of Mines, U. S. Department of the Interior.

(1a) Unpublished work, Bureau of Mines, U. S. Department of the Interior, College Park, Md.

(2) Makarow and Schulgina, *Bull. Acad. Sci. U. S. S. R. Classe sci. chim.*, 511 (1940); Vasiliev, *Trans. State Inst. Applied Chem.*, **23**, 110 (1935).

(3) Hill and Miller, THIS JOURNAL, **49**, 669 (1927).

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initial complexes were made by mixing standardized solutions of these compounds plus $Na_2CO_3 \cdot H_2O$ or $K_2CO_3 \cdot 3/2H_2O$ or both. Sodium carbonate monohydrate was prepared by recrystallizing anhydrous sodium carbonate, while $K_2CO_3 \cdot 3/2H_2O$ was purchased as such. In some cases the anhydrous compounds stored in the oven at 120° were used directly.

The equipment was the same as that employed by Schroeder, Berk, and Gabriel,[4] who have described it fully. Briefly, it consisted of a set of steel solubility bombs of about 250-milliliter capacity. The top of each was fitted with an internal solution sampler tube, and the bottom contained a wire screen and drain plug. A sample of solution was taken, and the solid was separated from the residual solution while maintaining the operating temperature. The air thermostat was arranged so that these operations could be performed without opening the door of the thermostat.

The bombs were thoroughly tested for leaks at 150° using sodium carbonate solution. The temperature of the bomb itself was determined by means of a thermocouple and potentiometer; the hot junction of the thermocouple was wrapped around one of the bomb studs. The temperature of the 100° runs was 101.1±0.1°, and the 150° runs were at 150.0±0.1°.

A separate set of runs was made at 100° in ordinary chemical glassware. A 1-liter, three-neck flask was fitted with a mercury-seal stirrer, a thermometer, and a sampling pipet and was mounted in an oil thermostat. Samples of solution were obtained by pipetting a portion of the clear supernatant solution into a weighing bottle, finding the weight and making up to volume for analysis. Solid samples were obtained by pipetting a slurry onto a preheated sintered-glass filtering crucible, to which suction was applied.

The chemical compositions were determined by an acid titration to the methyl orange end-point in conjunction with a direct sodium determination[5] by the triple acetate method. Potassium was determined by difference. When the weight ratio of potassium carbonate to sodium carbonate exceeded 10:1, potassium was removed as the perchlorate before the sodium determination.[6] The acid titration is accurate to ±0.1% and the sodium determination to ±0.5% when prior removal of potassium is unnecessary. When potassium is removed, however, the accuracy is only ±10%. Since this occurred when the sodium was less than 5% in solution, the error was never greater than 0.5 of a percentage unit of sodium carbonate and averaged much less than this.

Tests for equilibrium consisted of obtaining check results on duplicate mixtures run for widely different lengths of time. In the case of the glass apparatus, solution samples were taken at twelve-hour intervals until three successive analyses checked within 0.5%. The time allowed for equilibrium was at least thirty-eight hours at 100° and at least twenty-two hours at 150°. Working at 50° or lower Hill and Miller[3] allowed eighteen to twenty-four hours for equilibrium with a simple salt and forty-eight hours for equilibrium with a double salt or solid solution. Makarow[2] and Schulgina allowed thirty hours at 100°, five to six hours at 120°, and three to three and one-half hours at 140 to 145°. It is known that the proportion of solid in the mixture should be low if equilibrium is to be reached in a reasonable time. In this work the solid was below 10% of the mixture at 100° and below 25% at 150°.

Identification of Solid Phases.—The solids were removed from the bombs, dried in air or in a desiccator over anhydrous potassium carbonate, and submitted for microscopic examination and in some cases for X-ray analysis. The optical properties of Na_2CO_3 and $Na_2CO_3 \cdot H_2O$ were found in the literature,[7] while those of $K_2CO_3 \cdot Na_2CO_3$ and $K_2CO_3 \cdot 3/2H_2O$ were obtained at this station. $K_2CO_3 \cdot Na_2CO_3$ is hexagonal, $N_\epsilon = 1.422 \pm 0.003$, $N_\omega = 1.531 \pm 0.003$, crystals equi-dimensional or slightly elongate, $K_2CO_3 \cdot 3/2H_2O$ is monoclinic or triclinic, $N_\alpha = 1.474 \pm 0.003$, $N_\beta = 1.483$ (approx.), $N_\gamma = 1.510 \pm 0.003$, $2V(+) = 66°$ (computed), extinction inclined 15 to 20°. The examination effected a positive identification of all solid phases. One difficulty was encountered. In that part of the double-salt field nearest the $K_2CO_3 \cdot 3/2H_2O$ field, $K_2CO_3 \cdot 3/2H_2O$ was always found associated with $K_2CO_3 \cdot Na_2CO_3$. The cause was crystallization from the retained mother liquor which was always present in high proportion because of the extreme fineness of the double salt. Taking this into consideration, the point nearest the $K_2CO_3 \cdot 3/2H_2O$ field which showed double salt should be the invariant point, $K_2CO_3 \cdot 3/2H_2O$–$K_2CO_3 \cdot Na_2CO_3$. The invariant point as located by chemical evidence checked with this point at both temperatures.

As a further check on the identity of the solid phases, X-ray patterns were obtained on a few samples. These included the double salt at the two extremities of its field at 150° and one sample from each phase area at both temperatures. Patterns for all the compounds occurring in the system at these temperatures were found in the literature.[8] The patterns always agreed with the microscopic identifications.

Accuracy.—Sources of error included lack of equilibrium, weighing errors, and errors in the chemical analyses. The sampler tubes each weighed about a kilogram, and weighings were accurate to the nearest tenth of a gram. No runs were accepted in which the sample weighed less than 10 g. so that the weight of sample was accurate to at least 1%. The sample usually weighed 25 to 30 g. The error in the chemical analyses was less than this, except for the low sodium-concentrations.

A measure of the over-all accuracy of the results was obtained by algebraic extrapolation of the tie lines.[9] The composition of the solution, of the initial complex, and of the solid phase should all fall on the same straight line. Using the solid-phase composition as given by the microscope and the composition of the initial complex, a tie line is obtained, and the deviation of the solution composition from this line may be calculated. By means of this calculation, the average deviations were found to be ±0.5% potassium carbonate and ±0.3% sodium carbonate. These deviations show the combined effect of all the errors involved. At the invariant points, where such an extrapolation is not possible, duplicate determinations were averaged, and the average deviation from the mean was calculated. The average deviations were again ±0.5% potassium carbonate and ±0.3% sodium carbonate. Five determinations were made at each invariant point on the 100° isotherm, four determinations at the invariant point ($K_2CO_3 \cdot 3/2H_2O$–$K_2CO_3 \cdot Na_2CO_3$ at 150°), and one at the other 150° invariant.

The wet residues were also analyzed in some cases but were considerably less accurate than the other determinations. Nevertheless, they furnish further chemical evidence for the correctness of the results. The variation was usually no more than 1–2 percentage units.

Experimental Results and Discussion

The 100° Isotherm.—The chemical compositions are given in Table I. The solid phase in equilibrium with each solution is indicated in the last column. The table includes three sets of data: runs made in the glass apparatus, runs made in the solubility bombs, and a preliminary set of runs made in the bombs, in which equilibrium was attained in the solution but not in the solid. In the preliminary set, the initial complexes were made up by adding the anhydrous salts to

(4) Schroeder, Berk and Gabriel, THIS JOURNAL, **59**, 1783 (1937).
(5) Barber and Kolthoff, *ibid.*, **50**, 1625 (1928).
(6) Barber and Kolthoff, *ibid.*, **51**, 3233 (1929).
(7) Winchell, "Microscopic Characters of Artificial Minerals," John Wiley and Sons, New York, N. Y., 1931.
(8) Hanawalt, Rinn and Frevel, *Ind. Eng. Chem., Anal. Ed.*, **10**, 457 (1938).
(9) Hill and Ricci, THIS JOURNAL, **53**, 4306 (1931).

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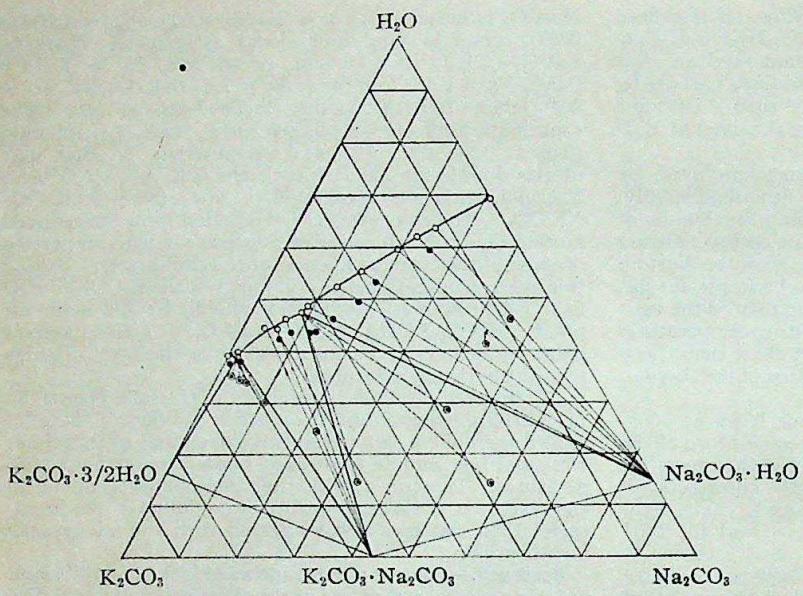

Fig. 1.—The 100° isotherm: O, solutions; ●, initial complexes; ◉, wet residues.

the bombs followed by the proper amount of water. Caking of the anhydrous salts prevented true equilibrium in the times allowed, as indicated by microscopic examination of the solids and by the divergence of the tie lines. The agreement with the subsequent experiments, in which the complexes were formed by mixing solutions and hydrated salts, indicates that equilibrium with respect to the solution was reached, and the results are included as a substantiation of the solubility curve. The type of run is designated in the first column as G for glass, B for bomb, and P for preliminary. The compositions of the mixtures given in the fourth and fifth columns are wet residues for the runs marked G and initial complexes for those marked B; they are not reported for those marked P because these mixtures were not at equilibrium.

The data of Table I are plotted in Fig. 1, omitting the preliminary set of runs. In drawing the tie lines the composition of the solid was taken as a fixed point and the best straight line drawn through that composition and the compositions of the mixture and solution. The isotherm has three branches, corresponding to $K_2CO_3 \cdot 3/2H_2O$, $K_2CO_3 \cdot Na_2CO_3$, and $Na_2CO_3 \cdot H_2O$ as solid phases. The monohydrate has the largest field, and $K_2CO_3 \cdot 3/2H_2O$ has a very small field in accord with its high solubility. The anhydrous double salt is seen to be incongruently soluble, reacting with water to give $Na_2CO_3 \cdot H_2O$ and a solution richer in potassium carbonate than the double salt.

The agreement of the authors' data with those of Makarow and Schulgina at 100° is fairly close. They report a composition of 45.8% K_2CO_3 and 8.5% Na_2CO_3 for the monohydrate-double salt invariant which compares with the present result of 44.0% K_2CO_3 and 8.6% Na_2CO_3. Their compositions at the invariant, $K_2CO_3 \cdot 3/2H_2O$–$K_2CO_3 \cdot Na_2CO_3$ are 58.6% K_2CO_3 and 2.0% Na_2CO_3 as compared with 59.2% K_2CO_3 and 1.5% Na_2CO_3 from the authors' data.

The 150° Isotherm.—The data are shown in Table II and plotted in Fig. 2. The only change from the 100° isotherm is the replacement of $Na_2CO_3 \cdot H_2O$ by anhydrous Na_2CO_3. The location of the invariant point Na_2CO_3–$K_2CO_3 \cdot Na_2CO_3$ is very close to the $Na_2CO_3 \cdot H_2O$–$K_2CO_3 \cdot NaCO_3$ invariant at 100°. The $K_2CO_3 \cdot 3/2H_2O$–$K_2CO_3 \cdot Na_2CO_3$ invariant is at a considerably higher potassium carbonate concentration so that the field has widened somewhat. The double salt is still incongruently soluble.

As stated in the introduction, results at 150° are directly contradictory to those of Makarow and Schulgina. The use of steel containers, adequate time for equilibrium, and positive identification of the solid phases by means of the microscope and the X-ray attest to the validity of the authors' results. Although no consistent explanation can be given for the disagreement with the results of Makarow and Schulgina, there

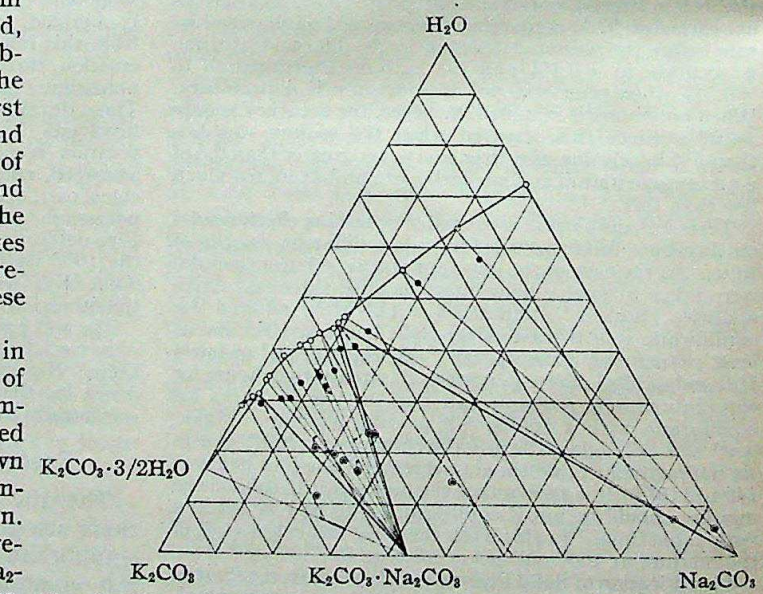

Fig. 2.—The 150° isotherm: O, solutions; ●, initial complexes; ◉, wet residues.

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TABLE I

THE 100° ISOTHERM

Type of run	Solution K₂CO₃	Solution Na₂CO₃	Initial Complex or wet residue K₂CO₃	Initial Complex or wet residue Na₂CO₃	Solid phase
..	60.9	0.0	..	..	$K_2CO_3 \cdot 3/2H_2O$
B	58.9	1.3	61.5	1.0	$K_2CO_3 \cdot 3/2H_2O$
G	59.4	1.5	62.3	2.5	
G	59.4	1.5	61.5	4.1	
G	59.4	1.5	60.6	5.5	$K_2CO_3 \cdot 3/2H_2O$ +
G	59.2	1.5	59.5	10.5	$K_2CO_3 \cdot Na_2CO_3$
B	58.4	1.6	59.3	2.6	
P	57.0	2.2	..	..	$K_2CO_3 \cdot Na_2CO_3$
P	57.0	2.7	..	..	$K_2CO_3 \cdot Na_2CO_3$
P	52.0	4.7	..	..	$K_2CO_3 \cdot Na_2CO_3$
G	51.9	3.8	53.1	22.5	$K_2CO_3 \cdot Na_2CO_3$
P	51.8	4.4	..	..	$K_2CO_3 \cdot Na_2CO_3$
B	49.9	6.0	50.6	7.1	$K_2CO_3 \cdot Na_2CO_3$
P	49.8	5.3	..	..	$K_2CO_3 \cdot Na_2CO_3$
B	47.2	6.6	47.7	8.7	$K_2CO_3 \cdot Na_2CO_3$
P	45.4	7.5	..	..	$K_2CO_3 \cdot Na_2CO_3$
P	44.6	8.4	..	..	$K_2CO_3 \cdot Na_2CO_3$
P	44.6	8.4	..	..	$K_2CO_3 \cdot Na_2CO_3$
G	44.7	8.3	51.3	34.2	
G	44.6	8.4	28.4	43.0	
B	43.9	9.0	44.6	12.0	$K_2CO_3 \cdot Na_2CO_3$ +
B	44.2	8.3	43.3	13.0	$Na_2CO_3 \cdot H_2O$
G	42.3	9.0	28.4	57.4	
B	42.2	9.1	39.1	14.8	$Na_2CO_3 \cdot H_2O$
P	41.4	9.3	..	..	$Na_2CO_3 \cdot H_2O$
P	40.5	10.1	..	..	$Na_2CO_3 \cdot H_2O$
G	37.7	10.3	19.4	63.8	$Na_2CO_3 \cdot H_2O$
B	35.1	12.4	33.0	17.5	$Na_2CO_3 \cdot H_2O$
P	29.7	14.8	..	..	$Na_2CO_3 \cdot H_2O$
B	29.4	15.3	28.0	18.8	$Na_2CO_3 \cdot H_2O$
P	28.6	16.1	..	..	$Na_2CO_3 \cdot H_2O$
P	27.0	15.2	..	..	$Na_2CO_3 \cdot H_2O$
G	20.8	19.7	15.4	43.4	$Na_2CO_3 \cdot H_2O$
P	17.0	20.0	..	..	$Na_2CO_3 \cdot H_2O$
B	16.2	21.8	15.9	25.0	$Na_2CO_3 \cdot H_2O$
G	12.2	24.1	8.5	45.5	$Na_2CO_3 \cdot H_2O$
..	0.0	30.9	..	..	$Na_2CO_3 \cdot H_2O$

are several factors which might have caused error in their work. These are the short times used for equilibrium, the use of glass containers with the resultant large contamination by silicon dioxide at the high temperatures, and the lack of optical examination of the solid phases.

No attempt was made in this study to determine the solubilities of the individual salts in water with accuracy. The values used are those reported in the literature,[10,11] which were checked within a few tenths of a per cent. The value for the solubility of potassium carbonate in water at

(10) Waldeck, Lynn and Hill, THIS JOURNAL, **54**, 928 (1932).
(11) Mulder, "Scheikundige Verhandelingen en Onderzochingen," Vol. 3, pt. 2, Rotterdam, 1864.

TABLE II

THE 150° ISOTHERM

Solution K₂CO₃	Solution Na₂CO₃	Initial complex K₂CO₃	Initial complex Na₂CO₃	Wet residue K₂CO₃	Wet residue Na₂CO₃	Solid phase
71.0	0.0	..	..	..	..	$K_2CO_3 \cdot 3/2H_2O$
68.2	1.0	..	..	..	..	$K_2CO_3 \cdot 3/2H_2O$
67.1	2.4	67.6	3.1	73.8	4.4	$K_2CO_3 \cdot 3/2H_2O$ +
65.7	1.7	66.9	3.9	..	..	$K_2CO_3 \cdot Na_2CO_3$
67.5	1.1	67.6	3.1	66.6	22.0	
67.6	2.1	67.6	3.1	..	..	
64.4	1.6	63.7	6.1	59.5	21.0	$K_2CO_3 \cdot Na_2CO_3$
63.3	2.0	61.8	7.8	62.1	17.0	$K_2CO_3 \cdot Na_2CO_3$
58.7	2.7	58.6	8.1	58 4	23.3	$K_2CO_3 \cdot Na_2CO_3$
55.0	4.2	54.4	10.9	57.0	26.8	$K_2CO_3 \cdot Na_2CO_3$
52.7	5.7	54.4	12.7	51.4	24.9	$K_2CO_3 \cdot Na_2CO_3$
50.2	6.6	51.3	12.8	..	..	$K_2CO_3 \cdot Na_2CO_3$
47.5	8.4	48.1	11.8	50.5	26.0	$K_2CO_3 \cdot Na_2CO_3$
46.4	8.6	45.2	14.0	41.7	44.0	$K_2CO_3 \cdot Na_2CO_3$ + Na_2CO_3
44.3	9.2	41.7	14.9	..	..	Na_2CO_3
29.6	14 8	28.3	18.6	7.2	85.4	Na_2CO_3
16.1	20.1	15.2	27.0	1.3	93.4	Na_2CO_3
0.0	27.7	..	..	..	..	Na_2CO_3

150° was obtained by extrapolation of the data of Mulder which extend up to 130°.

Acknowledgement is gratefully made to Mr. Robert D. Pike, consulting chemical engineer of Pittsburgh, Pa., who initiated the work and contributed many helpful suggestions. The authors also wish to express their indebtedness to Drs. A. Gabriel and F. Chayes for the petrographic examinations and to H. F. Carl for the X-ray identifications.

Summary

1. The system K_2CO_3–Na_2CO_3–H_2O has been investigated at 100° and 150°, employing the usual chemical methods and in addition identifying the solid phases by means of microscopic examination and X-ray patterns.

2. At 100° the isotherm has three branches: that of $K_2CO_3 \cdot 3/2H_2O$, $K_2CO_3 \cdot Na_2CO_3$, and $Na_2CO_3 \cdot H_2O$.

3. The 150° isotherm also has three branches corresponding to $K_2CO_3 \cdot 3/2H_2O$, $K_2CO_3 \cdot Na_2CO_3$, and Na_2CO_3. The field of the double salt is slightly more extensive here than at 100°. The continued existence of the anhydrous double salt on increasing the temperature is in accord with the theorem of Le Chatelier.

4. The double salt is incongruently soluble in the temperature range studied and decomposes in contact with water to give solid $Na_2CO_3 \cdot H_2O$ or Na_2CO_3 plus a solution relatively richer in potassium carbonate.

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[CONTRIBUTION FROM THE BUTTERFIELD CHEMICAL LABORATORY, UNION COLLEGE]

Studies on Silicic Acid Gels. XV. The Effect of Temperature upon the Time of Set of Alkaline Gel Mixtures

BY CHARLES B. HURD, RENATO C. POMATTI,[1] JOHN H. SPITTLE[2] AND FRANK J. ALOIS[3]

Introduction

The effect of temperature on the time of set of silicic acid gels is definite for gel mixtures with *p*H below 7. With these acidic mixtures, a rise in temperature causes a decrease in the time of set[4] in mixtures containing weak acids,[5] or strong acids.[6,7] The energies of activation for these acidic mixtures have been reported.[5,6,7]

The behavior of alkaline gel mixtures, with *p*H values above 8.0, shows some surprising results when the effect of temperature on time of set is studied. Increased temperature with alkaline gel mixtures of solutions of sodium silicate and phosphoric acid has been shown to decrease the time of set.[8] A calculation of the energy of activation gave about 24,000 calories. For these mixtures, due to the buffering power of the phosphates formed, the *p*H remained constant from the first reading after the solutions were mixed until the gel had set.

With alkaline gel mixtures made from solutions of sodium silicate and acetic acid having *p*H values above 8.5, the results of Munro and Pearce,[9] and results in this laboratory, have shown a curvature in the relation between logarithm of time of set and the reciprocal temperature. This made calculation of the energy of activation impossible. In addition, the *p*H of the sol has been shown to increase noticeably from the time of mixing until the gel has set. Our own earlier experiments showed that, in the highest *p*H range where it is possible for a gel to set, raising the temperature increased the time of set. This phenomenon deserved further investigation. The results are given herewith.

Experimental

The gel mixtures were prepared by mixing solutions of sodium silicate, E brand Philadelphia Quartz Company, diluted to 1.25 *N* in NaOH equivalent, and dilute acetic acid in the manner previously described.[4,5] Time of set was found by the "tilted rod" method.[4]

Measurement of the *p*H presented difficulty. The Quinhydrone method, which has been shown satisfactory for acidic mixtures[10] in the presence of silicic acid, fails above *p*H 8. Earlier work on alkaline gel mixtures,[11] and the more recent work of Munro and his co-workers,[12,13,9] have utilized indicators and standardized buffers to measure the *p*H. Munro and Pearce[9] found the *p*H measured by the glass electrode, in the range *p*H 9.5–11.0, to be 0.2 to 0.4 unit lower than that given by indicators. In our work on alkaline mixtures containing phosphoric acid,[8] we have found that the life of a Beckmann glass electrode was very short, the alkali and silica destroying the surface and also the reproducibility of the readings of the electrode after four or five determinations.

In the work reported here, we have used both the indicator method and the glass electrode. The indicators were phenol red for *p*H 7.8–8.4; thymol blue, *p*H 8.0–9.8, and LaMotte purple, 9.6–11.0. The buffer solutions were made up from directions from Clark[14] of boric acid, potassium chloride and sodium hydroxide, or of sodium carbonate and borax. The *p*H of the buffers was determined by the Beckmann Glass Electrode Apparatus, but the particular glass electrode was not allowed to come into contact with any silicates. The indicator method procedure was standard, using a white porcelain spot plate.

In addition, some determinations were made by the Leeds and Northrup Glass Electrode Apparatus, using home-made glass electrodes. These were blown from Corning #015 special electrode glass, and were checked in a buffer after each immersion in silicate mixtures. They were discarded when they failed to check.

Time of set was determined at three temperatures for a series of mixtures, using a fixed volume of sodium silicate solution and varying quantities of acetic acid. Mixtures were reproducible, that is, two mixtures made up with the same volumes of acetic acid gave the same *p*H and time of set.

In Fig. 1 are shown the logarithm of time of set against reciprocal absolute temperature for a series of silicic acid gel mixtures produced by mixing solutions of sodium silicate and acetic acid. Temperatures were 0°, 25.1°, and 38.5°. All mixtures were alkaline. The *p*H was determined with indicators. Between the first reading and the time of set, the *p*H rose 0.2 to 0.5 of a *p*H unit, especially in the higher range. The concentrations of Na^+, 0.391 gram ion per liter, and SiO_2, 0.642 gram mole per liter, were the same for all. The concentration of Ac^- in gram ions per liter, and the *p*H, are given by Table I. The *p*H given was recorded immediately after mixing.

TABLE I

CONCENTRATION OF ACETATE ION AND *p*H OF THE GEL MIXTURES SHOWN IN FIG. 1

Ac^-	0.379	0.366	0.353	0.341	0.328	0.315
*p*H	6.8	7.4	8.0	8.3	8.6	8.9
Ac^-	0.302	0.289	0.277	0.265	0.252	*0.246*
*p*H	9.3	9.8	10.1	10.3	10.43	*10.45*
Ac^-	0.239	0.227	0.214	0.201	0.189	0.176
*p*H	10.50	10.55	10.63	10.70	10.73	10.75

(1) Present address: The Texas Company, Beacon, N. Y.

(2) Present address: Lever Brothers Company, Cambridge, Mass.

(3) Present address: U. S. Army Air Corps.

(4) Hurd and Miller, *J. Phys. Chem.*, **36**, 2194 (1932).

(5) Hurd, *ibid.*, **40**, 21 (1936).

(6) Hurd, Frederick and Haynes, *ibid.*, **42**, 85 (1938).

(7) Hurd and Barclay, *ibid.*, **44**, 847 (1940).

(8) Hurd and Marotta, THIS JOURNAL, **62**, 2767 (1940).

(9) Munro and Pearce, *J. Phys. Chem.*, **44**, 1024 (1940).

(10) Hurd and Griffeth, *ibid.*, **39**, 1155 (1935).

(11) Prasad and Hattiangadi, *J. Indian Chem. Soc.*, **6**, 653 (1929); **6**, 893 (1929); **6**, 991 (1929).

(12) Munro and Alves, *Can. J. Res.*, **B15**, 353 (1937).

(13) Munro and Pearce, *ibid.*, **B16**, 390 (1938).

(14) Clark, "The Determination of Hydrogen Ions," Williams and Wilkins Company, Baltimore, Md., 3rd ed., 1928, pp. 195, 201.

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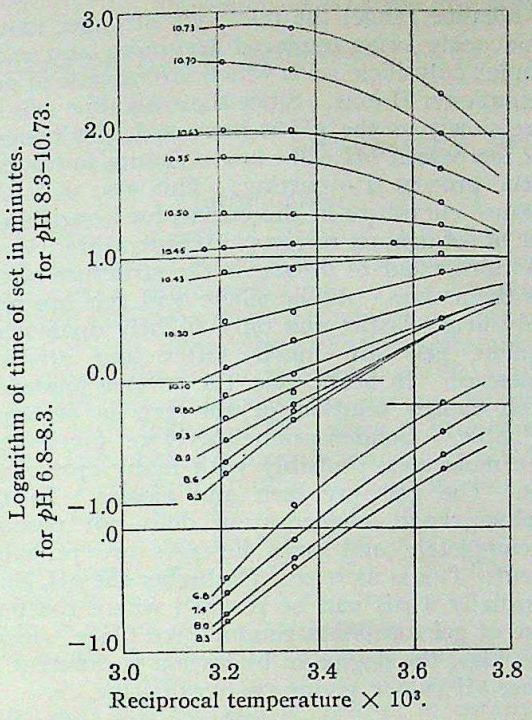

Fig. 1.—Logarithm of time of set of silicic acid gel mixtures of different *p*H as a function of the reciprocal absolute temperature.

The curvature shown by Munro and Pearce[9] is apparent here. Their Figs. 1, 2, 3, 4, and 5 for their control gels are duplicated among the 18 curves of our Fig. 1, although we have not found the decrease of logarithm of time of set at our highest temperature as pronounced as theirs. It is apparent that at least in our mixtures above *p*H 10.5, a rise of temperature from 0 to 38° increased the time of set. For *p*H 10.45, there was very little change in the time of set as the temperature was increased. This was checked at several more temperatures, and is shown in Fig. 1 by extra points for the mixture in Table I containing 0.246 gram ion of Ac^- per liter. This value is italicized in Table I.

Unfortunately, for simplicity of treatment, the *p*H in these mixtures was found to change somewhat with time and with temperature. Also, the concentration of silica changed, to a small degree, the slope of the curves, which are shown in Fig. 1. We have not yet studied this second effect carefully.

The change in *p*H with time was studied, using the Leeds and Northrup apparatus and Corning #015 home-made glass electrodes. Two curves are shown in Fig. 2, the *p*H being corrected for Na^+ ion effect. The concentrations are for Curve 1, $Na^+ = 0.394$, $SiO_2 = 0.652$, $Ac^- = 0.253$, and for Curve 2, $Na^+ = 0.394$, $SiO_2 = 0.652$, and $Ac^- = 0.238$. The *p*H is seen to rise and become constant after the gel has set. These mixtures contain a strong base and less than an equivalent amount of a weak acid.

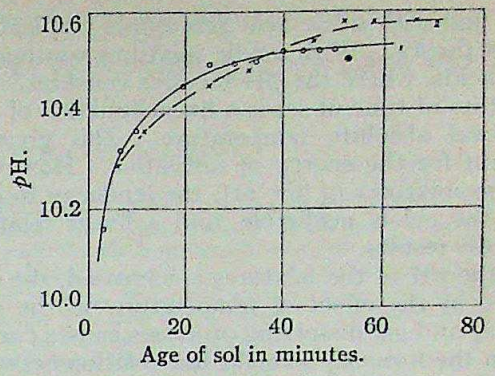

Fig. 2.—Effect of age of sol upon *p*H.

We have tried to liquefy these alkaline gels with *p*H over 10.5 by allowing them to set at 25° and then rapidly raising the temperature to 50° or dropping it to 0°. In no case have we been able to liquefy the gel. Apparently, once the gel is set, it remains set, even though the rate of setting at the higher temperature would not have allowed it to set in the time elapsed in setting at the lower temperature and the short time required for heating.

Discussion

There is general agreement that silicic acid gels produced by the setting of gel mixtures with *p*H above 8.0 differ in many ways from the acid gels. Several workers have noted that gel mixtures of *p*H above 11.0 apparently do not set to form gels.[15] Our results substantiate this. It is also well known that gels already set may be dissolved in dilute sodium hydroxide solution, *i. e.*, by raising the *p*H well above 11.0.

There must, therefore, be two processes possible so far as the hydrous silica is concerned. One may be described as the formation of a monosilicic acid, or at least a simple silicic acid, from the silicate ions. These simple silicic acids condense to form polysilicic acids and eventually form a gel.[16] This may be shown as follows:

$$\text{Silicate ion} \rightleftarrows \text{Simple silicic acid} \rightleftarrows \text{Polysilicic acid} \rightleftarrows \text{Gel}$$

$$\text{Setting of gel} \longrightarrow \qquad \longleftarrow \text{Solution of gel}$$

The action of strong alkali reverses the process which occurs during gelation. This occurs easily in solutions of *p*H 13 or higher.

In gel mixtures with *p*H between 11 and 13, the tendency to form a gel must be opposed by the reverse effect. This makes the gels set more and more slowly as the *p*H is raised, until somewhere between *p*H 11 and 13, the mixtures will never set. It is hardly likely that a rise in temperature will affect these two opposed tendencies equally. Such a situation is true in simple chemical equilibria, the temperature affecting the rates of the opposing reactions unequally, thus causing a change in the equilibrium constant.

(15) Ray and Ganguly, *J. Phys. Chem.*, **34**, 352 (1930); **35**, 596 (1931).

(16) Hurd, *Chem. Rev.*, **22**, 403 (1938).

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We find with silicic acid gels ample verification of this theory. With acidic mixtures containing weak acids, where the *p*H remains constant,[5] the logarithm of time of set is a linear function of the reciprocal absolute temperature. This gives a constant for the energy of activation. However, in these mixtures of low *p*H, the tendency to dissolve the gel is negligible, and a linear relation naturally results.

As the *p*H of the mixtures is increased, the difference in the effect of temperature on the gel-forming and gel-dissolving processes causes curvature in the formerly straight line relation between logarithm of time of set and reciprocal absolute temperature. This curvature is seen in the control curves of Munro and Pearce[9] and our curves of Fig. 1. It is unfortunate that only two temperatures were used for the alkaline gel mixtures containing phosphoric acid,[8] otherwise curvature might have been found there, also.

It would appear possible to find silicic acid gels in a very narrow *p*H range, above 11, which would be thermally reversible, since it is apparent that rise of temperature accelerates the dissolving process more than the setting process. We have been unable to find reports of such gels in the literature. We have made careful experiments to try to find such thermal reversibility, but have been unable to liquefy any of our alkaline gels by raising the temperature. Possibly this was because the gels could not be liquefied in the time available. We are attempting to find such gels, but the experiments will take a very long time, probably over six months or a year. They must be very slow setting gels and, if found, will be in a fairly narrow *p*H range between 11 and 13.

A second effect which changes the rate of the setting process is a change in the *p*H of the mixture between the time of mixing and time of set. This does not occur to a measurable degree in acidic mixtures which contain weak acids,[5,17] nor in the alkaline mixtures containing phosphoric acid,[8] since all of these mixtures are well buffered. It does occur, however, in acidic mixtures containing strong acids,[6,7] and in alkaline mixtures containing acetic acid, reported by Munro and Pearce,[9] and also in all of our work here. Figure 2 shows this.

In unbuffered mixtures, the *p*H rises between the time the mixture is produced and the time it sets to form a gel. This rise of *p*H is almost certainly due to the decrease in ionizability of the silicic acids during the condensation. This effect has already been described for acidic gel mixtures.[6] Now the same thing is occurring in the alkaline range, the relatively stronger monosilicic acids being replaced by more and more complex polysilicic acids which are capable of producing fewer H ions. Since these alkaline gels set more slowly as the *p*H is increased, this concurrent increase in *p*H will cause a change in the rate as the process is occurring. This also will tend to cause curvature in the curves for logarithm of time of set against reciprocal temperature.

A third point to discuss is the structure of the gels themselves. Acidic silicic acid gels are relatively firm, elastic, and only slightly opalescent. Alkaline gels are much softer and strongly opalescent. In acidic gels, the reverse tendency, which causes solution of the gel, is certainly negligible. Condensation therefore gives very large molecules, probably with many cross linkages. The gels are firm and elastic. In the alkaline range, condensation does not proceed so completely and cross linkages are probably absent. This is more true the higher the *p*H, since eventually a *p*H can be reached where the final stage of gel formation cannot take place. Probably, also, the degree of hydration is different at higher *p*H values, giving greater opacity.

Summary

A study has been made of the setting of alkaline silicic acid gels containing sodium silicate and acetic acid, especially as to the anomalous effect of temperature. In the higher *p*H range, above 10.5, rise of temperature produces increase in time of set. This differs from the effect with gel mixtures of *p*H below 10, where rise of temperature causes decrease in time of set.

No energy of activation can be calculated for these gel mixtures with *p*H above about 10.

The effect is probably due to the fact that rise of temperature accelerates the process of dissolving of the gel to a greater extent than it accelerates gel formation.

In mixtures with *p*H much above 11, the solution process is predominant and gels do not form.

During the process of setting, the *p*H of these poorly buffered alkaline mixtures increases considerably. This affects the rate of the process. It is probably due to the fact that the more complex the polysilicic acid is, the less is its tendency toward ionization.

No thermally reversible silicic acids were found.

Alkaline gels are softer and less elastic than acid gels, since condensation and cross linkage formation probably do not proceed so far in the alkaline gels.

(17) Hurd, Raymond, and Miller, *J. Phys. Chem.*, **38**, 663 (1934).

SCHENECTADY, NEW YORK RECEIVED NOVEMBER 8, 1943

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[CONTRIBUTION FROM THE BUTTERFIELD CHEMICAL LABORATORY, UNION COLLEGE]

Studies on Silicic Acid Gels. XVI. The Effect of Radiant Energy upon the Time of Set

BY CHARLES B. HURD AND WINTERTON U. DAY[1]

Introduction

The effect or lack of effect of radiant energy upon the time of set of silicic acid gels has been mentioned a number of times in the literature. With the exception of the statement by Ray and Ganguly[2] that ultraviolet radiation from a mercury vapor tube definitely accelerated the setting of the gel, the statements concerning the effect of light have indicated that there is little if any effect. One of us has already made such a statement.[3] A reading of these statements concerning the negligible effects of light upon the time of set, except for that of Ray and Ganguly,[3] already mentioned, leads to the belief that the matter has not been carefully studied. Such a study, however, is relatively simple.

It would be rather surprising if a reaction of the type believed to occur in the setting of a silicic acid gel, namely, a reaction of condensation,[3] should be found to be affected noticeably by radiant energy. We have therefore made some careful experiments to detect the effect, if any. The results are reported herewith.

In addition, we have conducted one series of experiments with the General Electric Company's Recording Spectrophotometer, giving transmittance curves in terms of the age of the gel mixture.

Experimental

The gel mixtures were prepared by mixing solutions of sodium silicate, "E" brand Philadelphia Quartz Company, and acetic acid, in the manner described in former publications from this Laboratory,[4] using the same water thermostats and testing for time of set by the "tilted rod" method.

The mixtures were placed in 100-cc. Pyrex Griffin beakers in the thermostat. The volume in each beaker was 80 cc. Several duplicate samples were run in each case, the result given being the average. Three sources of radiation were used, a 100-watt Mazda bulb, a highvoltage iron spark, 18,000 volts, which gave lines from 4000 to 2200 Å, and a capillary mercury arc giving about the same range.

With the Mazda lamp, the samples run in the "light" were in clear beakers covered by clear watch glasses or cellophane covers. It made no difference whether glass or cellophane covers were used. For the iron and mercury radiation experiments, only cellophane covers were used. All runs in the "dark" were made in the same size beakers, heavily painted on the outside with aluminum paint. They were covered with watch glasses, heavily painted on the upper side with aluminum paint. The mixtures, of course, were exposed to light for a few seconds as they were being prepared.

The most essential factor here is the temperature. It is very easy, unless great care is exercised, to have the radiation received by the gel mixture cause a slight temperature rise. Since the time of set is very greatly affected by the temperature, this can be a real source of error. We have controlled the temperature in the following manner. The 100-watt Mazda lamp was suspended over the beakers in the thermostat and it was lowered to the position nearest to the beakers, which still gave no noticeable temperature rise on a sensitive thermometer. The thermometer may not be left in the mixtures while the radiation is being received, since the bulb intercepts sufficient radiation to show a false indication of a rise. The radiation was allowed to fall in the beakers and their contents, both the unpainted and the painted, for about five minutes. Then the light was turned off and the thermometer inserted in the gel mixtures.

We are confident that the Mazda lamp was as near to the contents of the beakers as possible without causing a rise in temperature of the contents. Water filters for shutting off a portion of the rays were considered, but not used. We are not so confident that we succeeded in having the mercury and the iron spark sources as close as they might have been without producing a temperature rise, since the apparatus was clumsy and much more difficult to adjust to the minimum distance. However, the mixtures were exposed to intense radiation through their cellophane covers.

At this time, it was possible to run one series of mixtures using the General Electric Company Recording Spectrophotometer,[5] in order to determine the transmission characteristics of these silicic acid gel mixtures during the process of gel formation. A copy of the curve is shown.

Data and Discussion

The data reported in Table I are the averages of six determinations each, the "dark" and "light" running side by side in the thermostat.

TABLE I

EFFECT OF RADIATION UPON TIME OF SET OF SILICIC ACID GEL MIXTURES

Type of radiation	Time of set in minutes "Light"	"Dark"	Temp. in °C.	Concentrations in gram moles or gram ions per liter SiO_2	Na^+	$HC_2H_3O_2$
Mazda	150	149	25.6	0.667	0.407	0.875
Mazda	1186	1182	25.6	.498	.305	2.570
Iron	151	152	25.6	.667	.407	0.875
Iron and mercury	95	95	29.0	.667	.407	.624

It is obvious from this that we have been unable to detect any significant effect of radiation upon the time of set, using radiation which does not incidentally produce a rise in temperature. At least in the case of the radiation in the visible spectrum, the Mazda lamp, we had all of the radiation possible without a temperature rise. The discrepancies in time are certainly below the possible experimental error in determination of times of set, namely, about 1%.

In Fig. 1 is given a tracing of the curves drawn by the Recording Spectrophotometer for a mixture containing SiO_2 0.67, Na^+ 0.41, and $HC_2H_3O_2$, 0.55 g. mole per liter. The room temperature was 26°. The curves were drawn at

(1) Present address: Kimberly Clark Corporation, Neenah, Wisconsin.

(2) Ray and Ganguly, *J. Phys. Chem.*, **34**, 352 (1930).

(3) Hurd, *Chem. Revs.*, **22**, 403 (1938).

(4) Hurd, Raymond and Miller, *J. Phys. Chem.*, **38**, 663 (1934).

(5) We wish to thank the General Electric Company, and particularly Mr. J. L. Michaelson and Mr. W. R. Fanter, for their assistance.

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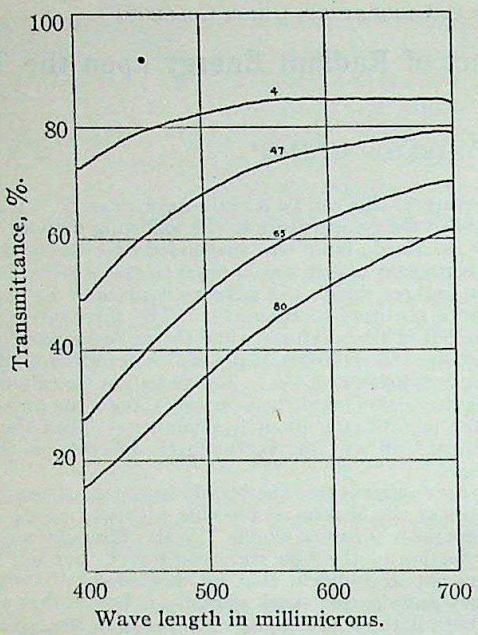

Fig. 1.—Transmittance of silicic acid gel mixtures as a function of wave length and age of sol.

four, forty-seven, sixty-five and eighty minutes after mixing, as indicated on the curve. The gel set in seventy-five minutes.

These transmittance curves are smooth, indicating no particularly strong absorption in any band. The curve of the mixture four minutes old shows the start of loss of the radiation of shorter wave length. This tendency increases with the age of the sol, until at age eighty minutes, which is five minutes after the gel has set, transmittance of radiation of 4000 Å. is only 0.15, while that of radiation 7000 Å. is 0.63 compared to a maximum of about 0.85 at the start, as shown on the four-minute curve. These results are probably due to the preferential scattering of radiation of smaller wave length. This scattering has been studied carefully by several investigators and the results reported.[6]

Summary

A study has been made of the effects of radiation upon the time of set of silicic acid gels, produced by mixing solutions of sodium silicate and acetic acid. Great care was taken that no measurable temperature change was produced by the radiation. Radiations from a Mazda lamp, a capillary mercury arc and an iron spark were used.

No significant effects of these types of radiation on the time of set were found.

A series of curves obtained with the Recording Spectrophotometer, showing the per cent. radiation transmitted by the sol are also given. The effect of age of the sol upon light transmitted is shown.

(6) Prasad, Mehta and Desai, *J. Phys. Chem.*, **36**, 1324 (1932).

SCHENECTADY, N. Y. RECEIVED NOVEMBER 8, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AT THE OHIO STATE UNIVERSITY]

Diolefins from Allylic Chlorides. II

BY ALBERT L. HENNE AND HENRY H. CHANAN

We have shown[1] that two molecules of butadiene hydrochloride react with magnesium in ether to give a mixture of 1,5-diolefins, the composition of which remains the same whether the primary form of the halide, its secondary form, or the equilibrated mixture of both forms is used as the starting material. These results were in agreement with some of Young's observations[2] on allylic equilibria.

This method of synthesizing 1,5-diolefins is now extended to five allylic chlorides grouped in a variety of pairs. Allyl and methallyl chlorides which exist in only one form (CH_2=$CHCH_2Cl$ and CH_2=$C(CH_3)CH_2Cl$) were purchased. Piperylene hydrochloride which also exists in only one form ($CH_3CHClCH$=$CHCH_3$) was made by adding dry hydrogen chloride to commercial piperylene. Butadiene and isoprene hydrochlorides were made similarly from commercial butadiene or isoprene; they both exist in two forms, namely, $CH_3CHClCH$=$CH_2 \rightleftarrows CH_3CH$=$CHCH_2Cl$; and $(CH_3)_2C$=$CHCH_2Cl \rightleftarrows (CH_3)_2$-$CClCH$=$CH_2$. All materials were supplied to us by a Research project of the American Petroleum Institute, directed here by Dr. C. E. Boord.

Experimentally, the condensations were carried out substantially as previously[1] described. Two different allylic chlorides were mixed in equimolecular proportion, and the mixture was added to magnesium turnings covered with dry ether. After completing the condensation and working up the products, a hydrocarbon fraction was obtained which amounted to about 35% of the quantity possible if pure allylic halides had been used and had condensed completely. It was, however, found more expedient to use the extremely impure materials obtained from a stream of hydrogen chloride through the commercial dienes and to discard from the condensation products all impurities, unreacted halides and resinified materials. From thirty to fifty moles

(1) Henne, Chanan and Turk, THIS JOURNAL, **63**, 3474 (1941).

(2) Young, *ibid.*, **54**, 404 (1932); **58**, 104, 289, 441 (1936); **59**, 2051 2441 (1937); **60**, 847, 900 (1938).

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TABLE I

CONDENSATION RESULTS OF EQUIMOLECULAR MIXTURES

Reacting chlorides	Molecular proportions and molecular percentages of condensed dienes					Total number of groups		
Allyl chloride and piperylene HCl	AA	PP	AP			A	P	
	1	4.8	15.3			17.3	24.9	
	4.7%	22.7%	72.5%					
Methallyl chloride and piperylene	MM	PP	MP			M	P	
	1	6	10			12	22	
	5.8%	35.4%	58.7%					
Butadiene HCl and piperylene HCl	B^2B^2	B^1B^2	B^1P	PP	B^2P	P	B^2	B^1
	1	13.2	21.3	22.0	29.3	94.6	44.5	34.5
	1.2%	15.2%	24.5%	25.3%	33.8%			
Allyl chloride and isoprene HCl	AI^3	I^1I^1	I^1I^3	AA	AI^1	A	I^1	I^3
	1	2.1	2.8	2.8	12.5	19.1	19.5	3.8
	4.7%	10.0%	13.2%	13.2%	58.9%			
Methallyl chloride and isoprene HCl	I^1I^3	I^1I^1	MI^3	MM	MI^1	M	I^1	I^3
	1	1.2	2.1	8.6	11.7	31	14.9	3.1
	4.0%	5.0%	8.5%	35.0%	47.5%			
Butadiene HCl and isoprene HCl	B^2B^2	I^1I^1	I^1I^3	B^1B^1	B^1I^3	B^1	B^2	
	1	5.6	8.2	11.3	13.1	92.1	89.3	
	0.65%	3.6%	5.3%	7.2%	8.4%			
	B^1B^2	B^1I^1	B^2I^1			I^1	I^3	
	28.2	28.2	59.1			106.7	21.3	
	18.3%	18.3%	38.3%					

of each halide was used to secure a quantity of hydrocarbons ample for adequate separation. Before subjecting them to repeated distillations through a 30-plate, helix-packed, total reflux-partial take-off, adiabatic column, the hydrocarbons were treated with sodium in liquid ammonia[3] until the disappearance of the Beilstein flame test indicated that they were free of halides. For physical measurements, only the centers of the distillation fractions were used. In the following list of results, the percentages of the various compounds refer only to the distilled product.

Experimental Results

Let each chloride be designated by its initial with a superscript (when needed) to denote a primary, secondary or tertiary isomer when two allylic isomers are possible. Thus A, M and P will designate allyl chloride, methallyl chloride and piperylene hydrochloride, while B^1 or B^2 will designate the two forms of butadiene hydrochloride, and I^1 or I^3 those of isoprene hydrochloride.

The results of the condensations are represented in Table I, where the relative amounts of the dienes obtained by condensation are given on a molar basis.

Quite a number of possible combinations were absent. In line with our previous observation[1] condensations between different molecules predominated over condensations between two identical molecules or two forms of the same molecule. In the fourth, fifth and sixth pairs, the ratio of the total number of I^1 groups to the total number of I^3 groups was consistently close to $I^1:I^3 = 5:1$. For the butadiene group, the ratio $B^1:B^2$ proved to be about 4:5 in the third pair, and about 1:1 in the sixth pair. In our preceding paper it had been found close to unity in the condensation of butadiene hydrochloride on itself, while it was about 5:3 in the condensation of butadiene hydrochloride with allyl chloride. The experimental data do not permit more precise generalizations.

The observed physical properties of the hydrocarbons, and the analyses of the new compounds, together with the symbols representing the diolefins appear in Table II.

Identifications

Most of the diolefins were new compounds. They were first analyzed as reported in the table, then hydrogenated to the corresponding paraffins to establish their carbon skeleton. Most of these paraffins were known. Where the paraffins were new compounds, it proved possible to show that their physical constants were measurably different from possible alternate formulas. Finally the position of the double bonds was determined by ozone oxidation, using procedures previously described.[4,5] In the following paragraphs, the observed data refer to the freezing point, the corrected boiling point at 760 mm, the density d^{20}_4 and the refractive index $n^{20}D$, in that order.

B reduced to 4-methylheptane,[6] glass, 117.6°, 0.7042, 1.3980. Ozonization gave formaldehyde, acetic acid and methylsuccinic acid, m. p. 110–

(3) Lebeau, *Bull. soc. chim.*, (3) **33**, 1089 (1905). Practical details will be published soon.

(4) Henne and Hill, *ibid.*, **65**, 752 (1943).

(5) Henne and Perilstein, *ibid.*, **65**, 2183 (1943).

(6) In agreement with information from the American Petroleum Institute.

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TABLE II

PHYSICAL CONSTANTS AND ANALYSES

	Name	Symbol	F. p., °C.	B. p., cor., °C.	d^{20}_4	$n^{20}D$	% C Calcd.	% C Found	% H Calcd.	% H Found	Other refs.
A	$CH_2=CHCH_2CH_2CH=CH_2$	AA			Known[1]						
B	$CH_2=CHCH_2CH(CH_3)CH=CHCH_3$	AP	Glass	110.3	0.7282	1.4231					*a*, *b*
C	$CH_3CH=CHCH(CH_3)CH(CH_3)CH=CHCH_3$	PP	− 64.8	153.3	.7662	1.4392					*b*
D	$CH_2=C(CH_3)CH_2CH_2C(CH_3)=CH_2$	MM			Known[1]						
E	$CH_3C(CH_3)CH_2CH(CH_3)CH=CHCH_3$	MP	Glass	132.1	0.7457	1.4312	87.0	87.0	13.0	13.2	
F	$CH_2=CHCH(CH_3)CH(CH_3)CH=CH_2$	B[1]B[1]			Known[1]						
G	$CH_2=CHCH(CH_3)CH_2CH=CHCH_3$	B[1]B[2]			Known[1]						
H	$CH_2=CHCH(CH_3)CH(CH_3)CH=CHCH_3$	B[2]P	Glass	129.8	0.7462	1.4312	87.0	87.0	13.0	12.9	*a*
I	$CH_2=CHC(CH_3)_2CH_2CH=CH_2$	AI[3]	Glass	101.6	.7249	1.4160	87.2	87.0	12.8	13.1	
J	$CH_2=CHCH_2CH_2CH=C(CH_3)CH_3$	AI[1]	Glass	119.1	.7406	1.4316	87.2	87.0	12.8	13.0	
K	$CH_2=CHC(CH_3)_2CH_2CH=C(CH_3)CH_3$	I[1]I[3]	Glass	149.7	.7657	1.4391	86.9	86.9	13.1	13.0	
L	$CH_3C(CH_3)=CHCH_2CH_2CH=C(CH_3)CH_3$	I[1]I[1]	−74.4	168.6	.7755	1.4478	86.9	87.0	13.1	13.2	*c*, *d*
M	$CH_2=C(CH_3)CH_2C(CH_3)_2CH=CH_2$	MI[3]	Glass	126.3	.7500	1.4288	87.0	86.8	13.0	13.2	
N	$CH_2=C(CH_3)CH_2CH_2CH=C(CH_3)CH_3$	MI[1]	−102.7	141.9	.7560	1.4389	87.0	87.1	13.0	13.1	*e*, *f*
O	$CH_3CH=CHCH_2CH_2CH=CHCH_3$	B[1]B[1]			Known[1]						
P	$CH_2=CHCH(CH_3)CH_2CH=C(CH_3)CH_3$	B[2]I[1]	Glass	134.6	0.7491	1.4330	87.0	87.2	13.0	13.0	
Q	$CH_3C(CH_3)=CHCH_2CH_2CH=CHCH_3$	B[1]I[1]	Not isolated from K				Separated as paraffin				
R	$CH_2=CHC(CH_3)_2CH_2CH=CHCH_3$	B[1]I[3]	Not isolated from O				Separated as paraffin				
S	$CH_3CH_2CH_2CH(CH_3)CH(CH_3)CH_2CH_2CH_3$		Glass	162.4	0.7446	1.4178					
T	$CH_3CH_2CH(CH_3)CH(CH_3)CH_2CH_2CH_3$		Glass	140.1	.7314	1.4108					
U	$CH_3CH_2C(CH_3)_2CH_2CH_2CH(CH_3)CH_3$		Glass	152.8	.7336	1.4123					

[a] Slotterbeck, Ph.D. Dissertation, O. S. U. (1936). [b] Mulliken, Wakeman and Gerry, THIS JOURNAL, 57, 1605 (1935). [c] Kresterisky, *J. Russ. Phys.-Chem. Soc.*, 46, 904 (1914). [d] Petrov, *J. Gen. Chem.* (U. S. S. R.), 9, 2129 (1939). [e] Harries and Weil, *Ber.*, 37, 846 (1904). [f] Escourrou, *Bull. soc. chim.*, [4] 39, 1249 (1926).

111°. C reduced to a new paraffin (S in table) measurably different from the possible known isomers. Ozonization gave acetaldehyde, acetic acid and a dicarboxylic acid m. p. 178–190° with a molecular weight of 147.4. This acid was regarded as a mixture of *dl*- and α,β-dimethylsuccinic acid. The pure *meso*-acid is said to melt[7] at 198° and 208° with decomposition, while the *dl*-mixture melts[7] at 127°; they can be separated by treatment with a benzene–ether mixture, in which the *dl*-form is more soluble than the *meso*-form. This treatment was applied to the dicarboxylic acid, and raised the m. p. to 188–189.5°. Further purification was deemed not to be indispensable, in view of the fact that the isomeric diacids melt much lower, *i. e.*, ethylsuccinic acid at 100°, and α,α-dimethylsuccinic at 141°. E reduced to 2,4-dimethylheptane,[8] glass, 133.1°, 0.7153, 1.4031. Ozonization gave formaldehyde, acetic acid and a keto-acid whose semicarbazone had m. p. 178° and analyzed correctly for $C_7H_{13}N_3O_3$ (calcd. C, 44.9; H, 7.0; N, 22.4. Found: C, 44.9; H, 7.0; N, 22.3). The keto acid was interpreted as being α-methyl-γ-ketovaleric acid, whose semicarbazone is said to melt[9] at 191° and also at 181°. H reduced to a new paraffin (T in table) measurably different from the known isomers. Ozonization gave formaldehyde, acetic acid and α,β-dimethylsuccinic acid m. p. 190° (*cf.* compound C) I reduced to 3,3-dimethylhexane,[6] glass, 112.2°, 0.7096, 1.4000. Ozonization gave formaldehyde and α,α-dimethylsuccinic acid m. p. 139°. J reduced to 2-methylheptane,[6] −109.6°, 117.6°, 0.6978, 1.3950. Ozonization gave formaldehyde, acetone with a 2,4-dinitrophenylhydrazone m. p. 125° and succinic acid m. p. 186°. K reduced to a new paraffin (U in table) measurably different from the known possible isomers. Ozonization gave formaldehyde and α,α-dimethylsuccinic acid m. p. 141°. L reduced to 2,7-dimethyloctane,[10] −50.7°; 160.0°; 0.7250; 1,4087. Ozonization gave acetone detected by the nitroprusside test, and succinic acid m. 187°. M reduced to 2,4,4-trimethylhexane,[11] −117.7°, 130.8°, 0.7231, 1.4068. Ozonization gave formaldehyde and α,α-dimethyl-γ-ketovaleric acid, with a semicarbazone, m. p. 196°. N reduced to 2,6-dimethylheptane,[12] −103.6°, 135.2°, 0.7102, 1.4009. Ozonization gave formaldehyde, acetone (color test) and levulinic acid with a semicarbazone m. p. 184.5° (calcd., N, 24.2. Found: N, 23.9). P reduced to 2.5-dimethylheptane,[13] glass, 136.2°, 0.7175, 1.4042. Ozonization gave formaldehyde, acetone (color test) and methylsuccinic acid, m. 110°. Q could not be isolated from K. The mixture was hydrogenated and the paraffins were separated. The paraffin ratio was taken to represent the diolefin ratio in the mixture. R could not be isolated from O. This ratio was computed from the relative quantities of paraffins, after hydrogenation.

Summary

Five allylic chlorides have been condensed in six different pairs to give a series of 1,5-diolefins, which were purified sufficiently to permit the listing of their physical properties and the determination of their relative abundance.

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(7) Heilbron, "Dictionary of Organic Compounds."
(8) Richards and Shipley, THIS JOURNAL, 38, 996 (1916).
(9) Béhal, *Bull. soc. chim.*, [3] 25, 245 (1901); also Baker and Laufer, *J. Chem. Soc.*, 1342 (1937).
(10) Calingaert, THIS JOURNAL, 58, 636 (1936).
(11) Mosher, Ph.D. Dissertation, Pennsylvania State College, 1940.
(12) White, *J. Research Natl. Bur. Standards*, 22, 317 (1939).
(13) Clarke and Beans, *Trans. Faraday Soc.*, 34, 54 (1912).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AT THE OHIO STATE UNIVERSITY]

Conjugated Diolefins by Double Bond Displacement. II

BY ALBERT L. HENNE AND HENRY H. CHANAN

The preceding paper[1] has described the rearrangement of seven 1,5-diolefins to conjugated dienes by passage over alumina heated to 365°. A new series of rearrangements has now been carried out at lower temperatures with a more efficient catalyst made of chromia deposited on alumina.

The use of chromia was proposed by Levina.[2] As chromia is a fine powder which packs and channels easily, it proved more convenient to use a mixed catalyst consisting of 5 mole per cent. of chromia on alumina, prepared by the method of Grosse and Ipatieff.[3] The equipment and the rearrangement procedure were substantially as described in our preceding paper, with refinements in temperature control to ensure uniform regulation within 2°, and increase in dimensions of the catalyst column to a width of 2 cm. and a length of 120 cm. The optimum temperature for rearrangement was determined in pilot experiments by passing 1,5-hexadiene (diallyl) over the catalyst at the rate of one drop in three seconds, at temperatures varied in 25° intervals, and separating the resulting 2,4-hexadiene (dipropenyl) by fractional distillation. As the temperature rose, the yield of dipropenyl went from 49% at 200° to 64% at 250°, 65% at 275° and 64% at 300°, but the amount of polymerization increased simultaneously from 7% to 9%, 12% and 14%. Consequently, a temperature of 250° was adopted as a standard for the whole study.

The progress of the rearrangement was followed by hourly readings of the refractive index. These readings which rose rapidly to a constant level due to the formation of the conjugated dienes, began in time to drop off markedly, showing that the catalyst was losing its efficacy. To regenerate the catalyst, the resinous deposit was first burned out by means of a stream of air at 450°. This treatment changed the color from the original blue-green to a bright orange, and at this stage a test for chromate ions was positive. After displacing the air with nitrogen, a stream of hydrogen was passed through at the same temperature for four hours; the catalyst, now green again, was then allowed to cool in a hydrogen atmosphere. This treatment restored the original efficacy, but became needed at increasingly shorter intervals.

All rearrangements were performed on freshly prepared or freshly regenerated catalysts. The diolefins tested were all of the 1,5-diene type; their synthesis was reported in another paper.[4]

TABLE I

TABLE OF EXPERIMENTAL RESULTS

Original diene	Rearrangement Products: Low boiling, %	Intermediates, %	Polymers, %	Orig. diene recov., %	Chief product	Yield, %	F. p., °C.	B. p., °C.	d^{20}_4	$n^{20}D$
$CH_2{=}CHCH_2CH_2CH{=}CH_2$	...	17.2	6.1	...	$CH_3CH{=}CHCH{=}CH_2$[a,b]	76.7	...	82.0	0.7242	1.4535
$CH_2{=}C(CH_3)CH_2CH_2C(CH_3){=}CH_2$	0.9	7.9	5.5	...	$(CH_3)_2C{=}CHCH{=}C(CH_3)_2$	85.5	−13.9	134.5	.7615	1.4781
$CH_2{=}CHCH(CH_3)CH_2CH{=}CHCH_3$	4.2	15.9	6.8	...	$CH_3CH{=}CHCH{=}C(CH_3)C_2H_5$[c]	73.1	Glass	136.9	.7621	1.4703
$CH_2{=}CHCH_2CH(CH_3)CH{=}CHCH_3$	5.7	31.9	15.0	8.1	$CH_3CH{=}CHC(CH_3){=}CHC_2H_5$[d]	37.1	Glass	135.9	.7653	1.4670
$CH_2{=}CHCH(CH_3)CH(CH_3)CH{=}CHCH_3$	4.4	51.5	11.5	9.9	$CH_3CH{=}CHC(CH_3){=}C(CH_3)C_2H_5$[e]	22.6	Glass	156.5	.7855	1.4768
$CH_2{=}CHCH_2CH_2CH{=}C(CH_3)_2$	5.6	27.7	5.4	6.7	$(CH_3)_2C{=}CHCH{=}CHCH_2CH_3$[f]	54.4	−96.4	135.8	.7559	1.4692
$CH_2{=}CHCH(CH_3)CH_2CH{=}C(CH_3)_2$	9.8	25.8	5.9	9.5	$(CH_3)_2C{=}CHCH{=}C(CH_3)C_2H_5$[g]	48.9	−63.1	156.9	.7732	1.4792

$CH_2{=}C(CH_3)CH_2CH(CH_3)CH{=}CHCH_3$; $CH_3CH{=}CHCH(CH_2)CH(CH_3)CH{=}CHCH_3$; $CH_3CHC(CH_3)_2CH_2CH{=}C(CH_3)_2$; $(CH_3)_2C{=}CHCH_2CH_2CH{=}C(CH_3)_2$; and $CH_2{=}C(CH_3)CH_2CH_2CH{=}C(CH_3)_2$ did not measurably rearrange.

[a] The intermediate was a mixture of original and rearranged materials, in which it proved impossible to detect the presence of 1,4- or 1,3-hexadiene. [b] Much better than the 39% yield reported by rearrangement over alumina. [c] Gave acetic acid, identified by Duclaux number and methyl ethyl ketone with a 2,4-dinitrophenylhydrazone, m. p. 115°. [d] Gave acetic acid identified by Duclaux number and propionic acid with a *p*-toluide m. p. 123.5°. [e] Gave methyl ethyl ketone with a 2,4-dinitrophenylhydrazone m. p. 115°, and acetic acid identified by Duclaux number. [f] Gave acetone with a 2,4-dinitrophenylhydrazone m. p. 125°; the sample in which the expected propionic acid was being worked up was accidentally lost. [g] Gave acetone and methyl ethyl ketone, with 2,4-dinitrophenylhydrazones m. p. 125 and 116°, respectively.

Experimental Results

The results of the rearrangements are listed in the table, together with the observed physical properties of the rearranged dienes. These physical measurements are equal to those reported

(1) Henne and Turk, THIS JOURNAL, **64**, 826 (1942).

(2) Levina, *J. Gen. Chem.* (U. S. S. R.), **7**, 1587 (1937); **9**, 1834 (1939).

(3) Grosse and Ipatieff, *Ind. Eng. Chem.*, **32**, 268 (1940).

(4) Henne and Chanan, THIS JOURNAL, **66**, 392 (1944).

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before[1] for the first three lines of the table and more precise than those in the literature for the third[5] and the fourth[6] line of the table.

Since the carbon skeleton of the molecules is not altered during the rearrangements, as shown before[1] by hydrogenation to known paraffins, the problem of identification is merely one of locating the double bonds. This was done by oxidation with ozone, using experimental procedures described previously.[7,8] The ozonization results are listed in the notes of the table.

Comments

For double bond displacement chromia-coated alumina proved considerably more efficient than plain alumina. It permitted operation at 250° instead of 365° and reduced polymer formation.

The ease of rearrangement was found contradictory. In agreement with our first experiments, terminal bonds shifted inwards with ease, particularly well over a methyl group in *iso*-position; yet two compounds so constructed failed to rearrange.

Summary

Twelve dienes of the 1,5-type were subjected to double bond shift at 250° over a catalyst made of chromia and alumina. Seven were transformed to conjugated diolefins, while five failed to rearrange to any appreciable extent.

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(5) Bjelouss, *Ber.*, **43**, 2332 (1910).
(6) v. Auwers and Westermann, *ibid.*, **54**, 2993 (1921).
(7) Henne and Hill, THIS JOURNAL, **65**, 752 (1943).
(8) Henne and Perilstein, *ibid.*, **65**, 2183 (1943).

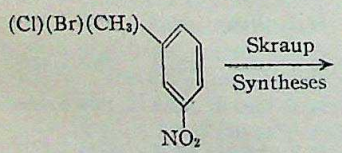
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Derivatives of 1,10-Phenanthroline[1]

BY FREDERIC RICHTER[2] AND G. FREDERICK SMITH

Although the application of the Skraup synthesis to 1,2-phenylenediamines suitably substituted in either the 4- and/or 5-positions might appear to be the most direct approach to the synthesis of 5 (6)-substituted (1,10)-phenthrolines the side reactions encountered practically preclude the isolation of the desired products.[3]

Application of the method of Skraup to suitably substituted 2-nitroanilines (I) followed by reduction of the resulting 8-nitroquinolines (II) and application of a second Skraup synthesis to the 8-aminoquinolines so formed (III) is the basis for the present series of syntheses



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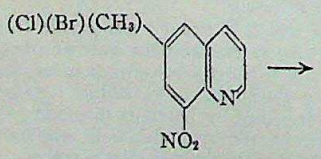

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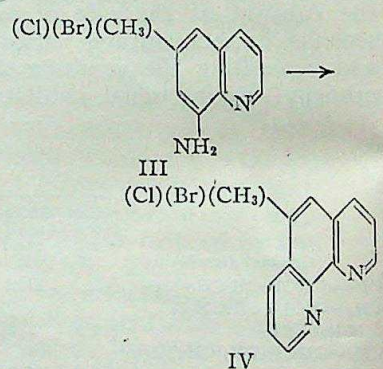
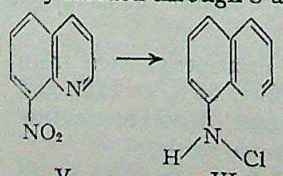


III IV

From the standpoint of orientation, at least, 2-nitroanilines substituted in either the 4- or 5-positions could be employed because these positions later become equivalent in 1,10-phenanthroline. In the present series only 4-substituted 2-nitroanilines were employed.

The 5(6)-chloro(1,10)-phenanthroline obtained by the above scheme agreed in melting point and other properties with that obtained by Kuczynski and Sucharda[4] who heated a mixture of 8-nitroquinoline, glycerol and hydrochloric acid under pressure. It is of interest to note that the chlorophenanthroline obtained by this method is probably formed through 8-amino-5-chloroquinoline



V VI

(1) This contribution contains material from a dissertation presented by Frederic Richter to the Graduate School of the University of Illinois in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1941.

(2) Aeration Processes Corporation Fellow in chemistry during the years 1939–1941. Present address: United States Rubber Company, Hogansville, Georgia.

(3) C. R. Smith, THIS JOURNAL, **52**, 397 (1930).

(4) Kuczynski and Sucharda, *Rocznicki Chem.*, **16**, 513 (1936).

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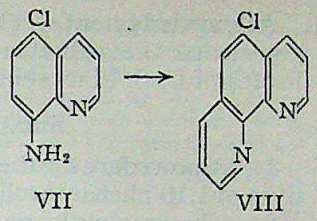

VII VIII

The first step is postulated as involving N-chlorination of (V). This is followed by rearrangement to (VII) and finally conversion to the phenanthroline. Under no condition would one expect the chlorine atom of (VI) to migrate to the 6-position (meta rearrangement). In the present series the chloro phenanthroline is obtained through 8-amino-6-chloroquinoline (III) and the fact that both products appear to be identical is good evidence for the equivalence of the 5- and 6-positions in 1,10-phenanthroline. This in turn points to a symmetrical structure for the base.

The synthesis of a 5(6)-bromo(1,10)-phenanthroline by a Skraup reaction on 4-bromo-1,2-phenylenediamine was previously claimed[5] and the melting point reported as 215° whereas the bromo derivative (IV) was found to melt at 119°. The analysis of our product and the correlation between the absorption spectra of the ferrous complexes of (IV) and the parent base, together with the difficulties encountered in attempting a synthesis from a 1,2-phenylenediamine indicate that the previously claimed[5] synthesis of 5(6)-bromo-(1,10)-phenanthroline is incorrect.

Attempts to obtain a 5(6) carboxylic acid by oxidation of the methyl derivative (IV) failed even under the mildest conditions, presumably because of the rupture of the 5,6-double bond. This is entirely analogous to the case of the corresponding methylphenanthrene where oxidation readily takes place at the 9,10-double bond to produce 2,2′-biphenyldicarboxylic acid.

The 5(6)-methyl derivative was found to undergo nitration with greater ease than the unsubstituted base. Under the same conditions, *viz.*, nitrating mixture, temperature and time, the methylphenanthroline gave a 20–25% higher yield of its nitration product than did the parent compound. This result was to be expected in view of the analogous case of toluene and benzene, the former undergoing the usual substitution reactions more readily than the latter. Nitration of either the methyl derivative or the parent compound undoubtedly takes place in the 5- or 6-position since one would hardly expect substitution to occur in the pyridine rings under the conditions employed.

Excellent correlation was found between the absorption spectra of the ferrous complexes of (IV) and that of the parent base over the wave length region of 400–670 millimicrons.

Experimental

Because of the difficulties encountered in the preliminary stages of this investigation in controlling the Skraup reactions a general procedure was developed. It was found that the directions usually given[6] include a ratio of sulfuric acid to glycerol which is too high and which usually results in excessive carbonization with consequent loss of yield. The best mass relations found were: one mole of the aromatic amine, four moles of glycerol (dried by passing dry air through the liquid for three hours at 170–180°), three-fourths mole of arsenic pentoxide and a weight of sulfuric acid (sp. gr. 1.84) equal to about 50–60% of the weight of glycerol employed. The use of stronger sulfuric acid, *e. g.*, 10–20% oleum, did not present any advantage.

In general, the amine, glycerol and arsenic oxide were weighed into a three-necked flask. This was then equipped with a glycerol-sealed stirrer, thermometer dipping into the liquid and a Pyrex water-cooled condenser with a calcium chloride tube for eliminating atmospheric moisture. The sulfuric acid was added through the condenser with vigorous stirring, and at such a rate as to maintain the temperature below 130°. The temperature was then held at 130–135° for one hour and finally the mixture was kept in active reflux for six additional hours. Longer heating did not improve the yields.

After cooling, the tarry reaction mixture was poured into water, neutralized in the cold with aqueous ammonia and the quinoline or phenanthroline recovered by filtration or extraction with boiling benzene. The nitroquinolines were employed without further purification. The reduction of the 6-chloro- and 6-bromo-nitroquinolines was accomplished with stannous chloride in hydrochloric acid solution; the nitromethylquinoline was reduced with ammonium sulfide formed *in situ* by passing hydrogen sulfide into an ammoniacal ethanol solution of the base.

8-Nitro-6-chloroquinoline.—Yield of dry, crude product 47–48 g. from 43.1 g. (0.25 mole) of 4-chloro-2-nitroaniline. A portion was recrystallized from ethanol, m. p. 159°.

5(6)-Chloro-(1,10)-phenanthroline.—Needles from benzene–petroleum ether, m. p. 123°; yield 24.0 g. (56%) from 35.7 g. (0.2 mole) of 8-amino-6-chloroquinoline.

Anal. Calcd. for $C_{12}H_7N_2Cl$: C, 67.13; H, 3.29; N, 13.06. Found: C, 67.17; H, 3.39; N, 12.92.

8-Nitro-6-bromoquinoline.—Yield of dry, crude product 60 g. from 54.3 g. (0.25 mole) of 4-bromo-2-nitroaniline, m. p. 170° (from ethanol).

8-Amino-6-bromoquinoline.—Recrystallized from petr. ether, m. p. 78°; yield 34.0 g. or 61% based on the 4-bromo-2-nitroaniline taken.

5(6)-Bromo-(1,10)-phenanthroline.—The monohydrate crystallized as white needles from moist benzene, m. p. 86°.

Anal. Calcd. for $C_{12}H_7N_2BrH_2O$: H_2O, 6.51. Found: H_2O, 6.93.

The anhydrous compound was obtained either by drying the monohydrate in a pistol (ethanol 1/2 mm.) or by recrystallizing from chloroform after distilling out the water of hydration, m. p. 119°; yield 11.8 g. or 46% based on the 8-amino-6-bromoquinoline (0.1 mole) taken.

Anal. Calcd. for $C_{12}H_7N_2Br$: C, 55.61; H, 2.72; N, 10.81. Found: C, 55.73; H, 2.85; N, 10.56.

5(6)-Bromo-(1,10)-phenanthroline Monopicrate.—Yellow needles from 95% ethanol, m. p. 228°.

Anal. Calcd. for $C_{18}H_{10}N_5O_7Br$: N, 14.34. Found: N, 14.28.

8-Nitro-6-methylquinoline.—Yield of dry, crude product 38–40 g. from 38.0 g. (0.25 mole) of 3-nitro-4-aminotoluene, m. p. 121–122° (from ethanol).

8-Amino-6-chloroquinoline.—Recrystallized from petroleum ether, m. p. 73°; yield 24.3 g. or 54% based on the 4-chloro-2-nitroaniline.

8-Amino-6-methylquinoline.—Recrystallized from petroleum ether, m. p. 60–62°; yield 19.2 g. or 49% based on the 3-nitro-4-aminotoluene.

5(6)-Methyl-(1,10)-phenanthroline.—The residue from the benzene extract was distilled *in vacuo* and the fraction,

(5) N. V. Nederlandsche Kininefabriek, French Patent 804454.

(6) E. G. Houben-Weyl, "Die Methoden der organischen Chemie," Part 3, Vol. 4, p. 369.

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b. p. 280–282° (13 mm.), recrystallized from benzene–petroleum ether, m. p. 114°; yield 38.2 g. or 66% based on the 8-amino-6-methylquinoline (0.3 mole) taken.

Anal. Calcd. for $C_{13}H_{10}N_2$: C, 80.38; H, 5.19; N, 14.43. Found: C, 80.58; H, 5.28; N, 14.60.

5(6)-Methyl-(1,10)-phenanthroline Monopicrate.—Fine yellow needles from 95% ethanol; m. p. 203–204°.

Anal. Calcd. for $C_{19}H_{13}N_5O_7$: C, 53.89; H, 3.10; N, 16.54. Found: C, 53.96; H, 3.27; N, 16.67.

5-Nitro-6-methyl-(1,10)-phenanthroline.—A mixture of 1.00 g. of 5(6)-methyl-(1,10)-phenanthroline (m. p. 114°), 5 cc. of sulfuric acid (sp. gr. 1.84) and 3 cc. of nitric acid (sp. gr. 1.42) was held at 120° for two hours. The yellow nitration mixture was poured onto 50 g. of ice and the cold solution neutralized with 30% sodium hydroxide. The precipitate was filtered off and dried: fine yellow needles from 95% ethanol; m. p. 268–270°; yield 0.98 g. (80%).

Anal. Calcd. for $C_{13}H_9N_3O_2$: N, 17.57. Found: N, 17.69.

Acknowledgment.—The authors gratefully acknowledge the valuable suggestions offered by Professor C. S. Marvel in the course of this work.

Summary

1. A procedure for the synthesis of 5(6) derivatives of 1,10-phenanthroline has been described.

2. The previously reported synthesis of 5(6)-bromo-1,10-phenanthroline has been proved erroneous.

3. Evidence for the equivalence of the 5- and 6-positions in 1,10-phenanthroline has been presented. This in turn indicates a symmetrical structure for 1,10-phenanthroline.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, MEDICAL RESEARCH DIVISION, SHARP & DOHME, INC.]

Tryptic Digestion of Bovine Serum and Other Proteins in the Presence of Ethyl Alcohol

BY EDWIN A. RISLEY, ANN C. BUFFINGTON AND L. EARLE ARNOW

In connection with some problems under investigation in this Laboratory, it became desirable to prepare tryptic digests of bovine serum. The chief difficulties encountered revolved around the slow digestion of relatively concentrated serum solutions and the development of putrefaction after a few days of digestion. It was found that both of these difficulties could be overcome if suitable amounts of ethyl alcohol were included in the digestive mixtures.

The effect of alcohol on tryptic digestion has not been investigated extensively. In 1896 Chittenden and Mendel[1] found that the digestion of fibrin by pancreatic extracts was inhibited by increasing concentrations of alcohol. However, appreciable digestion still occurred in 20% alcoholic solution. Vernon[2] stated that extracts of pancreas prepared with 25% alcohol were slightly less active in digesting fibrin than were similar extracts prepared with saline solution. Gizelt,[3] using egg white in Mett tubes as a substrate and pancreatic juice as a source of enzyme, found that alcohol in concentrations less than 20% inhibited enzymatic activity. Concentrations of 20% or higher abolished all enzymatic activity. Bayliss[4] suspended crude trypsin in 80% alcohol. This suspension was reported to digest gliadin slowly. Since most of the tryptic activity could be removed from the suspension by simple filtration, Bayliss concluded that trypsin in an insoluble form must still be active. Edie[5] concluded that the action of crude trypsin on fibrin was inhibited to some degree by concentrations of alcohol higher than 3%. Some digestion took place in 25% alcohol, but none was detected at 50%. On the other hand, no appreciable inhibition of digestion of casein was noted until the alcohol concentration was raised to 10% and, indeed, digestion in 25% alcohol was almost as efficient as in non-alcoholic media. Some digestion of casein occurred even in the presence of 50% alcohol. Abderhalden and Reich[6] studied the influence of various alcohols on the rate of tryptic digestion of *d,l*-leucylglycyl-*d,l*-leucine. No significant inhibition of digestion in concentrations of ethyl alcohol of 10% or lower was detected. Twenty per cent. alcohol markedly inhibited digestion of the peptide.

Experimental

The bovine serum used in these experiments was supplied to us in spray dried form through the courtesy of Dr. David Klein of the Wilson Laboratories. Difco trypsin, 1:250, was used as a source of enzyme. The alcohol employed was 95% ethyl alcohol. A micro-Kjeldahl method was used for nitrogen determinations. Amino nitrogen determinations were done with the Koch[7] modification of the Van Slyke[8] micro-apparatus.

Van Slyke[9] pointed out many years ago that the presence of alcohol causes the formation of excess gas in the amino nitrogen apparatus. Provided the concentration of alcohol is not too high, the excess gas can be removed by increasing the shaking time during absorption. In all the analyses reported in this paper, the solutions were diluted and, in the great majority of instances, contained approxi-

(1) R. H. Chittenden and L. B. Mendel, *Am. J. Med. Sci.*, **111**, 181 (1896).
(2) H. M. Vernon, *J. Physiol.*, **26**, 405 (1901).
(3) A. Gizelt, *Arch. ges. Physiol.*, **111**, 620 (1906).
(4) W. M. Bayliss, *J. Physiol.*, **50**, 85 (1915).
(5) E. S. Edie, *Biochem. J.*, **13**, 219 (1919).
(6) E. Abderhalden and F. Reich, *Fermentforsch.*, **11**, 64 (1929).
(7) F. C. Koch, *J. Biol. Chem.*, **84**, 601 (1929).
(8) D. D. Van Slyke, *ibid.*, **16**, 121 (1913).
(9) D. D. Van Slyke, *ibid.*, **12**, 275 (1912).

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mately 2% alcohol. In a few cases, the alcohol concentration in the diluted solution was as high as 10%. The following experiment indicates that analyses can be carried out accurately at these concentrations of alcohol. A tryptic digest of beef serum was diluted with water and with suitable alcohol water mixtures, and the various solutions thus formed were analyzed for total and amino nitrogen. The data are given in Table I.

TABLE I

ANALYSIS OF A DILUTED SERUM DIGEST IN THE PRESENCE AND IN THE ABSENCE OF ALCOHOL

Final alcohol concn., %		0	10	20
Nitrogen, mg. per cc.	Total	1.23	1.23	1.23
	Amino	0.32	0.32	0.33

Comparative Digestion of Bovine Serum and Casein in 20% Solution.—The following digestive mixtures were prepared: (1) 5 g. of bovine serum and 120 mg. of trypsin were suspended in sufficient 1% methyl *p*-hydroxybenzoate solution to make a volume of 25 cc. The mixture was well stirred. The methyl ester served as a preservative, although it was found to be ineffective for digestion periods of more than a few days. (2) 5 g. of serum, 120 mg. of trypsin, 5 cc. of alcohol, and sufficient water to make 25 cc. were mixed and well stirred. (3) Mixtures identical with the above two, except that casein was substituted for the dry serum, were prepared. All four mixtures were incubated at 37°. At the times indicated in Table II, aliquots were filtered and the filtrates were analyzed for total and amino nitrogen. The results obtained are given in Table II.

TABLE II

COMPARATIVE DIGESTION OF BOVINE SERUM AND CASEIN BY TRYPSIN

Time in hours	0[a]		24		48	
Substrate	TN[b]	AN%[c]	TN	AN%	TN	AN%
Bovine serum	12.5	7	23.0	16	21.0	26
Bovine serum + alcohol	10.6	10	20.1	30	24.1	32
Casein	0.7	4	22.7	39	23.2	44
Casein + alcohol	0.6	4	26.2	33	26.6	39

[a] Filtered at room temperature. [b] TN represents total nitrogen in mg. per cc. of filtrate. [c] AN% represents amino nitrogen as % of total nitrogen.

Under these experimental conditions, it is apparent that digestion of the beef serum proceeds more rapidly in the presence of the alcohol than in its absence. This difference in rate is most striking at twenty-four hours. The absolute values for amino nitrogen do not differ significantly in the presence or absence of alcohol when casein is the substrate, although somewhat more nitrogen goes into solution in the mixture containing alcohol.

Effect of Concentration of Trypsin on Digestion of Serum in the Presence of Alcohol.—Ten grams of dried serum was dissolved in 150 cc. of water with rapid stirring. After solution was complete, an additional 10 cc. of water was added. This serum solution was divided into 4 aliquots of 40 cc. each. To each aliquot were added 10 cc. of alcohol and the quantity of trypsin indicated in Table III. After stirring, all four mixtures were placed in the incubator at 37°. At various times, samples were removed and filtered, and the filtrates were analyzed for total and amino nitrogen. The results obtained are given in Table III.

As might have been anticipated, these data indicate that both the rate and extent of hydrolysis increase as the concentration of trypsin is increased. Incubation of serum with alcohol, but without added trypsin, resulted in precipitation of material containing nitrogen. The soluble material remaining after ninety-six hours of incubation was rich in amino nitrogen as compared with the original serum,

TABLE III

TRYPTIC DIGESTION OF BOVINE SERUM IN 20% ALCOHOLIC SOLUTION

Hours	Mg. of trypsin 0		50		100		150	
	TN[a]	AN%[a]	TN	AN%	TN	AN%	TN	AN%
0	5.8	6	5.9	8	6.2	9	5.9	12
2	5.7	8	6.0	20	6.2	17	6.5	20
22	5.7	7	5.5	25	6.2	33	6.4	45
96	3.6	17	6.0	39	6.0	53	6.3	59
119	3.5	19	6.0	39	6.0	52	5.9	61

[a] See footnotes after Table II.

and it is apparent that some slight digestion occurred. Probably this was due to the presence of enzymes in the serum.

Effect of Concentration of Alcohol on Digestion of Serum.—Mixtures containing 5% serum, 0.3% trypsin, and varying concentrations of alcohol were prepared and incubated at 37°. Total and amino nitrogen determinations were made on filtrates at intervals. The results are given in Table IV.

The data in this table indicate that the rate and extent of hydrolysis were decreased in the presence of alcohol concentrations exceeding 30%, although appreciable hydrolysis occurred even in the presence of 60% alcohol. Digestion proceeded steadily for long periods of time in concentrations of 10 to 30% alcohol. Five per cent. alcohol was not sufficient to prevent the development of putrefaction.

Digestion of Various Proteins in the Presence of Alcohol.—In addition to the use of alcohol, we have also frequently utilized digestion at 60° as a means of preventing putrefaction. Comparative figures for tryptic digestion of several proteins, with and without 20% alcohol, and at 37 and 60°, are given in Table V. The digestive mixtures employed contained 5% protein and 0.3% trypsin, and were adjusted to *p*H 7.6 (the *p*H of the serum solution). Where alcohol was not present, 1% methyl *p*-hydroxybenzoate was added as a preservative.

At the intervals indicated in Table V, filtered samples of each mixture were analyzed for total and amino nitrogen. The figures for one hundred forty-eight hours cannot be compared directly with the other data, since they were obtained in a separate experiment carried out at a later date.

These data indicate that, in general, digestion at 37° is as efficient in the presence of alcohol as in its absence except in the case of serum during early phases of digestion. In the case of soy bean protein considerably more nitrogen went into solution when alcohol was present. When the digestion was allowed to proceed at 60°, the presence of the alcohol decreased the rate and extent of digestion of all the proteins tested. This effect was most marked in the case of egg albumin.

Discussion

The experimental data recorded in this paper make it evident that efficient tryptic digestion at 37° can be obtained in the presence of ethyl alcohol in concentrations of 30% or less. When 5% dried serum in 8 *N* sulfuric acid was heated under reflux for twenty-four hours, the soluble amino nitrogen was found to be 82% of the total soluble nitrogen. Under the conditions used in our experiments, then, 70 to 80% of the potential amino groups were liberated after one or two weeks of incubation with a single charge of trypsin.

Putrefaction was not observed when the concentration of alcohol was 10% or higher. It would appear that alcohol should be a useful reagent for preventing putrefaction during the lengthy

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TABLE IV

TRYPTIC DIGESTION OF BOVINE SERUM IN THE PRESENCE OF VARYING CONCENTRATIONS OF ALCOHOL

Hours	% Ethyl alcohol: 5 TN[a]	5 AN%[a]	10 TN	10 AN%	20 TN	20 AN%	30 TN	30 AN%	40 TN	40 AN%	50 TN	50 AN%	60 TN	60 AN%
0	5.3	13	5.8	13	6.0	13	5.9	14	3.1	15	3.0	19	1.0	20
24	5.6	43	5.7	37	6.0	39	5.5	43	4.1	38	3.8	35	2.4	30
47			5.7	46	6.2	46	5.5	53						
71			5.7	52	6.2	51	5.5	58						
96	5.7	59							4.8	43	3.6	40	2.9	36
119	[b]		5.6	55	6.2	52	5.6	58						
144									4.8	46	3.9	44	3.1	39
172									4.8	47	3.9	45	3.0	39
191			5.6	63	6.2	54	5.6	58						
220									4.8	48	4.0	46	3.1	46
263			5.9	63	5.9	57	5.5	60						

[a] See footnotes after Table II. [b] After ninety-six hours this sample developed an odor indicative of putrefaction, and the experiment was terminated.

TABLE V

EFFECT OF ALCOHOL (20%) ON TRYPTIC DIGESTION OF VARIOUS PROTEINS

Substrate	37°C. Time, hours: 24 TN[a]	24 AN%[a]	48 TN	48 AN%	148 TN	148 AN%	60°C. Time, hours: 24 TN	24 AN%	48 TN	48 AN%	148 TN	148 AN%
Bovine serum	6.4	43	6.9	55	6.6	57	6.4	49	6.6	51	6.3	61
Bovine serum + alcohol	6.1	53	6.0	59	6.5	62	5.8	36	5.8	38	5.1	53
Casein	7.1	54	7.3	59	7.0	56	6.9	44	7.4	53	6.9	49
Casein + alcohol	4.6	51	5.9	58	7.5	54	6.2	40	7.2	41	6.9	47
Soy bean protein	2.5	52	2.4	60	2.7	71	4.0	41	4.5	41	4.8	44
Soy bean protein + alcohol	3.1	47	3.6	55	4.3	62	2.9	38	3.4	39	2.9	44
Lactalbumin	5.6	59	5.6	65	5.6	75	5.7	57	5.8	60	5.6	54
Lactalbumin + alcohol	5.4	61	5.6	67	6.2	55	5.4	41	5.7	43	..	..
Egg albumin	6.4	55	6.7	60	6.2	68	6.7	57	6.9	58	6.4	60
Egg albumin + alcohol	5.6	48	6.4	54	6.6	62	2.6	56	3.0	57	2.6	72

[a] See footnotes after Table II.

digestion periods required for certain experimental procedures and for the commercial preparation of some types of peptone.

It has been known for years that an antitrypsin is present in blood sera. A purified preparation of this material has been described by Schmitz.[10] The same worker has suggested that the trypsin (or trypsin-like protease) normally present in plasma is combined with its antiprotease.[11] The data in Table II indicate that concentrated (*i. e.*, 20%) solutions of dried bovine serum are resistant to tryptic digestion in the absence of alcohol. It is possible that this resistance is caused by the presence of serum antiproteases. If this is true, the role of the alcohol would appear to be the inactivation of (or the release of trypsin from) these antiproteases. This explanation of the action of the alcohol in our experiments is made more probable by reports indicating that the antitryptic power of serum is removed by treatment with acetone, phenol or chloroform.[12]

The probable importance of serum proteases and antiproteases both in physiological and pathological processes has become increasingly evident in recent years. Much of the important work in this field has been reviewed by Grob.[13] The possible roles of serum antiprotease and protease in the blood-clotting mechanism have been stressed by Ferguson.[14] Marked changes in the antitryptic power of the blood associated with anaphylaxis were observed by Burdon.[15] There is good evidence that serum antiproteases inhibit the growth of bacteria.[13] Holmes, Keefer and Myers[16] have made the interesting suggestion that the antiproteases in body fluids are of importance in the prevention of damage to tissue by proteases liberated from the leukocytes that accumulate in regions of suppuration. It is possible that some of the beneficial effects produced by the parenteral administration of blood, plasma, and serum may be related to the proteases and antiproteases present in these fluids.

Summary

1. Concentrated (20%) solutions of dried bovine serum are resistant to the action of trypsin.

(10) A. Schmitz, *Z. physiol. Chem.*, **255**, 234 (1938).
(11) A. Schmitz, *ibid.*, **250**, 37 (1937).
(12) K. Okubo, *Tohôku J. Exptl. Med.*, **4**, 427, 441 (1924); *Chem. Abs.*, **18**, 2533 (1924).
(13) D. Grob, *J. Gen. Physiol.*, **26**, 405, 423, 431 (1943).
(14) J. H. Ferguson, *Science*, **97**, 319 (1943); *Proc. Soc. Exptl. Biol. Med.*, **51**, 373 (1942).
(15) K. L. Burdon, *ibid.*, **49**, 24 (1942).
(16) W. F. Holmes, C. S. Keefer and W. K. Myers, *J. Clin. Investig.*, **14**, 181 (1935).

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This resistance can be overcome by the use of digestion mixtures containing 20% alcohol. It is suggested that the effect of the alcohol may be due to an inhibition of antiproteases present in the serum.

2. Tryptic digestion of serum proceeded smoothly in concentrations of 10 to 30% alcohol for as long as two weeks, at which time approximately 70 to 80% of the potential amino groups had been liberated.

3. Concentrations of alcohol higher than 30% inhibited tryptic digestion of serum, but appreciable hydrolysis occurred even in 60% alcohol.

4. Efficient digestion of several other proteins (casein, lactalbumin, soy bean protein, egg albumin) was obtained in the presence of alcohol (20%).

5. Digestion at 60°, instead of the more usual 37°, was less rapid and complete when alcohol (20%) was present in the digestion mixture.

6. It is suggested that ethyl alcohol is a useful reagent for preventing putrefaction during tryptic digestion.

Glenolden, Pa. Received October 30, 1943

[Contribution from the Avery Laboratory of Chemistry of the University of Nebraska]

α,β-Diamino Ketones. II.[1] Reactions of Thalline and Open Chain Secondary Amines with α-Bromo-β-aminoketones

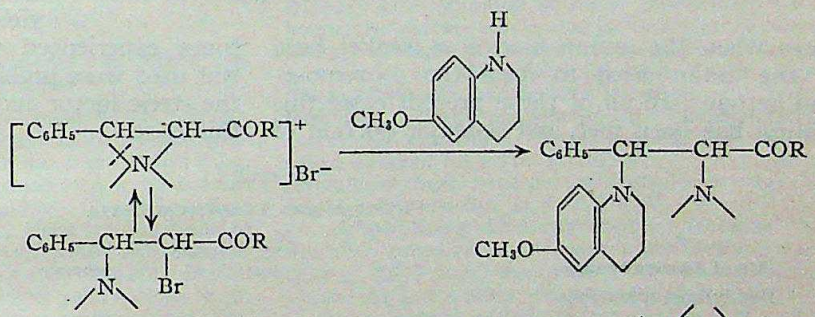
By Norman H. Cromwell, John A. Caughlan[2] and Gordon F. Gilbert

A wide variety of mixed diamino ketones may be prepared from α-bromo-α,β-unsaturated ketones. Since tetrahydroquinoline had been shown to react with α-bromo-β-aminoketones to give excellent yields of mixed diamino ketones[3] it seemed important to prepare for chemotherapeutic investigations the analogous tetrahydro-6-methoxyquinolino (thallino) compounds. Thalline for these investigations was prepared by a high pressure reduction of 6-methoxyquinoline using hydrogen and a copper chromite catalyst. The 6-methoxyquinoline was prepared by a modified Skraup reaction.

β-Piperidino- and β-morpholino - α - bromobenzylacetophenone and the corresponding benzylacetones reacted readily with thalline to give good yields of the mixed diamino ketones.

The only diamino ketone which had been prepared by treating an α-bromo-β-amino ketone with an open chain type of secondary amine was α,β-di-N-methylbenzylaminobenzylacetophenone.[4] Since this product was obtained in such low yields it seemed of interest to establish whether or not such low yields are to be expected generally when an open chain secondary amine is used in these reactions.

It was found that β-piperidino-α-bromobenzylacetophenone and β-piperidino-α-bromobenzylacetone reacted with N-methylbenzylamine, di-



I, N⟨ ⟩ = R = C_6H_5

II, N⟨ ⟩O = R = C_6H_5

VI, N⟨ ⟩ = R = CH_3

VII, N⟨ ⟩O = R = CH_3

benzylamine and N-methylethanolamine[5] to give from fair to poor yields, of the mixed diamino ketones.

It has been shown previously[3b] that these reactions give the best yields of the mixed diamino

(1) For the previous paper in this series see: Cromwell, Harris and Cram, This Journal, 66, 134 (1944).

(2) Eastman Kodak Co. Fellow, 1942–1943.

(3) (a) Cromwell, This Journal, 63, 2984 (1941); (b) Cromwell and Cram, *ibid.*, 65, 301 (1943).

(4) Cromwell and Witt, *ibid.*, 65, 308 (1943).

(5) The N-methylethanol amine for these experiments was generously furnished to us by the Carbide and Carbon Chemicals Corporation, New York, N. Y.

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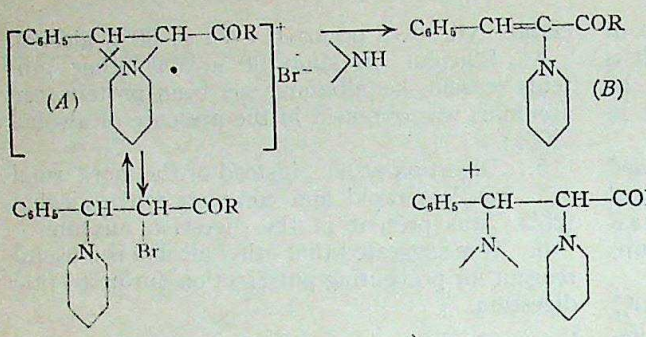

III, $>N = C_6H_5—CH_2$ (with $CH_3—N$) R = C_6H_5

IV, $>N = (C_6H_5—CH_2)_2N$ R = C_6H_5

V, $>N = HOCH_2CH_2—CH_3—N$ R = C_6H_5

VIII, $>N = C_6H_5—CH_2$ (with CH_3N) R = CH_3

IX, $>N = (C_6H_5—CH_2)_2N$ R = CH_3

X, $>N = HOCH_2—CH_2$ (with CH_3N) R = CH_3

ketones when the amine used is a weaker base than the amine used to form the α-bromo-β-amino ketone. In all of these present cases this condition has been met, but a major portion of the reaction seems to have proceeded in such a manner as to form the colored α-piperidinobenzalacetophenone and α-piperidinobenzalacetone (B).

This difference in the nature of the reactions of α-bromo-β-aminoketones with heterocyclic secondary amines as compared with the reactions with open chain secondary amines can possibly be explained on the basis of the relative steric effects of these two types of amines on the relative rates of the two competing reactions. The formation of the mixed diamino ketones from the quaternary ammonium salt (A) comes about through an attack of the amine, >NH, at the β-carbon atom. Open chain secondary amines might be expected to be more hindered in their approach to the β-carbon atom than the heterocyclic secondary amines such as thalline, etc. Moreover, the α-piperidino-α,β-unsaturated ketones (B) are formed from (A) by loss of a proton from the α-carbon atom of (A) followed by rearrangement to the products (B). This latter reaction to form (B) is more dependent on the basic strength and less dependent on the structure of the amine, >NH, than the former reaction that leads to the mixed diamino ketone. Thus the rate of formation of the mixed diamino ketone is slowed so as to allow more of (A) to be converted into (B), when open chain secondary amines are used in these reactions. The very low yields of the mixed diamino ketones experienced when N-methylethanolamine was used were probably due to a combination of the steric factor and the considerable strength of this base.

TABLE I

PHYSICAL AND ANALYTICAL DATA

Mixed diamino ketones	No.	M. p., °C., dec.	Yield, %	Formula	Percentage composition Calcd. C	Calcd. H	Found C	Found H
Benzylacetophenones								
α-Piperidino-β-thallino-	(I)	160	85	$C_{30}H_{34}N_2O_2$	79.26	7.54	79.06	7.82
α-Morpholino-β-thallino-	(II)	143	68	$C_{29}H_{32}N_2O_3$	76.28	7.07	76.27	7.22
α-Piperidino-β-N-methylbenzylamino-	(III)	140	36	$C_{28}H_{32}N_2O$	81.51	7.82	81.50	7.94
α-Piperidino-β-dibenzylamino-	(IV)	175	13	$C_{34}H_{36}N_2O$	83.56	7.43	83.46	7.49
α-Piperidino-β-N-methylethanolamino-	(V)	108	10	$C_{23}H_{30}N_2O_2$	75.37	8.25	75.48	8.32
Benzylacetones								
α-Piperidino-β-thallino-	(VI)	124	39	$C_{25}H_{32}N_2O_2$	76.49	8.17	76.35	8.43
α-Morpholino-β-thallino-	(VII)	126	40	$C_{24}H_{30}N_2O_3$	73.06	7.69	72.96	7.78
α-Piperidino-β-N-methylbenzylamino-	(VIII)	111	14	$C_{23}H_{30}N_2O$	78.81	8.63	78.67	8.59
α-Piperidino-β-dibenzylamino-	(IX)	160	4	$C_{29}H_{34}N_2O$	81.65	8.03	81.41	8.08
α-Piperidino-β-N-methylethanolamino-	(X)	132	5	$C_{18}H_{28}N_2O_2$	71.01	9.27	70.96	9.11

Experimental[6]

6-Methoxyquinoline.—A modified Skraup reaction[7] was applied to this preparation. In a liter round-bottom flask were placed 14 g. of well-powdered ferrous sulfate, 50.6 g. (0.41 mole) of *p*-anisidine and 36.8 g. (0.24 mole) of *p*-nitroanisole. A solution of 25 g. of boric acid dis-

(6) All m. p.'s were obtained by placing the sample in the bath about 10° below the m. p. and heating at the rate of 3° per minute. Micro-Dumas analyses for nitrogen and semi-micro carbon-hydrogen analyses are by the Analytical Laboratory, Department of Chemistry, University of Nebraska, under supervision of H. Armin Pagel.

(7) E. W. Cohn, THIS JOURNAL, 52, 3685 (1930).

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solved in 150 g. (1.63 mole) of dry glycerol was then added and the flask contents thoroughly mixed. To this mixture was then slowly added 69.8 ml. of 95% sulfuric acid with good stirring. The mixture was refluxed over a direct flame for twenty hours. The reaction solution was then diluted with one half its volume of water and cooled to 0° to precipitate some unchanged *p*-nitroanisole which was filtered off.

The filtrate was steam distilled to remove the last traces of *p*-nitroanisole, cooled and made alkaline with strong sodium hydroxide. The mixture was again steam distilled until the distillate was clear. The distillate was extracted with benzene and the benzene extract evaporated to give an oil which was diazotized with saturated sodium nitrite solution in an acid mixture of 20 ml. of concd. sulfuric acid and 150 ml. of water. After allowing the diazotized mixture to stand for one hour at 0° it was steam distilled for about two hours. The residual solution was then made alkaline and the 6-methoxy-quinoline steam distilled, and extracted from the distillate with benzene. The product was distilled under reduced pressure to give 35 g. of a light yellow oil, b. p. 182–184° (34 mm.) (yield 53% based on *p*-anisidine). This product was quite pure, m. p. 18–20°.[8]

Tetrahydro-6-methoxyquinoline (Thalline).—A solution of 88.5 g. (0.555 mole) of 6-methoxyquinoline dissolved in 175 ml. of absolute alcohol, and 9 g. of copper chromite catalyst[9] were placed in the bomb of a high pressure hydrogenator. This mixture was reduced under a pressure of 1800 lb./sq. in., and at a temperature of 180°, the theoretical amount of hydrogen being absorbed in fifteen minutes. The product was purified by vacuum distillation to give 84.1 g. (93% yield) of a pale yellow oil, b. p. 127–130° (1 mm.). The oil solidified on cooling, m. p. 42–43°[8]; n_{50}, 1.5718. The bright yellow picrate, which is not very stable in air was prepared, m. p. 164–165°.[10]

Mixed α,β-Diaminobenzylacetophenones and Mixed α,β-Diaminobenzylacetones

α-Piperidino-β-thallinobenzylacetophenone (I).—A suspension of 11.2 g. of α-bromo-β-piperidinobenzylacetophenone[11] in 18 ml. of absolute alcohol was treated with 9.7 g. of thalline. The mixture was warmed on a water-bath to 70° for one hour with frequent shaking. The clear orange solution was then cooled in the ice chest for five hours to give a yellow precipitate. The precipitated material was filtered, washed with 95% alcohol, water, then 95% alcohol and dried, to give 10.6 g. of a bright yellow solid, m. p. 151–153°. This crude product was recrystallized successively from chloroform and alcohol, and from benzene and petroleum ether and dried under vacuum at 90° for two hours, m. p. 159–160°.

The other new mixed diamino ketones prepared by essentially this same procedure were: (II) from α-bromo-β-morpholinobenzylacetophenone[12] and thalline; (VI) from α-bromo-β-piperidinobenzylacetone,[4] and thalline; and (VII) from α-bromo-β-morpholinobenzylacetone[13] and thalline.

α-Piperidino-β-N-methylbenzylaminobenzylacetophenone (III).—α-Bromo-β-piperidinobenzylacetophenone[11] (23.5 g., 0.063 mole) was made pasty with a 25% absolute alcohol–75% dry ether solution, and 15.3 g. (0.126 mole) of N-methylbenzylamine[14] added. After the mixture had stood at room temperature for twelve hours, it was placed in the ice chest for two days. The yellow precipitate was filtered off and purified in the previously described manner, to give 9.3 g. of light yellow needles, m. p. 138–140°.

The other new mixed diamino ketones prepared by essentially this same procedure were (V) from α-bromo-β-piperidinobenzylacetone[4] and N-methylethanolamine[5]; (VIII) from α-bromo-β-piperidinobenzylacetone and N-methylbenzylamine; and (X) from α-bromo-β-piperidinobenzylacetone and N-methylethanolamine, the product, however, was recrystallized from alcohol and water.

Hydrolysis of (III).—This diamino ketone (III) (5.0 g.) was heated on the steam-bath with 30 ml. of 15% sulfuric acid for two hours. The precipitated benzaldehyde was extracted with ether. Neutralization of the residual acid solution gave an oily precipitate which was removed by ether extraction. The ether extract was evaporated and the residual oil taken up in a small amount of methyl alcohol to which was added 8.5 g. of potassium hydroxide and 4.35 g. of hydroxylamine hydrochloride in 50 ml. of methyl alcohol and 9 ml. of water. After this reaction mixture had stood at room temperature for two days it was neutralized with dilute hydrochloric acid to give a white precipitate. Several recrystallizations of this product from alcohol and water gave 1.5 g. of white plates, m. p. 112–115°. This product was identical with a mixture of the high and low melting forms of the oxime of ω-piperidinoacetophenone, prepared from ω-piperidinoacetophenone.

Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.52; H, 8.31; N, 12.83. Found: C, 71.69; H, 8.50; N, 12.59.

α-Piperidino-β-dibenzylaminobenzylacetophenone (IV).—Freshly prepared α-bromo-β-piperidinobenzylacetophenone[11] (6.0 g., 0.0161 mole) was suspended in 15 ml. of absolute alcohol, and 6.35 g. (0.0322 mole) of dibenzylamine added. After standing at room temperature for twelve hours, the mixture was cooled in the icebox for forty-eight hours. A bright yellow precipitate formed. The solution was filtered and the precipitate washed with chloroform. The insoluble amine hydrobromide remained. The chloroform was partially evaporated from the diamino ketone and alcohol was added. A yellow precipitate was obtained which weighed 1.0 g., m. p. 167–169°, dec. This was recrystallized from benzene and petroleum ether to give bright yellow needles, m. p. 173–175°, dec.

α-Piperidino-β-dibenzylaminobenzylacetone (IX).—Freshly prepared α-bromo-β-piperidinobenzylacetone[4] (23.0 g., 0.074 mole) was made pasty with a 37% absolute alcohol–63% dry ether solution, and 29.5 g. (0.150 mole) of dibenzylamine added. After standing at room temperature for thirty minutes the mixture was cooled in the ice chest for four days to give a white precipitate. The solution was filtered and the precipitate was suspended in warm chloroform and again filtered. The insoluble amine hydrobromide remained. The chloroform was evaporated from the diamino ketone and the resulting oil taken up in ether, washed with three 25-ml. portions of water and dried over anhydrous sodium sulfate. This was filtered and the ether partially evaporated and petroleum ether added. A white precipitate was obtained which weighed 1.2 g., m. p. 144–148°, dec. This was recrystallized from 95% alcohol to give white crystals, m. p. 158–160°, dec.

Summary

1. A method of preparing tetrahydro-6-methoxyquinoline (thalline) has been described.

2. The preparation of ten new mixed diamino ketones has been outlined, and the general nature of the reaction of open chain secondary amines with α-bromo-β-amino ketones discussed.

Lincoln, Nebraska Received October 14, 1943

(8) Z. H. Skraup, *Monatsh.*, **6**, 760–784 (1885).
(9) "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., **19**, 31 (1939).
(10) Heilbron, "Dictionary of Organic Compounds," Vol. III, p. 740.
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(12) Cromwell, This Journal, **62**, 2897 (1940).
(13) Cromwell, *ibid.*, **62**, 3470 (1940).
(14) Cromwell, Babson and Harris, *ibid.*, **65**, 313 (1943).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH, AND THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH]

Some Derivatives of *cis*-3,6-Endomethylene-Δ^4-tetrahydrophthalic Acid

BY MARCUS S. MORGAN,[1] R. STUART TIPSON, ALEXANDER LOWY[2] AND W. E. BALDWIN

The compound *cis*-3,6-endomethylene-Δ^4-tetrahydrophthalic anhydride (I), formed by the addition of cyclopentadiene to maleic anhydride, was first described[3] in 1928. Although it has since been investigated extensively as regards reactions of its double bond,[4] very little has been reported on reactions involving its dicarboxylic anhydride grouping.

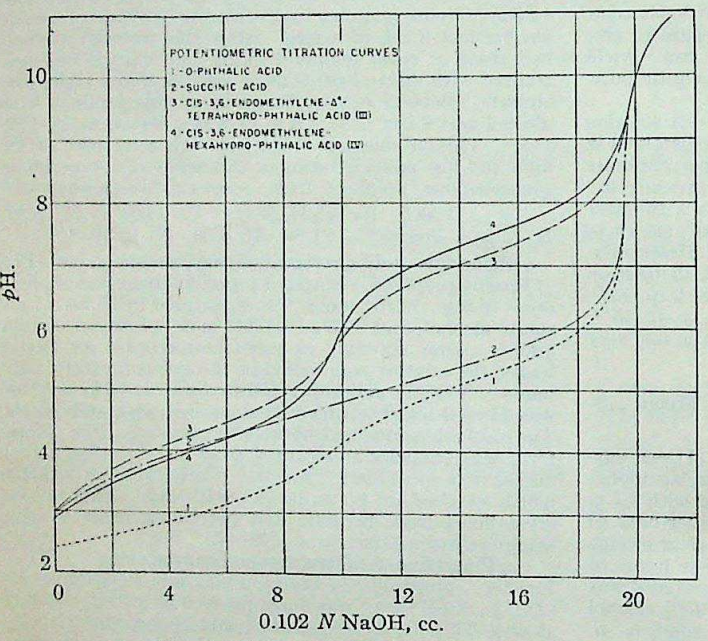


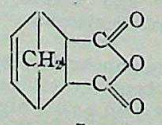
Fig. 1.—Potentiometric titration curves.

The present study was therefore initiated to obtain information on this aspect of the chemistry of compound I and its dihydro derivative II. Known reactions of phthalic anhydride served as a guide for the experimental procedures employed but modifications in mode of preparation and isolation of the products were usually necessary since compounds I and II were found to behave differently, in many respects, from phthalic anhydride.

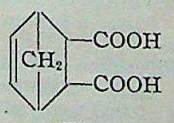
Diels and Alder[3] had prepared compound II by converting I to the free acid III, thence to the sodium salt which was hydrogenated (palladium catalyst) under low pressure; the free saturated acid IV was then liberated and transformed to the saturated anhydride II. This method is tedious for the preparation of II in large quantities and we have now found that hydrogenation of I to give II can be accomplished directly, in one step and in quantitative yield, by catalytic hydrogenation (Raney nickel catalyst) under high pressure.

The potentiometric titration curves for the two dibasic acids, III and IV, determined by means of a glass-electrode titration assembly, are given in Fig. 1. For comparison, the potentiometric titration curves for succinic and *o*-phthalic acids were determined under identical experimental conditions and the four curves have been superimposed on the same set of coördinates. The magnitude of the inflection at the midpoint of each curve is proportional to the value of K_1/K_2, calculated for acids III and IV from the figures for K_1 and K_2 determined by Bode.[5]

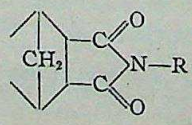
Certain di-esters of the unsaturated acid III were prepared using *p*-toluenesulfonic acid as catalyst (since it was found to have no effect on the sensitive double bond at position 4). The monomethyl ester, monoamide, monoamide monoammonium salt, ammonium salts, and certain imides (V) of acids III and IV have been prepared. It is seen that, with the exception of the unsubstituted imide, the melting point of each saturated compound is higher than that of its unsaturated analog. Attempts to isolate an anilic acid derivative of III or IV invariably resulted in the anil (V, R = C_6H_5).



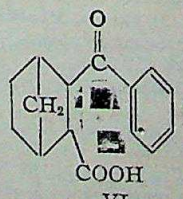
I
(II = dihydro deriv.)



III
(IV = dihydro deriv.)



V



VI

The unsubstituted imide was not changed by prolonged boiling with concentrated ammonium

(1) Based on a thesis submitted by M. S. Morgan to the Graduate School of the University of Pittsburgh in partial fulfillment of the requirements for the degree of Doctor of Philosophy, January, 1943. Contribution No. 507 of the Department of Chemistry, University of Pittsburgh.

(2) Deceased December 25, 1941.

(3) Diels and Alder, *Ann.*, **460**, 98 (1928).

(4) Alder and Stein, *ibid.*, **504**, 216 (1933); **514**, 1 (1934); Alder and Schneider, *ibid.*, **524**, 189 (1936).

(5) Bode, *Z. physik. Chem.*, **170A**, 231 (1934).

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hydroxide. Similarly, the dimethyl ester of III was unaffected by treatment with a saturated solution of ammonia in methanol, during several days at room temperature. This resistance to ammonolysis may be contrasted with the reactivity of the corresponding phthalic acid derivatives.

Anhydride II reacts readily with benzene in the presence of anhydrous aluminum chloride (Friedel–Crafts) to form the expected 3-benzoylnorcamphane-2-carboxylic acid (VI). However, formation of the corresponding derivative of anhydride I by this reaction could not be detected. On heating VI with concentrated sulfuric acid at 100°, ring closure to a quinone structure did not appear to take place.

Experimental

Dicyclopentadiene was obtained by purification of the commercial material[6] by distillation at atmospheric pressure to give the monomer and repolymerization to the dimer which was fractionally distilled at diminished pressure (about 10 mm.). **Cyclopentadiene** was prepared, as needed, by distillation of the purified dimer at atmospheric pressure in an atmosphere of nitrogen. The fraction boiling at 40.5 to 41° at 760 mm. was retained, and stored in a receptacle cooled in solid carbon dioxide–acetone.

***cis*-3,6-Endomethylene-Δ^4-tetrahydrophthalic anhydride** (I) was prepared as described by Diels and Alder[3] and recrystallized from dry benzene. It had m. p. 165°.

***cis*-3,6-Endomethylene-hexahydrophthalic Anhydride** (II).—The unsaturated anhydride (250 g.) was dissolved in 500 cc. of dry dioxane, 30 g. of Raney nickel catalyst was added and the suspension shaken, in an atmosphere of hydrogen at 45° and an initial pressure of 2,050 pounds per square inch, during ninety minutes. The suspension was then cooled, filtered and the filtrate evaporated to small volume; yield of crude product, 245 g. (97% of theoretical). It was recrystallized from dry benzene and then had m. p. 167.5–168°.

Potentiometric Titration.—Acids III and IV were prepared and purified as described by Diels and Alder.[3] A dry sample of the dibasic acid (0.001 mole) was dissolved in 75 ml. of carbon dioxide-free water. The *p*H of the original solution was measured and sodium hydroxide solution (0.102 *N*) then added in small increments of such size as to yield *p*H readings which were about 0.3 *p*H unit apart. All measurements were made under equilibrium conditions. The *p*H values corresponding to the volume of alkali added are summarized in the titration curves shown in Fig. 1.

Alkyl Esters: Monomethyl.—A solution of 6 g. of the appropriate anhydride (I or II) in 30 cc. of absolute methanol was boiled under a reflux condenser (closed by a calcium chloride tube) during ninety minutes. It was then cooled and evaporated to dryness under diminished pressure at 25°, giving a quantitative yield of crystalline product.

The Δ^4-compound was purified by washing with three successive 5-cc. portions of pentane. It had m. p. 76–78.5°.

Anal.[7] Calcd. for $C_{10}H_{12}O_4$: C, 61.21; H, 6.17; neut. equiv., 196.1. Found: C, 61.23; H, 6.14; neut. equiv., 200.7.

The saturated compound was recrystallized from hexane. It had m. p. 77–79°. The melting point of an intimate 50:50 mixture of the two esters was 60–62°.

Anal. Calcd. for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12; neut. equiv., 198.2. Found: C, 60.96; H, 6.58; neut. equiv., 201.5.

Dimethyl.—A mixture of 32.8 g. of the unsaturated anhydride with 0.5 g. of *p*-toluenesulfonic acid was dissolved in 60 cc. of absolute methanol and the solution boiled under a reflux condenser during ten hours. It was then cooled, evaporated to small volume and dissolved in 96% ether. The solution was washed successively with water, dilute sodium bicarbonate solution and water, dried with anhydrous calcium sulfate, filtered and the filtrate evaporated to dryness. The sirupy product was purified by distillation under diminished pressure: yield, 29 g. (69%) boiling at 136–137° at 12.5 mm. It was redistilled at 9 mm. (b. p. 129–130°) and then had $n^{20}D$ 1.4852, d^{21}_4 1.164 and neutral equiv., zero.

Anal. Calcd. for $C_{11}H_{14}O_4$: sapon. equiv., 105.1. Found: sapon. equiv., 106.5.

A solution of 5.4 g. of the dimethyl ester in absolute methanol saturated with dry ammonia at 0° was kept in the refrigerator during three days. The dimethyl ester was recovered unchanged on evaporation of the alcohol and ammonia in a vacuum desiccator over concentrated sulfuric acid. The refractive index was practically identical with that of the dimethyl ester and the nitrogen content was zero.

Diethyl.—The unsaturated anhydride (32.8 g.) was treated with 60 cc. of absolute ethanol, as for the dimethyl ester, giving 28 g. (59%) of product boiling at 136–140° at 7 mm. It was redistilled at 8 mm. (b. p. 138–140°) and then had $n^{20}D$ 1.4761, d^{21}_4 1.100 and neutral equiv., zero.

Anal. Calcd. for $C_{13}H_{18}O_4$: sapon. equiv., 119.1. Found: sapon. equiv., 118.5.

Di-*n*-butyl.—A mixture of the unsaturated anhydride (20 g.) with 0.5 g. of *p*-toluenesulfonic acid was dissolved in 50 g. of *n*-butanol and the solution boiled under reflux during ten hours, in an apparatus having a water-trap between the condenser and the flask. Most of the water formed during the reaction collected in this trap. The product was then isolated as for the dimethyl ester, giving 30.6 g. (85%) of material boiling at 187–188° at 12.5 mm. It was redistilled at 8 mm. (b. p. 174–176.6°) and then had $n^{20}D$ 1.4721, d^{21}_4 1.044, and neutral equiv., zero.

Anal. Calcd. for $C_{17}H_{26}O_4$: sapon. equiv., 147.1. Found: sapon. equiv., 148.6.

Imides—Unsubstituted Imides: (a) Using Ammonium Carbonate.—An intimately ground mixture of anhydride I (16.4 g.) and dry ammonium carbonate (18.0 g.) was heated slowly in an oil-bath until no more vapors were evolved (maximum reaction temperature, 200°). The product was extracted with hot 95% ethyl alcohol. On cooling, the extract yielded 7.3 g. of imide, m. p. 183–185°. With a maximum reaction temperature of 250° a dark red product, from which no imide could be readily isolated, was obtained.

(b) Using Dry Ammonia.—Dry ammonia was passed over the molten anhydride (I or II) in an oil-bath at 170° until the gas was no longer absorbed.

(Δ^4) Imide.—As the ammonia was absorbed, the product solidified to an almost colorless substance (except for a yellowish color on the surface, due to oxidation). Recrystallization from hot water resulted in a yield of 13.7 g. (84% of theoretical) of crystalline imide, m. p. 186.5–187°. On admixture with a sample of the product from (a) the m. p. was 185–186.5°.

Anal. Calcd. for $C_9H_9O_2N$: C, 66.23; H, 5.56; N, 8.59. Found: C, 66.30; H, 5.53; N, 8.58.

(Sat.) Imide.—On cooling, the product solidified to a colorless mass, m. p. 143–149°. A portion of the crude imide (9 g.) was extracted with pure, dry ethyl acetate in a Soxhlet extractor. On evaporation at room temperature, the extract yielded a colorless, crystalline product weighing 7.5 g. and having m. p. 168–174°.

The following method of recrystallization gives an analytically pure, crystalline product. The imide (5 g.) was dissolved in dilute ammonium hydroxide (30 cc. of 2:1)

(6) Kindly presented by the Carnegie-Illinois Steel Corporation Fellowship at Mellon Institute.

(7) All carbon and hydrogen determinations were performed microanalytically by Dr. Carl Tiedcke, New York, N. Y.

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and refluxed during thirty minutes. On slowly cooling the solution to 5°, colorless, hexagonal-shaped crystals, m. p. 174–175.5°, separated in quantitative yield.

Anal. Calcd. for $C_9H_{11}O_2N$: N, 8.48. Found: N, 8.47.

Substituted Imides. (Δ^4) N-Phenyl-imide.—A solution of 5 ml. (slight excess) of aniline in 20 ml. of dry benzene was added to a warm solution of 8.2 g. of anhydride I in 40 ml. of benzene. The resulting precipitate was filtered off and washed successively with benzene, hydrochloric acid (1:1) and cold water. It was recrystallized by dissolving in hot glacial acetic acid and adding water to the warm solution almost to turbidity, resulting in the crystalline anil, m. p. 144°.

Anal. Calcd. for $C_{15}H_{13}O_2N$: N, 5.85. Found: N, 5.59.

(Sat.) N-Phenyl-imide.—Aniline (4.4 ml.) was slowly added to a solution of 8.3 g. (slight excess) of anhydride II in 25 ml. of chloroform. An exothermic reaction took place with the formation of a heavy, colorless precipitate. This was filtered off, washed with chloroform and air-dried. The yield was 12 g. of product having m. p. 175–176° (dec.). If the anhydride (II) exhibits all the properties typical of a dicarboxylic anhydride,[8] this material is the anilic acid derivative. However, all attempts to purify the "anilic acid" resulted in the anil. (a) Recrystallization from either hot glacial acetic acid or hot ethyl alcohol (95%) (to each of which water was added almost to turbidity) resulted solely in the crystalline anil, m. p. 152–153°. A mixed m. p. with the analytically pure anil described in (b) showed no depression.

(b) An attempt to isolate the sodium salt of the anilic acid resulted in the anil. The substance (3 g.) with m. p. 175–176° (dec.) was suspended in 100 ml. of 50% ethyl alcohol (at 25°) and the suspension rendered slightly alkaline with 10% sodium carbonate solution (15 ml.). Evaporation of the solution at room temperature (vacuum desiccator) to half its original volume gave 2.3 g. of beautiful, needle-like crystals, m. p. 151.5–152.5°. On recrystallization from ethyl alcohol–water (5:3), the crystalline anil had m. p. 152–153°.

Anal. Calcd. for $C_{15}H_{15}O_2N$: C, 74.65; H, 6.27; N, 5.81. Found: C, 74.58; H, 6.50; N, 5.81 (Dumas); N, 5.55 (Kjeldahl).

(Δ^4)-N-*p*-Tolyl-imide.—A solution of 5.4 g. of *p*-toluidine in 20 ml. of dry benzene was added to a solution of 8.2 g. of anhydride I in 30 ml. of dry benzene. On standing, a heavy colorless precipitate (11.2 g.) was formed. This was filtered off and washed successively with benzene, dilute hydrochloric acid and water. Crystallization from either hot glacial acetic acid or ethanol, each diluted with water almost to turbidity, resulted in the N-*p*-tolyl-imide, m. p. 156.5–157°.

Anal. Calcd. for $C_{16}H_{15}O_2N$: N, 5.53. Found: N, 5.52 (Dumas); N, 5.20 (Kjeldahl).

N-Benzyl Imides.—A solution of sodium ethoxide was prepared by dissolving 0.15 g. of oxide-free sodium in absolute ethanol (25 ml.) under a reflux condenser (anhydrous calcium sulfate tube). The imide (1.12 g.) was then added and the mixture refluxed during twenty minutes. A solution of benzyl chloride in 10 ml. of absolute ethanol was now added to the suspension and refluxing was continued during one hour. The ethanol suspension was filtered while still hot and water added to the hot filtrate, almost to turbidity. This solution gave the crystalline N-benzyl-imide on rapid cooling and agitation with a glass rod or, preferably, on evaporating under diminished pressure at 40°.

Unsaturated: m. p. 82.5–83.5°.

Anal. Calcd. for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found: C, 75.31; H, 5.87; N, 5.46.

Saturated: m. p. 101–103°.

Anal. Calcd. for $C_{16}H_{17}O_2N$: N, 5.49. Found: N, 5.47.

Amides—A. Monoamide Monoammonium Salts.—The finely powdered anhydride (0.05 mole) was added in small portions to 20 ml. of concentrated ammonium hydroxide in a mortar and the mixture intimately ground after each addition. Finally, 10 ml. of ethyl alcohol was added, the insoluble salt filtered off and dried to constant weight in a vacuum desiccator over sulfuric acid.

Unsaturated: m. p. 172° (dec.).

Anal. Calcd. for $C_9H_{14}O_3N_2$: N, 14.14. Found: N, 14.00.

Saturated: m. p. 177° (dec.).

Anal. Calcd. for $C_9H_{16}O_3N_2$: N, 13.99. Found: N, 13.20.

B. Amidic Acids.—Concentrated hydrochloric acid (5.8 ml.) was added dropwise, with continuous stirring, to a suspension of the monoamide monoammonium salt in water (55 ml.) until just acid to congo red, while maintaining the temperature between 0 and 5°. The resulting colorless precipitate was filtered off and washed with successive small portions of cold water until the last washing was not acid to congo red. The product was lixiviated with two 20-ml. portions of acetone, giving a dry, colorless product. Owing to its instability, recrystallization was not attempted. (When a solution of the monoamide monoammonium salt was treated in the cold with an excess of concentrated hydrochloric acid and allowed to stand at 5° for twenty-four hours before filtering, the resulting product proved to be the dibasic acid.)

Unsaturated: m. p. 136° (dec.).

Anal. Calcd. for $C_9H_{11}O_3N$: N, 7.73. Found: N, 7.93.

Saturated: m. p. 165–166° (dec.).

Anal. Calcd. for $C_9H_{13}O_3N$: N, 7.65. Found: N, 7.74.

Ammonium Acid Salts.—The amidic acid (0.8 g.) was suspended in carbon dioxide-free water (10 ml.) and the acid was dissolved by boiling the suspension under a reflux condenser on a steam-bath during forty minutes. The colorless solution was then evaporated to dryness in a vacuum desiccator. After washing the crystalline residue with 20 ml. of purified acetone (dried with anhydrous potassium carbonate and distilled), it was dried in a vacuum desiccator over phosphorus pentoxide.

Unsaturated: m. p. 148° (dec.).

Anal. Calcd. for $C_9H_{13}O_4N$: N, 7.03. Found: N, 6.91.

Saturated: m. p. 149–150° (dec.).

Anal. Calcd. for $C_9H_{15}O_4N$: C, 53.72; H, 7.51; N, 6.96. Found: C, 53.82; H, 7.58; N, 6.96.

Diammonium Salt.—An excess of concentrated ammonium hydroxide (6 ml.) was added to a suspension of 5 g. of the dibasic acid (III) in 80 ml. of water, with constant stirring. The resulting solution was evaporated in a vacuum desiccator over concentrated sulfuric acid. On removal of most of the solvent the product set to a solid mass of colorless crystals. It was filtered off and dried thoroughly at room temperature.

Unsaturated: m. p., indefinite.

Anal. Calcd. for $C_9H_{16}O_4N_2$: C, 49.99; H, 7.46; N, 12.97. Found: C, 49.83; H, 7.06; N, 12.51.

Attempted Preparation of the Diamide.—A solution of the saturated unsubstituted imide (1.5 g.) in concentrated ammonium hydroxide (6 ml.) was refluxed during twenty minutes. On cooling, a crystalline product was obtained which, after drying, weighed 1.3 g. and had m. p. 175–176°. After sublimation at 160° under reduced pressure it had m. p. 174.5–175°.

Anal. Calcd. for $C_9H_{14}O_2N_2$ (diamide): N, 15.38. Calcd. for $C_9H_{11}O_2N$ (imide): N, 8.48. Found: N, 8.47.

3-Benzoyl-norcamphane-2-carboxylic Acid (VI).—One-tenth mole (16.6 g.) of II was dissolved in 100 ml. of dry,

(8) W. J. Hickinbottom, "Reactions of Organic Compounds," Longmans, Green and Co., New York, N. Y., 1936, p. 198.

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thiophene-free benzene, and anhydrous aluminum chloride (30.5 g.; 0.23 mole) added in one portion with continuous stirring and cooling. The temperature of the reaction mixture was now raised slowly to 45° during thirty minutes and maintained at 45° for thirty minutes.

After cooling the reaction mixture in an ice-bath, 100 g. of chopped ice was added slowly, followed by 20 cc. of concentrated hydrochloric acid and enough water to bring the final volume to about 250 ml. The excess benzene was then removed by steam distillation. The colorless reaction product was filtered, washed with cold water, dissolved in 75 ml. of aqueous sodium carbonate solution (10%) and the solution boiled during three hours. After filtering, the solution was rendered acid to congo red by addition of concentrated hydrochloric acid (10 ml.) and the resulting colorless precipitate was filtered off, and washed with cold water. The yield of dry, crude 3-benzoyl-norcamphane-2-carboxylic acid was 20.3 g. (87% of theoretical), m. p. 150–158°.

The compound is soluble in benzene, ether, glacial acetic acid, hot ethyl acetate, acetone or chloroform. It is insoluble in water or petroleum ether.

A portion (12 g.) of the acid was recrystallized by dissolving in 300 ml. of hot, dry benzene and adding 50 ml. of petroleum ether to the warm solution. On cooling, a crystalline precipitate was obtained which, after filtering and drying, weighed 6.7 g. and had m. p. 170–173°. The filtrate was evaporated until the volume was about 50 ml., whereupon an equal volume of petroleum ether was added, resulting in a second crop of crystalline product (5.2 g.) having m. p. 170–171°.

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60; neut. equiv., 244.2. Found: C, 74.12; H, 6.84; neut. equiv., 247.0.

Attempted Cyclization of VI to the Substituted Anthraquinone.—A small portion of the acid (VI) was dissolved in 1 ml. of concentrated sulfuric acid and heated on the steam-bath during forty-five minutes. On pouring the resulting yellow-colored solution into 10 ml. of water, a colorless precipitate was formed. It was filtered off and washed free of acid. On examining the product for the presence of the quinone structure, the tests were negative, indicating that cyclization to the substituted anthraquinone had not occurred.

Summary

1. *cis*-3,6-Endomethylene-hexahydrophthalic anhydride (II) has been prepared by direct catalytic hydrogenation (under high pressure) of *cis*-3,6-endomethylene-Δ^4-tetrahydrophthalic anhydride (I).

2. A number of new alkyl esters, imides, amides and ammonium salts of the two acids corresponding are described.

3. The synthesis of 3-benzoyl-norcamphane-2-carboxylic acid (VI) by a Friedel–Crafts reaction is given.

PITTSBURGH, PA. RECEIVED OCTOBER 6, 1943

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF MERCK & CO., INC.]

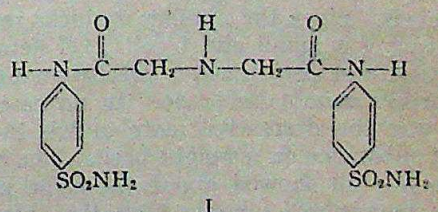
N⁴-Substituted Sulfonamides

BY JACOB FINKELSTEIN*

In 1938, Fourneau and co-workers[1] showed the formyl and acetyl sulfanilamides were considerably less active than sulfanilamide against streptococcal infections. However, in a rather thorough study of the effect of various acyl groups on the activity of sulfanilamide, Miller, Rock and Moore[2] found that the caproyl derivative was as effective as the parent drug and yet, less toxic. During that time, we have prepared several N⁴-substituted derivatives of the several widely used sulfa drugs. Among these compounds are several already recorded in the literature. However, they are included in this report because the work has been extended to include their action against other pathogenic organisms and to present a more complete basis for comparison with related substances.

The chloroacetyl compounds were prepared by two methods. In one, the required chloroacetyl chloride was added dropwise to an ice-cooled suspension of the drug in an inert solvent, and in the other, the chloroacetyl chloride was added to an aqueous solution of the sulfa drug in dilute sodium hydroxide. The aminoacetyl compounds were obtained by dissolving the chloroacetyl derivatives in aqueous ammonia, warming at 40° for twenty-four to forty-eight hours, followed by evaporation of the solvent. These compounds were difficult to purify because of their unfavorable solubility properties.

The preparation of N⁴-aminoacetylsulfanilamide was reported by Pollak, *et al.*,[3] who recorded a melting point of 259°, whereas our product melted at 216–218°. Therefore, we repeated their work using liquid ammonia in place of aqueous ammonia, and obtained a product which melted at 256–258°. The analysis of this compound indicated the empirical formula $C_{16}H_{19}N_3S_2O_6$ and it most likely is (I) α,α'-iminobis-(N⁴-



I

acetylsulfanilamide), which the above authors erroneously reported as glycyl sulfanilamide, in spite of the fact that their recorded analytical values agree with those of the desired compound.

The substances here discussed were tested at the Merck Institute for Therapeutic Research by

* Present address: Hoffmann-LaRoche, Inc., Nutley, N. J.

(1) Fourneau, *Compt. rend. soc. biol.*, **122**, 258 (1938).

(2) Miller, Rock and Moore, THIS JOURNAL, **61**, 1198 (1939).

(3) Pollak, *et al.*, *Monatsh.*, **58**, 118 (1931).

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TABLE I

Compound	From	M. p., °C.	Empirical formula	Calcd., % C	H	N	Found, %[e] C	H	N
N^4-Chloroacetylsulfanilamide[a]	Water	211–213	$C_8H_9N_2SO_3Cl$	38.64	3.64	11.26	38.62	3.38	11.02
2-(N^4-Chloroacetylsulfanilamido)-pyridine	Dioxane	192–193	$C_{13}H_{12}N_4SO_3Cl$	47.94	3.71	12.90	47.93	3.86	13.07
2-(N^4-Chloroacetylsulfanilamido)-thiazole	Abs. alc.	205–206	$C_{11}H_{10}N_4S_2O_3Cl$	39.83	3.04	12.66	39.82	3.14	12.46
2-(N^4-Chloroacetylsulfanilamido)-4-methylthiazole	Abs. alc.	231–232	$C_{12}H_{12}N_4S_2O_3Cl$	41.69	3.50	12.15	42.38	3.76	11.72
2-(N^4-Chloroacetylsulfanilamido)-pyrimidine	Abs. alc.	208–210	$C_{12}H_{11}N_4SO_3Cl$	44.12	3.40	17.14	44.36	3.66	17.36
N^4-Aminoacetylsulfanilamide[a]	Water	216–218	$C_8H_{11}N_3SO_3$	41.93	4.84	18.33	41.95	5.03	18.57
2-(N^4-Aminoacetylsulfanilamido)-pyridine	Water	220–221	$C_{13}H_{14}N_4SO_3$	50.98	4.53	18.29	50.70	4.76	17.97
2-(N^4-Aminoacetylsulfanilamido)-thiazole	Water	215–216	$C_{11}H_{12}N_4S_2O_3$	42.31	3.88	17.94	41.87	3.88	17.34
2-(N^4-Aminoacetylsulfanilamido)-4-methylthiazole	Abs. alc.[b]	205–206	$C_{12}H_{14}N_4S_2O_3$	44.18	4.23	17.17	43.75	4.36	16.78
2-(N^4-Aminoacetylsulfanilamido)-pyrimidine	Water	238–240	$C_{12}H_{13}N_5SO_3$	46.91	4.24	22.79	47.04	4.27	22.57
α,α'-Iminobis-(N^4-acetylsulfanilamide)[c]	Water	260	$C_{16}H_{19}N_5S_2O_6$	43.54	4.34	15.86	43.62	4.37	15.33
2-(N^4-Caproylsulfanilamido)-pyridine[d]	Abs. alc.	193–194	$C_{17}H_{21}N_3SO_3$	58.78	6.10	12.09	58.31	5.96	12.25
2-(N^4-Caproylsulfanilamido)-thiazole[d]	Aq. alc.	193–195	$C_{15}H_{19}N_3S_2O_3$	50.99	5.42	11.89	51.16	5.42	12.20
2-(N^4-Caproylsulfanilamido)-pyrimidine	Abs. alc.	214–215	$C_{16}H_{20}N_4SO_3$	55.17	5.79	16.08	55.26	5.86	16.37

[a] Mietzach, *et al.*, U. S. P. 2,289,029; July 7, 1942. [b] After six recrystallizations. [c] Pollak, *et al.*[3] [d] Raiziss, *et al.*, *J. Lab. Clin. Med.*, **27**, 1276 (1942). [e] All recorded analyses were performed by Messrs. Hayman, Reiss, Clark and Boos.

Dr. A. O. Seeler and Dr. Harry Robinson against malaria and pathogenic organisms.

Dr. Robinson reported that "preliminary toxicity experiments in mice suggest that the acute oral toxicity of these derivatives is similar to that of sulfadiazine, sulfapyridine, and sulfathiazole. This apparent low acute toxicity may be due in part to the poor absorption from the gastrointestinal tract. Efficacy experiments in mice indicate that these compounds afford good protection against severe experimental infections produced by the intraperitoneal injection of *Streptococcus hemolyticus, Staphylococcus aureus, Diplococcus pneumonia* Type I and *Salmonella schottmülleri*. However, more accurate evaluations will be based upon blood level determinations."

These compounds were tested for activity against the schizonts of *Plasmodium lophurae* in Pekin ducklings. Fifty-gram ducklings were inoculated intravenously with 2,000,000 parasitized erythrocytes. Administration of the drugs was begun on the day of inoculation and was continued for six days. In order to maintain a reasonably constant blood level, the drugs were mixed into the diet in such fashion that the birds would consume their daily dose throughout the twenty-four hours. The relative activity was estimated by comparing the effects on the parasite count when the drugs were given at the same dose levels. Since the number of ducks receiving each drug was small and blood level determinations were not performed, a precise quantitative comparison cannot be made. In no case, however, was the derivative more active than the parent substance on a weight basis. The caproyl compounds all showed about the same activity as the parent sulfonamides and the chloracetyl derivatives seemed uniformly less active.

The solubility determinations of the compounds were performed by Mr. Walter A. Bastedo, Jr., of these Laboratories. All derivatives are soluble in 100 ml. of water at 37° to the extent of less than four-tenths of mg. except glycylsulfanilamide (157 mg./100 ml.) and glycylsulfathiazole (0.7 mg./100 ml.).

Acknowledgments.—The author wishes to acknowledge his indebtedness to Drs. R. T. Major and K. Folkers for their advice and interest, and to express his appreciation to Dr. A. O. Seeler and Dr. Harry Robinson of the Merck Institute for Therapeutic Research for their evaluation of the products as therapeutic agents.

Experimental

Preparation of N^4-Chloroacetyl Derivative

Method I.—To a well-stirred solution of 24.9 g. of sulfapyridine in 80 cc. of 1.25 *N* sodium hydroxide, 18 g. of chloroacetyl chloride was added slowly and dropwise. There was only a slight rise in temperature. One hour after the addition was completed, the white insoluble product was filtered and washed with water. After several recrystallizations from dioxane, the pure product was obtained.

Method II.—To a well-stirred suspension of 10 g. of sulfadiazine in 3.2 g. of dry pyridine and 60 cc. of dry chloroform cooled in an ice–salt mixture, 4.6 g. of chloroacetyl chloride was added slowly and dropwise. The reaction mixture was kept at room temperature for some time and the insoluble product filtered. It was stirred for a short time with 40 cc. of 2.5 *N* hydrochloric acid, collected by filtration and, after washing with water, recrystallized from boiling absolute alcohol.

Preparation of N^4-Aminoacetyl Derivatives

The preparation of the glycyl derivatives may be illustrated as follows. A solution of 50 g. of N^4-(chloroacetyl)-sulfanilamide was prepared by adding small amounts to 600 cc. of concentrated aqueous ammonia with stirring. The solution was placed in a pressure bottle and heated in a water-bath at 40° for two days. The solution was filtered from a small amount of insoluble material and evaporated in a shallow dish until a colorless, crystalline product separated. After three recrystallizations from water, there was obtained pure N^4-aminoacetylsulfanilamide.

The caproyl derivatives of sulfapyridine, sulfathiazole and sulfadiazine were prepared according to the method of Miller, Rock and Moore.[2]

Summary

A series of chloroacetyl and aminoacetyl derivatives of sulfonamides has been prepared for study as agents to combat infectious organisms. Many of these drugs were found to be very effective against such organisms as streptococcus, pneumococcus (type I), *Staphylococcus aureus* and *Salmonella schottmülleri*.

RAHWAY, N. J. RECEIVED SEPTEMBER 24, 1943

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[Contribution from the Charles Edward Coates Chemistry Laboratory, Louisiana State University]

1,*n*-Alkyl-cyclopentanols and their Derivatives[1,2]

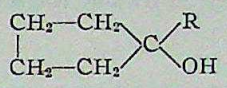
By C. R. McLellan[3] and W. R. Edwards, Jr.

As a series, the 1,*n*-alkyl-cyclopentanols have not previously received comprehensive study. Different authors[4] have reported the preparations of the first seven members of the series; but most of these have been characterized incompletely. Existing data concerning their physical properties were not obtained under uniform conditions; some contradictions appear in them; and few derivatives have been made from these alcohols, either for identification purposes or with a view toward their possible practical value. The peculiar structures of these compounds, in which the cyclopentyl ring fills the dual role taken by two distinct radicals in most tertiary alcohols, make prediction of their properties by analogy unreliable. The purposes of the present work were to prepare a number of these alcohols; to characterize them more completely and uniformly; to compare some of their properties with the corresponding properties of other relevant series; and to prepare and study some of their derivatives.

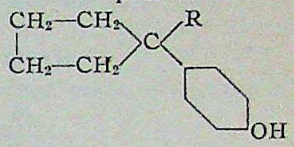
To accomplish these purposes, ten compounds of Type (I) were prepared; those in which R contained 1, 2, 3, 4, 6, 7, 8, 10, 12 and 14 carbon atoms, respectively. Compounds of Type (II) were prepared from the first seven of these.

Other derivatives prepared from Type (I) included the *p*-nitrobenzoates of five of them and the 3,5-dinitrobenzoates of all ten. Dibromo derivatives were prepared from three compounds of Type (II). With the exception of the first six alcohols of Type (I), these were new compounds.

Type (I)
1,*n*-alkyl-cyclopentanols



Type (II)
p-(1,*n*-alkyl-cyclopentyl)-phenols



Apparently no condensations of phenols with such alicyclic tertiary alcohols have been reported previously, regardless of the size of the alicyclic ring.

The 1,*n*-alkyl-cyclopentanols were prepared by the Grignard reaction from cyclopentanone and the appropriate alkyl bromides. Their purifications presented some difficulty, due chiefly to the formation of alkanes during the syntheses, and to ready dehydration of the products themselves at distillation temperatures. Data serving to characterize the members of this series appear in Tables I and III; properties of crystalline esters are included in Table II. Table IV contains data pertaining to compounds of Type II.

Table I

Properties of 1,*n*-Alkyl-cyclopentanols

Alkyl	B. p., °C., at various *p* in mm. 760[a]	300	100	20	below 10	d^{0}_{4}	d^{25}_{4}	$n^{25}D$	M. p., °C.	Analyses,[h] % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
CH_3[b]	134	110	81	..	...	..	..	..	36	..	..	..	..
C_2H_5[c]	152.5	125	96.5	74.5	...	0.9354	0.9149	1.4494	−10	73.61	73.25	12.37	12.53
C_3H_7[d]	173.5	143.5	115	83	71(8.5)	.9222	.9040	1.4502	−37.5	74.92	74.49	12.59	12.83
C_4H_9[e]	193	163	133	99	86(9)	.9144	.8957	1.4535	..	75.98	75.82	12.76	12.76
C_6H_{13}[f]	235.5	200.5	166.5[i]	124	114(9)	.9082	.8903	1.4562	..	77.57	77.63	13.03	13.14
C_7H_{15}[g]	250.5[j]	221	179.5[i]	136.5	122(9)	.9075	.8890	1.4568	..	78.18	78.09	13.13	13.16
C_8H_{17}	267.5[j]	233	198	151.5[i]	135.5(9)	.8989	.8810	1.4581	−17.5	78.70	78.49	13.23	13.20
$C_{10}H_{21}$	...	..	...	...	133(7)[i]	.8906	.8728	1.4590	−18	79.56	78.84	13.37	13.34
$C_{12}H_{25}$	...	..	...	...	142.5(3)[j]	...	.8626	1.4574	2	80.23	79.91	13.48	13.52
$C_{14}H_{29}$	...	..	...	...	164.5(2)[j]	...	.8556	1.4570	16.2	80.76	80.80	13.57	13.59

[a] Interpolated values. [b] B. p. 135° (759 mm.), m. p. 35–37° (ref. 4). [c] B. p. 154.5–155.2°, d^{15}_{4} 0.9225, $n^{11.5}D$ 1.4578 (ref. 4). [d] B. p. 175.2–175.7°, d^{20}_{4} 0.9044, d^{15}_{4} 0.9083, $n^{20}D$ 1.4540 (ref. 4). [e] B. p. 195.4–195.9°, $d^{19.6}_{4}$ 0.8989, $n^{19.15}D$ 1.4562 (ref. 4). [f] B. p. 85–86° (4 mm.) (ref. 4); d^{20}_{4} 0.8921 by Plate and 0.9019 by Zelinsky and co-workers; $n^{20}D$ 1.4600 by Plate and 1.4629 by Zelinsky and co-workers. [g] B. p. 91–92° (3 mm.), d^{20}_{4} 0.8817, $n^{20}D$ 1.4604 (ref. 4). [h] Analyses are the averages of duplicate determinations. [i] First slight visible evidence of decomposition. [j] Pronounced decomposition.

Table II

Esters of 1,*n*-Alkyl-cyclopentanols

Alkyl	*p*-Nitrobenzoates M. p., °C.[a]	% N Calcd.	% N Found	3,5-Dinitrobenzoates M. p., °C.[a]	% N Calcd.	% N Found
CH_3	83	5.62	5.54	115.5	9.52	9.02
C_2H_5	52.5	5.32	5.58	108.3	9.09	8.90
C_3H_7	59.5	5.05	5.21	82	8.69	8.66
C_4H_9	31	4.81	5.49	75.3	8.33	7.80
C_6H_{13}	...	...	...	86.5	7.69	7.92
C_7H_{15}	26	4.20	4.69	76.8	7.40	8.05
C_8H_{17}	...	...	...	77	7.14	7.35
$C_{10}H_{21}$	...	...	...	78	6.66	6.78
$C_{12}H_{25}$	...	...	...	81.3	6.25	6.48
$C_{14}H_{29}$	...	...	...	81.5	5.88	6.18

[a] Melting points listed are mean values of melting ranges of 1° or less.

(1) Taken from Ph.D. dissertation of C. R. McLellan, Louisiana State University, May, 1941.

(2) Presented before the Division of Organic Chemistry of the American Chemical Society, Atlantic City, N. J., September, 1941.

(3) Ethyl Gasoline Corporation Fellow.

(4) Zelinsky and co-workers, *Ber.*, **35**, 2683 (1902); **66B**, 1422 (1933); Chavanne and Becker, *Bull. soc. chim. belg.*, **36**, 591 (1927); Plate, *Compt. rend. Acad. Sci. U. R. S. S.*, **34**, 257 (1939).

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TABLE III

PARACHORS OF 1,*n*-ALKYL-CYCLOPENTANOLS

Alkyl	d^{25}_4	d^{50}_4	Surface tension at 25°	Surface tension at 50°	Parachor at 25°	Parachor at 50°
CH_3	...	0.8935	...	26.45	...	254.2
C_2H_5	0.9148	.8930	30.05	27.40	292.2	292.5
C_3H_7	.9041	.8805	29.17	26.76	330.5	331.1

Data in this table were obtained by Katherine Owen and O. R. Quayle, of Emory University, in friendly coöperation.

TABLE IV

PROPERTIES OF *p*-(1,*n*-ALKYL-CYCLOPENTYL)-PHENOLS

Alkyl	B. p., °C. (mm.)[a]	M. p., °C.[b]	M. p., °C., 2,6-dibromo deriv.[b]	Analyses,[c] equiv. Br abs. per mole phenol	Bacteriostatic power,[d] zone of inhib., mm. *Staph. aureus*
CH_3	..	95.5	...	3.99, 3.93	5.0
C_2H_5	137(2.5)	96.3	97	4.07, 4.05	6.0
C_3H_7	135(1.0)	67.5	104.5	3.90, 3.95[e]	5.0
C_4H_9	151(2.0)	57.5	69	3.92, 3.96	5.0
C_6H_{13}	163(2.1)	61.8	...	4.04, 4.00	0
C_7H_{15}	174.5(2.5)	53.3	...	4.06, 4.03	0
C_8H_{17}	..	42.8	...	.. .. [f]	0

[a] Boiling points given are mean values of 2° boiling ranges or less. [b] Melting points given are mean values of melting ranges of 1° or less. [c] Analysis by reaction with bromine to give the 2,6-dibromo derivative. Theoretical value, 4.00. [d] Bacteriostatic powers determined by Agar Cup-plate test, by W. C. Harden and associates, Hynson, Westcott and Dunning, Inc., Baltimore, Md., in friendly coöperation. Control: no. 390 (3,5-dibromo-hydroxybenzyl-phenol): 3.0 mm. All compounds, including control, gave negative results with *E. coli*. [e] *Anal.* Calcd. for $C_{14}H_{20}O$: C, 82.29; H, 9.87. Found: C, 82.73; H, 9.82. [f] *Anal.* Calcd. for $C_{15}H_{30}O$: C, 83.14; H, 11.03. Found: C, 82.51; H, 11.16.

In Fig. 1, the boiling points of the 1,*n*-alkyl-cyclopentanols are plotted against their molecular weights, along with the boiling points of compounds of several other series. Between the curve

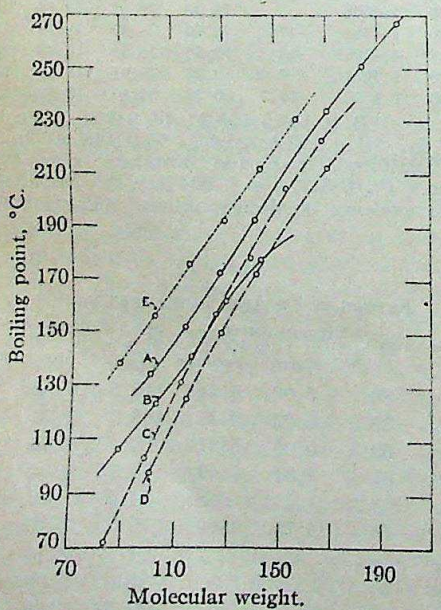

Fig. 1.—A, 1,*N*-Alkyl-cyclopentanols; B, *N*-alkyl-dimethylcarbinols; C, *N*-alkyl-cyclopentanes; D, *N*-alkanes; E, normal primary alcohols.

for the 1,*n*-alkyl-cyclopentanols and the one given by a series of non-cyclic tertiary alcohols, there is a relationship approximately similar to the relationship between the curves for *n*-alkylcyclopentanes, and for *n*-alkanes, respectively. The quantitative difference produced by the ring is slightly greater in the case of the alcohols. The difference in boiling point which may be ascribed to the presence of a cyclopentyl ring is seen (by reference to curves A, B and E) to be small compared to the difference between primary and tertiary alcohols of non-cyclic type.

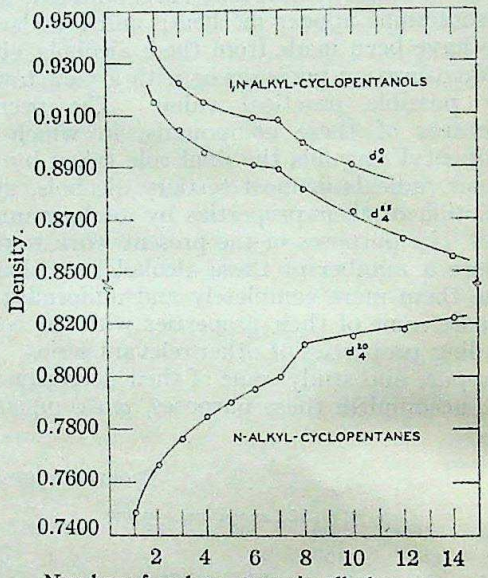

Fig. 2.

Figure 2 shows a remarkable break at the heptyl in the curve given by the densities. The densities of the *n*-alkylcyclopentanes taken from the literature[4,5] show a similar break in the same region. This appears to be due to the relationship between the sizes of the alkyl groups and of the cyclopentyl ring, and to the distinct difference in their configurations, a difference which includes the relative elasticity of the alkyl groups as compared to the rigidity of a five-membered ring. When the alkyl group is small, the cyclopentyl group is dominant, in the sense that it presents the chief obstacle to closer packing of the molecules; therefore it is chiefly responsible for the molecular volume. The curve from the methyl to the heptyl compound reflects this condition. At the point where the alkyl group has so increased in size as to become the dominant group, the situation changes sharply. Above this point, the alkyl-cyclopentanols constitute what is actually a different series as far as densities are concerned. An abrupt change in the slope of the density curve

(5) Schmidt and Gemassmer, *Ber.*, **73**, 359 (1940). The value for the density of *n*-hexylcyclopentane was taken from Plate (ref. 4). Use of the much lower value reported at an earlier date by Zelinski (ref. 4) would have caused the break to appear at this point rather than at the heptyl.

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results, at the point at which dominance shifts from one group to the other.

An analogous series of *n*-alkyl-cyclohexanols is now being investigated, to determine whether or not they exhibit the same phenomenon.

Condensation of 1,*n*-alkyl-cyclopentanols with phenol to form *p*-(1,*n*-alkyl-cyclopentyl)-phenols resulted in somewhat smaller yields than usual for this type of reaction. The octyl compound was never thoroughly purified; and an attempted preparation of the decyl compound was unsuccessful. Tests of the bacteriostatic strengths of these substituted phenols showed the first four to be rather effective toward the Gram-positive *Staphylococcus aureus*, but wholly ineffective toward the Gram-negative *E. coli*. The higher members of the series were ineffective toward both organisms.

Experimental

Cyclopentanone.—Cyclopentanone was prepared from adipic acid[6] by the method of Thorpe and Kon,[7] and purified by the modification of Wagner.[8]

1,*n*-Alkyl-cyclopentanols.—These compounds were prepared from cyclopentanone and the appropriate alkylmagnesium bromides, by the method of Zelinsky and Namjetkin.[4] All but the lauryl and myristyl compounds were purified by repeated fractional distillations, at pressures ranging from atmospheric to 1 mm. All were colorless liquids, except the methyl compound which was a crystalline solid, and the lauryl which possessed a faint yellow color. They had peppermint-like odors. The methyl compound was slightly soluble in water; this solubility diminished regularly with increase in size of the alkyl group. They were all soluble in the usual organic solvents; yields were 50% for the methyl, 35–40% for ethyl through decyl, and 20% for lauryl and myristyl.

The 1,*n*-heptyl-cyclopentanol presented a special problem, since the tetradecane formed during its synthesis boils very close to the alcohol at all pressures between a few millimeters and one atmosphere. Consequently, although the crude alcohol was redistilled several times until an almost constant-boiling product was obtained, it seems unlikely that this impurity was eliminated completely.[9]

Purification of 1,*n*-Lauryl-cyclopentanol-1 and 1,*n*-Myristylcyclopentanol-1.—As these compounds decomposed on distillation even at 1 mm., they were purified by recrystallization at low temperatures. At the conclusion of the preparation by the Grignard reaction, the ethereal extract containing crude 1,*n*-lauryl-cyclopentanol-1 was washed with water and dried; the ether was then removed by evaporation on a steam-bath, gradually reducing the pressure to 4 mm. The oily residue was dissolved in three times its volume of 95% ethanol and chilled in an ice–salt-bath. Solid impurities consisting chiefly of tetracosane precipitated, and were removed by filtration. The filtrate was concentrated on a steam-bath, at a pressure of 2.5 mm. The oily residue was dissolved in an equal volume of anhydrous ether, and chilled in dry-ice. Crystals of the product precipitated. These were filtered on a Buchner funnel packed with dry-ice, washed once with ether previously chilled, and quickly transferred to a suitable container. Upon reaching room temperature, these crystals melted, forming an oily liquid with a faint yellow color; this was taken to be 1,*n*-lauryl-cyclopentanol-1. Further recrystallizations yielded a smaller amount of product having the same physical characteristics. Minor differences in details were observed in purifying the myristyl compound.

1,*n*-Alkyl-cyclopentyl-*p*-nitrobenzoates and -3,5-dinitrobenzoates.—These esters were prepared from the 1,*n*-alkyl-cyclopentanols by the method of Conn, Collett and Lazzell,[10] allowing several days for each reaction. They were recrystallized from ether, or petroleum ether, or a mixture of the two.

***p*-(1,*n*-Alkyl-cyclopentyl)-phenols.**—These were prepared by condensation of the 1,*n*-alkyl-cyclopentanols with phenol, employing two different methods; that of Huston and Hedrick,[11] and that of Welsh and Drake,[12] a method which had given particularly good yields with certain tertiary alcohols containing aromatic rings. In the present work, however, there was little to choose between results of the two methods. The products were purified by fractional distillation at reduced pressures, followed by recrystallization from petroleum ether; the methyl member of the series was purified solely by successive recrystallizations; yields ranged from 27 to 39%.

For analytical purposes, the *p*-(1,*n*-alkyl-cyclopentyl)-phenols were titrated with 0.13 *N* potassium bromide–potassium bromate solution, using the method of Francis and Hill.[13]

The *p*-(1,*n*-alkyl-cyclopentyl)-phenols were colorless crystalline solids, possessing faint phenolic odors. They were soluble in most of the ordinary organic solvents, the solubility in petroleum ether increasing appreciably with increase in the size of the alkyl group. The methyl member of the series was slightly soluble in water; water solubility decreased with increase in the size of the alkyl group.

2,6-Dibromo-4-(1,*n*-alkyl-cyclopentyl)-phenols.—The *p*-(1,*n*-alkyl-cyclopentyl)-phenols were dissolved in chloroform or ligroin, and the calculated amount of a dilute solution of bromine in the same solvent added. Reaction was practically instantaneous. The solvent was removed by evaporation on a steam-bath, and the products recrystallized from ethanol–water mixtures.

Determination of Boiling Points of 1,*n*-Alkyl-cyclopentanols.—These were determined with a modified Cottrell boiling point apparatus,[14] which is drawn to scale in Fig. 3. The diameter of the tube was 3 cm. Quantities as small as 3 cc. gave satisfactory results. Short-stemmed Allihn thermometers were used. Boiling points were determined at five pressures, except when prevented by (a) thermal decomposition of the three highest alcohols; or (b) difficulty in condensing the two lowest ones at very low pressures.

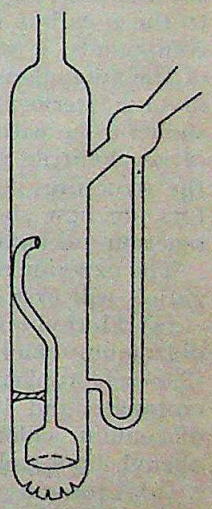

Fig. 3.—Boiling point apparatus.

Determination of Melting Points.—Melting points of the 1,*n*-alkyl-cyclopentanols were determined by the method of cooling curves, readings being taken every thirty seconds. Tubes containing the samples undergoing such treatment were separated from the cooling baths by an air jacket, so that slow and uniform cooling was achieved. The methyl member of the series was an exception; its melting point was determined in the usual way, as were the melting points of the various esters and phenols.

Acknowledgment.—The authors thank Dr. E. Emmet Reid for his interest in the problem, and

(6) The authors are indebted to Dr. C. D. Graves, Du Pont Experimental Station, Wilmington, Del., for a supply of adipic acid.

(7) Thorpe and Kon, "Organic Syntheses," Vol. V, John Wiley and Sons, New York, N. Y., pp. 37–39.

(8) Wagner, *J. Chem. Ed.*, **10**, 115 (1933).

(9) Plate's recent preparation of this compound (ref. 4) is subject to the same criticism, since it was purified in a similar manner. His analysis showed the carbon and hydrogen contents of his product to be high.

(10) Conn, Collett and Lazzell, THIS JOURNAL, **54**, 4370 (1932).

(11) Huston and Hedrick, *ibid.*, **59**, 2001 (1937).

(12) Welsh and Drake, *ibid.*, **60**, 59 (1938).

(13) Francis and Hill, *ibid.*, **46**, 2498 (1924).

(14) Cottrell, *ibid.*, **41**, 721 (1919). The modified tube was designed by A. R. Choppin, and constructed by E. L. Compere.

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for the gift of most of the alcohols from which the bromides were prepared.

Summary

1. The 1,*n*-alkyl-cyclopentanols have been characterized as a series, through the preparation and study of four new members, together with a more complete and uniform study of six previously prepared members.

2. Some of the data thus obtained have been plotted, and compared with similar curves representing other relevant series. The unusual form of the density curves has been discussed.

3. Esters of *p*-nitrobenzoic acid have been prepared from five of these alcohols, and esters of 3,5-dinitrobenzoic acid have been prepared from all ten, and the melting points of these esters have been determined.

4. Seven *p*-(1,*n*-alkyl-cyclopentyl)-phenols have been prepared by condensation of these alcohols with phenol, and characterized. Their bacteriostatic strengths have been determined. Four of them were found to be effective toward *Staph. aureus*.

5. Three 2,6-dibromo-4-(1,*n*-alkyl-cyclopentyl)-phenols have been prepared, and their melting points determined.

BATON ROUGE, LA. RECEIVED AUGUST 2, 1943

[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Coupling of α,β-Unsaturated Compounds with Diazonium Salts[1]

BY C. F. KOELSCH AND VIRGIL BOEKELHEIDE

In a previous paper[2] it was shown that the reaction between acrylonitrile and diazonium chlorides in buffered solutions and in the presence of cupric chloride led to the formation of α-chlorohydrocinnamonitriles. Since Meerwein, Buchner and van Emster[3] had considered that in similar reactions the aryl group always became attached to the α-carbon of β-substituted α,β-unsaturated compounds, it was believed that an explanation of the anomalous results with acrylonitrile might involve steric hindrance. This belief is now shown to be without foundation, for the behavior of acrylonitrile is not anomalous. Also some of the structures advanced by the earlier investigators are now shown to be incorrect, and a new reaction mechanism is proposed.

The experimental results of the present investigation will first be summarized.

(a) Methyl crotonate and 2,4-dichlorobenzenediazonium chloride yielded methyl α-chloro-β-(2,4-dichlorophenyl)-butyrate.[4] Similarly ethyl crotonate and benzene- (and *p*-chlorobenzene-) diazonium chloride yielded ethyl α-chloro-β-phenyl- (and *p*-chlorophenyl-) butyrate.

(b) Crotonic acid and *p*-nitrobenzenediazonium chloride gave α-chloro-β-(*p*-nitrophenyl)-butyric acid.[5]

(c) Methyl cinnamate and *p*-chlorobenzenediazonium chloride yielded methyl β-chloro-α-(*p*-chlorophenyl)-hydrocinnamate.[6]

(d) Cinnamalacetic acid and benzenediazonium chloride gave 1,4-diphenylbutadiene.

(e) Methyl cinnamalacetate and benzene- (and *p*-chlorobenzene-) diazonium chloride gave methyl α-phenyl- (and *p*-chlorophenyl)-cinnamalacetate.

(f) Sorbic acid and benzenediazonium chloride gave 1-phenylpentadiene-1,3.

It is clearly seen that the volume occupied by the group on the β-carbon atom of the unsaturated compound is not a factor in determining the point of entry of the aryl group. A methyl group occupies at least as large a portion of the space in the immediate vicinity of the β-carbon atom as does a vinyl group, yet crotonic acid and its derivatives undergo β-coupling, whereas α-coupling takes place with the vinyl compounds listed in paragraphs d, e and f.

The following mechanism appears to account for the products obtained.

$$C_6H_5N_2^+ + CH_3COO^- \rightleftharpoons C_6H_5N{=}NOCOCH_3 \longrightarrow C_6H_5\cdot + N_2 + CH_3COO\cdot \quad (1)$$

$$C_6H_5\cdot + RCH{=}CHR' \longrightarrow C_6H_5CHR{-}C\cdot HR' \text{ (I)} \quad (2)$$

$$\text{(I)} + Cu^{++} \longrightarrow Cu^+ + C_6H_5CHR{-}C^+HR' \text{ (II)} \quad (3)$$

$$Cu^+ + CH_3COO\cdot \longrightarrow Cu^{++} + CH_3COO^- \quad (3a)$$

$$\text{(II)} + Cl^- \longrightarrow C_6H_5CHR{-}CHClR' \quad (4)$$

$$\text{(II)} \longrightarrow H^+ + C_6H_5CR{=}CHR' \quad (4a)$$

Equation 1 shows the function of the buffer; the diazonium salt cannot, but the homopolar diazoacetate can decompose easily into a free phenyl radical.[7] Equation 2 represents the "electron pairing"[8] attack of the free radical on the unsaturated compound. The structure of I is determined by considerations analogous to those advanced by Mayo and Walling[9] to account for the orientations observed in Kharasch's peroxide

(1) From the Ph. D. Thesis of Virgil Boekelheide, September, 1943.

(2) Koelsch, THIS JOURNAL, **65**, 57 (1943).

(3) Meerwein, Buchner and van Emster, *J. prakt. Chem.*, **152**, 237 (1939).

(4) Meerwein, Buchner and van Emster believed that this compound was methyl β-chloro-α-(2,4-dichlorophenyl)-butyrate.

(5) Meerwein, Buchner and van Emster reported that this compound was β-chloro-α-(*p*-nitrophenyl)-butyric acid.

(6) The structure of this product was reported correctly by Meerwein, Buchner and van Emster.

(7) Hey, *Ann. Rep. Chem. Soc.*, **37**, 280 (1940).

(8) Remick, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 259.

(9) Mayo and Walling, *Chem. Rev.*, **27**, 351 (1940).

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directed addition of hydrogen bromide to olefins; coupling takes place to yield the more stable of the two possible products. If R is saturated and R′ contains C=O (or C≡N), the free radical I will be stabilized by resonance of the odd electron into R′. But if R is phenyl or vinyl, then the more stable free radical (I) will be the one with the odd electron on the carbon attached to R,[10] since the resonance in the more symmetrical system $\overset{\curvearrowleft}{C}=C-\overset{\curvearrowleft}{C}\cdot$ will be greater than the resonance $\cdot\overset{\curvearrowright}{C}-C=\overset{\curvearrowright}{O}$.

Equations 3 and 3a show the function of the cupric salt, while equations 4 and 4a indicate how two characteristic products of the reaction are formed. It is of some interest that if in II R is COOH and α-coupling has taken place (*e. g.*, cinnamic acid, cinnamalacetic acid and sorbic acid), then decarboxylation of II follows, as would be predicted; whereas if in II R′ is COOH and β-coupling has taken place (*e. g.*, crotonic acid), then the ion II retains the carboxyl group and acquires an anion (Cl^-), again as would be predicted.

The foregoing equations do not show all of the processes involved in the reaction. For example, the rate of nitrogen evolution from a reaction mixture is highly dependent on the particular unsaturated compound used, and this must indicate that a complex is formed between the unsaturated compound and a nitrogen-containing reactant. However, the structure of this complex cannot now be determined. Furthermore, the yields of pure products are always low; the by-products are non-volatile tarry substances.

Experimental

Orienting experiments were made in the following way. A mixture of 0.1 mole of an aromatic amine with 10 ml. of water and 20 ml. of hydrochloric acid was warmed until homogeneous and then cooled in ice. Ten grams of ice was added, and then a concentrated solution of 7 g. of sodium nitrite was dropped in. The resulting solution was filtered and added dropwise and with stirring to a mixture (at 0°) of 0.1 mole of the unsaturated compound in 75 ml. of acetone with 0.1 mole of sodium acetate and 3 g. of cupric chloride in a minimum amount of water. The reaction mixture was warmed to a temperature (3 to 30°) at which gas was evolved evenly and not too rapidly, and stirring was continued until approximately the theoretical amount of nitrogen had been collected (two to six hours). The gases evolved were passed through sulfuric acid, then through a weighed Ascarite tube, and finally collected over water. When the reaction was complete, two liquid phases were present, a green aqueous layer containing mainly inorganic salts, and a brown oily layer which contained most of the product.

Ethyl Crotonate and *p*-Chlorobenzenediazonium Chloride.—An experiment was carried out using 1 mole of each of the reactants in 500 ml. of acetone, etc. The reaction required five hours at 20°. The product (108 g., 41%), isolated by ether extraction and distillation, was a pale red oil, b. p. 100–150° at 6 mm. A second distillation through a short column gave 88 g. (34%) of **ethyl α-chloro-β-(*p*-chlorophenyl)-butyrate**, a pale yellow oil, b. p. 125–140° at 2–3 mm.

Anal. Calcd. for $C_{12}H_{14}Cl_2O_2$: C, 55.2; H, 5.4; Cl, 27.2. Found: C, 55.3; H, 5.1; Cl, 27.7.

When 6.8 g. of this ester was allowed to stand for twelve hours with 12 g. of potassium hydroxide in 75 ml. of methanol, it furnished 3.2 g. (62%) of *p*-chloro-β-methylcinnamic acid, colorless crystals from ligroin, m. p. 134° (reported,[11] 133.5°). The acid formed a liquid-crystalline melt that became clear at 138.5°. For comparison the acid was synthesized from 30 g. of *p*-chloroacetophenone, through ethyl *p*-chloro-β-hydroxy-β-methylhydrocinnamate[12] (yield, 52%; b. p. 160–162° at 11 mm.), which was dehydrated with formic acid[11] to ethyl *p*-chloro-β-methylcinnamate (yield, 93%); the latter ester was hydrolyzed with 10% sodium hydroxide, giving the desired acid in 93% yield; it melted at 134° to a turbid liquid that became clear at 138.5°, and a mixture with the acid from the coupling showed the same behavior. Furthermore, each product was partly rearranged to a stereoisomer, m. p. 92–99° (reported[11] 94°) when it was warmed in concd. sulfuric acid for a few minutes.

That the coupling reaction yielded no ethyl β-chloro-α-(*p*-chlorophenyl)-butyrate was shown in the following way. Forty-one grams of once-distilled material from another experiment was boiled for ten minutes with 200 g. of diethylaniline, giving 33 g. of crude unsaturated ester. This was saponified, and 22.5 g. of the resulting crude acid was dissolved in 250 ml. of 5% sodium hydroxide and shaken with hydrogen at 40 lb. in the presence of Raney nickel. Gas absorption stopped after twenty-four hours, and titration then showed the presence of 0.14 mole of chloride ion (calcd. 0.11 mole). There was isolated 12.8 g. of an oily acid, b. p. 126–128° at 3 mm., neut. equiv., 164 (calcd. for phenylbutyric acid 164). Twelve grams of this acid in 40 ml. of benzene was treated with 18 g. of phosphorus pentachloride and then with 10 g. of aluminum chloride. This reaction yielded 4.4 g. (40%) of 3-methylindanone, b. p. 128–131° at 16 mm. (identified through its oxime and by comparison with an authentic sample), and 2 g. of a neutral substance, b. p. 144–148° at 16 mm. The higher boiling fraction was not ethyldesoxybenzoin, for it gave no solid oxime under conditions which were found to yield this oxime, m. p. 127–129°, when an authentic sample of the ketone was used.

Ethyl Crotonate and Benzenediazonium Chloride.—A one-mole experiment required three and one-half hours at 20–35° for completion of the nitrogen evolution. There was obtained 26.5 g. (11.5%) of once-distilled product, b. p. 110–150° at 11 mm., and this furnished 17 g. (7.5%) of a refractionated ester, b. p. 100–104° at 4 mm. Analysis indicated that the expected **ethyl α-chloro-β-phenylbutyrate** lost some hydrogen chloride on distillation.

Anal. Calcd. for $C_{12}H_{15}ClO_2$: C, 63.6; H, 6.6. Found: C, 65.1; H, 6.7.

When 3.8 g. of the chloro ester was allowed to stand for twelve hours with 4.5 g. of potassium hydroxide in 30 ml. of methanol, it gave 1.75 g. (65%) of β-methylcinnamic acid, which melted at 97–98° (reported[13] 97–98°) after it had been made sterically homogeneous by boiling it for three hours with excess 5% sodium hydroxide. The acid was identified by comparison with an authentic sample synthesized[11,12] from acetophenone.

Methyl Crotonate and 2,4-Dichlorobenzenediazonium Chloride.—A solution of 20.3 g. (0.13 mole) of 2,4-dichloroaniline in 100 g. of hydrochloric acid was diazotized and then partly neutralized by adding 26.2 g. (0.65 mole) of sodium hydroxide in 100 ml. of water at −5°. The solution was mixed with 12.5 g. of methyl crotonate in 200 ml. of acetone, then with 23.3 g. of sodium chloroacetate in 50 ml. of water, and finally with 5.3 g. of cupric

(10) It is to be noted that the present results indicate that the normal mode of addition of hydrogen bromide to cinnamic acid may be reversed by peroxides. It has been stated (ref. 9, p. 363) that this reversal cannot be achieved, but actually a conclusive experimental test of the matter has not been made (*cf.* Michael, *J. Org. Chem.*, **4**, 128 (1939)).

(11) v. Braun and Heider, *Ber.*, **49**, 1272 (1916).

(12) Rupe, *Ann.*, **369**, 322 (1909).

(13) Schroeter and Wulfing, *Ber.*, **40**, 1593 (1907).

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chloride in 10 ml. of water. Nitrogen was evolved rapidly at 5°, and the reaction was complete after two and one-half hours. There was obtained 7 g. (20%) of methyl α-chloro-β-(2,4-dichlorophenyl)-butyrate,[4] b. p. 155–170° at 3 mm. (reported[3] 130–140° at 0.1 mm.).

Treatment of 5 g. of the ester with potassium hydroxide in methanol yielded **2,4-dichloro-β-methylcinnamic acid**, which formed colorless crystals (1.2 g., 30%) from ligroin, m. p. 126–127°.

Anal. Calcd. for $C_{10}H_8Cl_2O_2$: C, 52.0; H, 3.5. Found: C, 52.5; H, 3.6.

When 0.62 g. of the unsaturated acid was dissolved in a solution of 0.4 g. of sodium hydroxide in 30 ml. of water and shaken with Raney nickel under hydrogen at atmospheric pressure, it absorbed 230 ml. of the gas (calcd. 210 ml.) in ninety minutes. The resulting β-phenylbutyric acid was identified by comparison with an authentic sample, and by conversion into its amide (yield 50%), which melted at 105–106° (mixed m. p.) in agreement with the reported figure.[14]

Crotonic Acid and *p*-Nitrobenzenediazonium Chloride.—A diazonium salt solution prepared from 69 g. of *p*-nitroaniline, 138 g. of hydrochloric acid, and 35 g. of sodium nitrite was stirred into a mixture containing 43 g. of crotonic acid, 600 ml. of acetone, 100 g. of sodium chloroacetate, 20 g. of cupric chloride, and 100 ml. of water. Gas was evolved rapidly at 0°, and after one hour the reaction was complete. Extraction of the mixture with ether and of the ether with aqueous sodium bicarbonate furnished 16 g. of a nearly black oily acidic material, which could not be distilled, and from which no crystalline material could be obtained.[15] Fifteen grams of the oil was boiled for four hours with 40 ml. of methanol containing 5 g. of hydrogen chloride. There was obtained 11.3 g. of **methyl α-chloro-β-(*p*-nitrophenyl)-butyrate**, a pale red oil that distilled at 175–180° at 3 mm. with some loss of hydrogen chloride.

Anal. Calcd. for $C_{11}H_{12}ClNO_4$: C, 51.3; H, 4.7. Found: C, 53.5; H, 4.7.

When 10.7 g. of the ester was boiled for fifteen minutes with 60 g. of diethylaniline, it was dehalogenated, giving 7.2 g. (76%) of methyl β-methyl-*p*-nitrocinnamate, b. p. 156–160° at 3 mm., m. p. 120–121° (reported[13] 121–122°). Saponification of this product with 5% sodium hydroxide gave β-methyl-*p*-nitrocinnamic acid in 52% yield, m. p. 167–168° (reported[13] 168–169°). The melting points of the cinnamic ester and of the acid were unchanged when the substances were mixed with the corresponding compounds synthesized by the methods of Schroeter and Wulfing.[13]

Methyl Cinnamate and *p*-Chlorobenzenediazonium Chloride.—A solution prepared from 25.6 g. (0.2 mole) of *p*-chloroaniline, 54 g. of hydrochloric acid and 14 g. of sodium nitrite was stirred slowly into a mixture of 32.4 g. of methyl cinnamate, 150 ml. of acetone, 26 g. of pyridine, 20 g. of acetic acid, 6 g. of cupric chloride, and 100 ml. of water. Gas evolution began at 30° and ended after two hours. The volatile constituents were removed by distillation from a steam-bath, and the remaining oil was extracted with 500 ml. of benzene. From this extract there was obtained 12.8 g. of pure methyl β-chloro-α-(*p*-chlorophenyl)-hydrocinnamate,[6] colorless crystals from methanol, m. p. 121–122° (reported[3] 124–124.5°).

When 2.2 g. of the ester was allowed to stand for twelve hours at room temperature with 3.5 g. of potassium hydroxide in 30 ml. of methanol, it yielded 1.65 g. (86%) of α-(*p*-chlorophenyl)-cinnamic acid, m. p. 180–181°. And when a solution of 0.75 g. of this acid in 35 ml. of 1% aqueous sodium hydroxide was shaken with hydrogen under atmospheric pressure and in the presence of Raney nickel, it yielded 0.52 g. (84%) of α-phenylhydrocinnamic acid, m. p. 95–96° alone or mixed with a sample prepared by reducing α-phenylcinnamic acid.

(14) Kohler and Reimer, *Am. Chem. J.*, **33**, 353 (1905).

(15) Meerwein, Buchner and van Emster reported that this procedure gave 3.5 g. of an acid $C_{10}H_9NO_4$, m. p. 173.5–174.5°.

Cinnamalacetic Acid and Benzenediazonium Chloride.—A mixture of 0.1 mole of each of the reactants (but containing 0.2 mole of sodium acetate and 160 ml. of acetone) evolved gas at 10°. The reaction was complete after five hours, and 1.4 g. of carbon dioxide was collected. Only 0.9 g. of acidic product was obtained, and this was unchanged cinnamalacetic acid. Crystallization of the neutral products from benzene–ligroin gave 5.7 g. (28%) of 1,4-diphenylbutadiene, m. p. 149–150° alone or mixed with a sample synthesized by the method of Thiele and Schleussner.[16]

Methyl Cinnamalacetate[17] and Benzenediazonium Chloride.—A mixture of one mole of each of the reactants prepared in the usual way, but containing 0.17 mole of pyridine acetate in place of sodium acetate, began to evolve nitrogen at 15°, and the reaction was complete after five hours. Distillation of the products gave 4 g. of unchanged methyl cinnamalacetate and 5 g. (19%) of the expected coupling product, a pale red oil, b. p. 180–190° at 2 mm. Since some decomposition had accompanied its distillation, the substance was treated directly with 10% potassium hydroxide in methanol. No chloride ion was formed, but there was obtained 2.5 g. (10%) of pure α-phenylcinnamalacetic acid, faintly yellow crystals from benzene–ligroin, m. p. 186–187° alone or mixed with a sample prepared by the method of Thiele.[16]

Methyl Cinnamalacetate and *p*-Chlorobenzenediazonium Chloride.—A mixture containing 0.17 mole of each of the reactants, 0.16 mole of sodium acetate, 5 g. of cupric chloride, and the necessary solvents began to evolve gas at 15°, and the reaction was complete after two hours. There was obtained 53 g. of a dark oily product from which no pure substance could be isolated directly. Eighteen grams of this oil was allowed to stand with 15 g. of potassium hydroxide in 120 ml. of methanol, and the potassium salt which had separated after thirty minutes was removed. This salt yielded 4.4 g. of cinnamalacetic acid. The solution was allowed to stand for twelve hours and then acidified. The resulting sticky acid was dissolved in 50 ml. of hot concd. aqueous sodium carbonate. The sodium salt which separated when the solution was cooled was washed with ether, then dissolved in water and decomposed, giving 1.7 g. of **α-(*p*-chlorophenyl)-cinnamalacetic acid**, faintly yellow needles from acetic acid, m. p. 233–234°.

Anal. Calcd. for $C_{17}H_{13}ClO_2$: C, 71.8; H, 4.6. Found: C, 72.0; H, 5.0.

Sorbic Acid and Benzenediazonium Chloride.—A solution prepared from 0.125 mole of aniline, 0.375 mole of hydrochloric acid, and 0.125 mole of sodium nitrite was added to a mixture containing 0.1 mole of sorbic acid,[18] 0.2 mole of sodium acetate, 5 g. of cupric chloride, and 160 ml. of acetone. Nitrogen was evolved at 0°, and the reaction was complete after two and one-half hours. Steam distillation gave 3.8 g. (26%) of 1-phenylpentadiene-1,3, b. p. 118–124° at 24 mm.; $n^{30}D$ 1.6002; $n^{25}D$ 1.6025 (reported[19] b. p. 116° at 16 mm.; n^{13} 1.6111). A sample of the hydrocarbon obtained in 57% yield by the method of Klages[20] boiled at 118–120° at 24 mm. and had a refractive index ($n^{25}D$) of 1.6010. Both samples of the hydrocarbon yielded an adduct with maleic anhydride, m. p. 157–158° (reported[21] 157–158°), alone or mixed.

Summary

It is suggested that aryl radicals arising from the decomposition of diazo acetates attack the C–C double bond of an α,β-unsaturated compound in such a way that the new radical formed will have

(16) Thiele and Schleussner, *Ann.*, **306**, 198 (1899).

(17) Hinrichsen and Triepel, *ibid.*, **336**, 198 (1904).

(18) Doebner, *Ber.*, **35**, 2137 (1902).

(19) Klages, *ibid.*, **40**, 1769 (1907).

(20) Ref. 19, *cf.* Muskat and Herman, THIS JOURNAL, **53**, 252 (1931).

(21) Diels and Alder, *Ber.*, **62**, 2086 (1929).

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the more stable structure. This suggestion is used to explain the products obtained in several new examples of the coupling reaction, and has led to corrections in the structures of some of the compounds prepared in the same way by earlier workers.

MINNEAPOLIS, MINNESOTA RECEIVED NOVEMBER 26, 1943

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Dissociation of Hexaarylethanes.[1] XV. Methoxyl Substituents

BY C. S. MARVEL, JOHN WHITSON AND H. W. JOHNSTON

Substitution of methoxyl groups for hydrogen atoms in the aryl rings of a hexaphenylethane has been reported[2] to lead to compounds which dissociate to a much greater extent than does the parent hydrocarbon. In all of these reports the degrees of dissociation were determined by cryoscopic molecular weight methods. In this paper we are reporting figures on the degrees of dissociation of certain methoxyl substituted hexaarylethanes determined by the magnetic susceptibility method.[3] Our values are much lower than those previously reported. All of the methoxyl substituted hexaarylethanes were found to be relatively unstable, and the change in magnetic susceptibility with the age of the solution showed that these radicals decompose quickly. The molecular weight determinations undoubtedly show too high values for the radical because of the presence of disproportionation products in the aged solution of the ethanes.

The ethanes which have been prepared and whose dissociations have been measured by the magnetic susceptibility method are listed in Table I. The dissociations reported are on benzene solutions and are calculated for 0.1 *M* solutions from the actual data measured at other concentrations.

TABLE I

DISSOCIATIONS OF VARIOUS METHOXYL SUBSTITUTED HEXAPHENYLETHANES

Ethane	α at 0.1 *M*, %	Reported dissociation, %	Ref.
Tetraphenyldi-*o*-anisyl	3.8 ± 1	26	2a
Tetraphenyldi-*m*-anisyl	2.6 ± 1		
Tetraphenyldi-*p*-anisyl	4.4 ± 1	24	2b
Diphenyltetra-*o*-anisyl	7.3 ± 1	40	2d
Hexa-*o*-anisyl	42 ± 5	100	2d
Hexa-*m*-anisyl	8.5 ± 1.5		

The ethanes with ortho- and para-methoxyl groups used in our work were made from triarylchloromethanes described by the earlier workers and the physical properties checked those reported and the analyses indicated the chlorides were pure. In general we used new reactions to produce our intermediates and brief descriptions of our processes are given. The *m*-methoxyl substituted ethanes are new but the carbinols have been described.[4] We have also used different methods for the preparation of these compounds but have found the properties to be identical with those previously reported.

The degrees of dissociation for these ethanes which we have determined by the magnetic susceptibility method are much nearer those which would be expected by comparison with other substituted ethanes studied in this Laboratory than were the older values. It has been rather generally observed that an ortho substituent has the most marked effect on dissociation and hexa-*o*-anisylethane is highly dissociated. The very low value for the dissociation of tetraphenyl-di-*o*-anisylethane is surprising yet the relative interference value of the methoxyl group as measured by the ease of racemization of ortho-substituted diphenyls[5] indicates that it has much less steric effect than a methyl group.

Experimental

Ethyl *m*-Methoxybenzoate.—One hundred grams of *m*-methoxybenzoic acid (m. p. 106°), 600 cc. of absolute ethyl alcohol, 150 cc. of thiophene-free benzene especially dried by distillation and 3 cc. of concentrated sulfuric acid were placed in a 1-liter round-bottomed flask. A 200-cc. Soxhlet extractor filled with anhydrous potassium carbonate was inserted between the flask and a reflux condenser whose top was connected to a calcium chloride tube. The contents of the flask were refluxed for twenty-four hours. After this the reaction mixture was filtered and the product was then distilled until all solvents boiling below 82° were removed. The residue, which contained the ester, was washed with 10% sodium hydroxide. The mixture formed an emulsion which was extracted with benzene. The benzene extract was washed with water and distilled from a modified Claisen flask. The yield was 75 g. (60%) of product which boiled at 130–135° (15 mm.).

Preparation of Triarylcarbinols.—The triarylcarbinols were prepared from the appropriate Grignard reagents and carbonyl compounds by the usual procedures using the forced conditions of Bachmann and Kloetzel.[6] The crude carbinols were obtained as viscous liquids and in some cases steam distillation was employed to purify the product of the reaction. In cases where the viscous oil could not be caused to crystallize it was converted directly into the corresponding chloromethane. All of these carbinols have been prepared previously but by more complex methods.

(1) For the fourteenth communication in this series, see THIS JOURNAL, **64**, 2227 (1942).

(2) (a) Gomberg and Nishida, *ibid.*, **45**, 190 (1923); (b) Gomberg and Buchler, *ibid.*, **45**, 207 (1923); (c) Gomberg and Forester, *ibid.*, **47**, 2373 (1925); (d) Lund, *ibid.*, **49**, 1346 (1927); (e) Bowden, *J. Chem. Soc.*, 33 (1939).

(3) Müller, Müller-Rodloff and Bunge, *Ann.*, **520**, 235 (1935); Roy and Marvel, THIS JOURNAL, **59**, 2622 (1937).

(4) (a) Baeyer, *Ann.*, **354**, 152 (1907); (b) Baeyer and Villiger, *Ber.*, **35**, 3013 (1902).

(5) Adams and Yuan, *Chem. Rev.*, **12**, 261 (1933).

(6) Bachmann and Kloetzel, *J. Org. Chem.*, **2**, 356 (1937).

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o-Anisyldiphenylcarbinol.—From 26 g. of magnesium, 172.5 g. of bromobenzene, and 45 g. of methyl *o*-methoxybenzoate there was obtained 53 g. (68%) of product; m. p. 128–129° recrystallized from absolute alcohol. Baeyer reported a melting point of 128–129°.[4a]

This compound was also prepared from the reaction of 8 g. of magnesium with 63 g. of *o*-bromoanisole, and the subsequent addition of 61 g. of benzophenone; the yield was 92 g. (95%).

Phenyldi-*o*-anisylcarbinol.—From 25.7 g. of magnesium, 200 g. of *o*-bromoanisole and 75 g. of ethyl benzoate there was obtained 105 g. (66%) of product; m. p. 115–116°, recrystallized from a mixture of ligroin and ethyl acetate. Baeyer reported a melting point of 115°.[4a]

Tri-*o*-anisylcarbinol.—From 40.5 g. of magnesium, 323 g. of *o*-bromoanisole, and 59 g. of diethyl carbonate there was recovered 157.5 g. (90%) of product. The carbinol was highly insoluble in organic solvents; glacial acetic acid was the most suitable solvent for recrystallization; m. p. 181°. Baeyer and Villiger reported the melting point as 181°.[4b]

m-Anisyldiphenylcarbinol.—From 28 g. of magnesium, 185 g. of bromobenzene and 72 g. of ethyl *m*-methoxybenzoate there was obtained 110 g. (95%) of product which melted at 88° after recrystallization from a mixture of ligroin and ethyl acetate. Baeyer reported a melting point of 88°.[4a]

Tri-*m*-anisylcarbinol.—From 25.7 g. of magnesium, 200 g. of *m*-bromoanisole and 39.3 g. of diethyl carbonate there was obtained 57.5 g. (56%) of product having a melting point of 119° after recrystallization from benzene followed by a second recrystallization from absolute ethanol. Baeyer and Villiger reported a melting point of 119.5°.[4b]

p-Anisyldiphenylcarbinol.—From 15 g. of magnesium, 118 g. of *p*-bromoanisole and 91 g. of benzophenone there was obtained 101 g. (70%) of product. The carbinol was difficult to crystallize. Crystallization was induced by dissolving the oily product in ether and adding low-boiling petroleum ether to the point of turbidity. After several recrystallizations the carbinol had a melting point of 60°. Baeyer and Villiger have reported a melting point of 58–61°[4b] and later also reported a melting point of 84°.[7] Kauffmann and Pannwitz obtained a melting point of 84°[8] and Gomberg and Buchler reported 82°.[9] The compound can evidently exist in two crystalline modifications.

Triarylchloromethanes.—The chloromethanes were prepared from the pure crystalline carbinols. The carbinol was dissolved in dry benzene, excess acetyl chloride[10] was added, and the solution refluxed for several hours. The excess acetyl chloride was removed under reduced pressure and the crude chloromethane crystallized out on standing at 5°. The chloromethanes were hydrolyzed readily by moisture and the usual precautions were observed to avoid decomposition of the products in moist air. All of the crude chloromethanes were recrystallized to constant melting point and the emphasis of each experiment was on obtaining a pure compound rather than maximum yield. The new chloromethanes are listed in Table II and the appropriate solvent used for recrystallization of the crude product is indicated.

TABLE II

METHOXYSUBSTITUTED TRIPHENYLCHLOROMETHANES

Chloromethanes	M. p. found, °C.	M. p. reported, °C.	Ref.
o-Anisyldiphenyl	125–126	126	4a
Di-*o*-anisylphenyl	95– 96	95	2e
Tri-*o*-anisyl	170–173	170–175 (dec.)	2d
p-Anisyldiphenyl	122–123	124	9
		122	2b
m-Anisyldiphenyl	89– 90[a]		
Tri-*m*-anisyl	123–124[b]		

[a] Recrystallized from ethyl acetate. *Anal.* Calcd. for $C_{20}H_{17}OCl$: Cl, 11.48. Found: Cl, 11.50. [b] Recrystallized from ethyl acetate. *Anal.* Calcd. for $C_{22}H_{21}O_3Cl$: Cl, 9.61. Found: Cl, 9.49.

Magnetic Susceptibility Measurements.—The hexaarylethanes were prepared in the apparatus previously described,[3,11] for magnetic susceptibility measurements. Dissociation measurements were made on 0.1 *M* benzene solutions except in certain experiments in which the ethane was found to be insoluble in 0.1 *M* benzene. More dilute solutions were used and the dissociation values were calculated back to 0.1 *M* by use of the mass law.[12] Measurements were made over varying periods of time to check stability of the ethanes. Ethanes carrying methoxy groups were found to undergo slow decomposition on standing twenty-four hours. A decomposition of 40% was estimated for diphenyl-tetra-*o*-anisylethane over a twenty-four hour period. It was interesting to note that solutions of tri-*o*-anisylchloromethane when cooled to −70° during the preparation of the ethane solidified to a purple ice. The original colorless benzene solution was obtained upon warming to room temperature. Other chloromethanes of this series did not show this phenomenon. The chloromethane and the corresponding ethane were insoluble in 0.1 *M* benzene solution and heat was necessary to dissolve the chloromethane in benzene to make up a 0.05 *M* solution.

The experimental data are summarized in Table III.

TABLE III

EXPERIMENTAL DATA ON MAGNETIC SUSCEPTIBILITY

Ethane	% in benzene	Molarity	$-\chi$ Sol. 10^6	α% (observed)
Tetraphenyldi-	6.199	0.1	0.6938	3.8
o-anisyl	3.118	.05	.6988	5.32
Tetraphenyldi-	6.18	.1	.7001	2.1
m-anisyl	6.14	.1	.6959	3.1
Tetraphenyldi-	6.20	.1	.6900	5.2
p-anisyl	3.06	.05	.6982	5.8
	6.21	.1	.6944	3.8
Diphenyltetra-	6.9	.1	.6842	6.8
o-anisyl	7.0	.1	.6806	8.0
	6.9	.1	.6835	7.0
Hexa-*o*-anisyl	1.9	.025	.6638	60
	3.75	.05	.6332	52
Hexa-*m*-anisyl	3.8	.05	.6920	9.4
	7.5	.1	.6750	10

Peroxides.—Exposure of the fresh solutions from the magnetic susceptibility measurement to air produced the peroxides except in the case of diphenyltetra-*o*-anisylethane. In this case we isolated a product which melted at 114–116°, whereas the diphenyl-di-*o*-anisylcarbinol melts at 115° and a mixed melting point was found to be 113–115°. Bowden has reported[2e] the peroxide as melting at 110°. It is possible that our chloromethane hydrolyzed for some reason and that our dissociation value on this ethane is too low.

The *m*-anisyl derivatives gave new peroxides which were isolated and purified in the standard manner.

Diphenyl-*m*-anisylmethyl peroxide, m. p. 156–157°. *Anal.* Calcd. for $C_{40}H_{34}O_4$: C, 83.04; H, 5.91. Found: C, 83.02; H, 6.20.

Tri-*m*-anisylmethyl peroxide, m. p. 155–156°. *Anal.* Calcd. for $C_{44}H_{42}O_8$: C, 75.64; H, 6.07. Found: C, 75.55; H, 6.35.

(7) Baeyer and Villiger, *Ber.*, **36**, 2774 (1913).
(8) Kauffmann and Pannwitz, *ibid.*, **45**, 766 (1912).
(9) Gomberg and Buchler, THIS JOURNAL, **45**, 207 (1923).
(10) Gomberg, *Chem. Rev.*, **1**, 91 (1924).
(11) Marvel, Mueller, Himel and Kaplan, THIS JOURNAL, **61**, 2771 (1939).
(12) (a) Preckel and Selwood, *ibid.*, **63**, 3397 (1941); (b) Marvel, Shackleton, Himel and Whitson, *ibid.*, **64**, 1824 (1942).

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Summary

Redetermination of the degrees of dissociation of methoxyl substituted hexaarylethanes by the magnetic susceptibility method has shown that the values in the literature determined by cryoscopic molecular weight values are too high due to the instability of these ethanes. The new values show that the *o*-methoxyl group is much less effective than the *o*-methyl group in causing dissociation. In the *m*- and *p*-positions the methoxyl groups are also somewhat less effective than methyl groups but the difference is less marked.

URBANA, ILLINOIS RECEIVED DECEMBER 16, 1943

[CONTRIBUTION NO. 35 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

The Action of Formaldehyde on *m*-Hydroxybenzoic Acid. I

BY C. A. BUEHLER, TROY A. POWERS[1] AND JULIAN G. MICHELS[2]

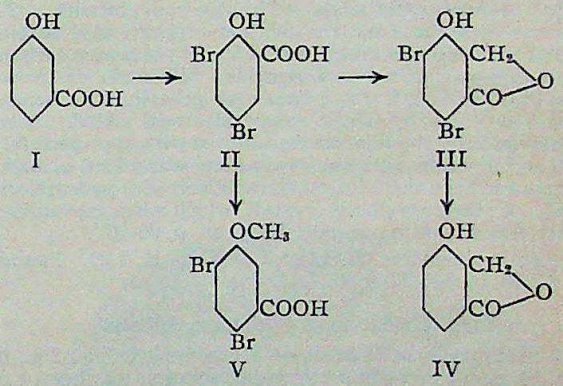
This study is one of a series[3] dealing with the action of formaldehyde on substituted phenols in hydrochloric acid solution. At room temperature *m*-hydroxybenzoic acid produces chiefly two compounds melting at 175 and 254°. The latter is the subject of this investigation. This compound, of formula $C_8H_6O_3$, contains a hydroxyl group since it gives unsaponifiable methoxy and ethoxy derivatives, and an acetyl derivative. In addition, the presence of a phthalide ring is indicated by the fluorescence which develops with resorcinol and sulfuric acid.

Of the possible structures, 4-hydroxy- or 6-hydroxyphthalide, for the condensation product, the latter is ruled out since the melting points of our product and of its methoxy and ethoxy derivatives do not agree with those of the known 6-hydroxyphthalide and its known methoxy and ethoxy derivatives. Indirectly, then, the structure of our compound corresponds to that of 4-hydroxyphthalide.

Direct methods for proving the structure were:

1. Oxidation of the methoxy derivative with dilute potassium permanganate produced the known 3-methoxyphthalic acid, which in turn with methyl alcohol and hydrogen chloride gave the known dimethyl 3-methoxyphthalate.

2. It was found possible to synthesize 4-hydroxyphthalide by blocking the reactive positions (those *o*- or *p*- to the hydroxyl) with the exception of 2-, then introducing the phthalide ring and finally removing the blocking groups. This synthesis was accomplished by brominating *m*-hydrobenzoic acid, I, in glacial acetic acid solution to give 4,6-dibromo-3-hydroxybenzoic acid, II. Although the structure of this acid was arrived at by analogy by Coppadoro,[4] we confirmed its structure by conversion into the known 4,6-dibromo-3-methoxybenzoic acid, V. On treatment of II with methylal, hydrochloric and sulfuric acids, 4-hydroxy-5,7-dibromophthalide, III, was obtained. The latter could not be debrominated with sodium and ethyl or amyl alcohols, or with zinc and alcoholic potassium hydroxide, but on hydrogenation under pressure with Raney nickel at a temperature of 150–200°, it gave 4-hydroxyphthalide, IV, identical with the original condensation product.



It is interesting to note that the orientation in this condensation is similar to that which occurred at low temperatures in the case of *m*-nitrophenol,[5] in that the entering group takes the position ortho to the two substituents.

Experimental

I. Preparation of 4-Hydroxyphthalide.—*m*-Hydroxybenzoic acid, m. p. 200–201°, 25 g., was dissolved in 500 cc. of 40% U. S. P. formaldehyde, and 500 cc. of concentrated hydrochloric acid and 25 cc. of concentrated sulfuric acid were added. The solution was stirred at 30–40° in a three-necked, round-bottomed flask, equipped with a mercury-sealed stirrer, a thermometer, and a glass tube with an opening of about 1 mm. in diameter leading to the bottom of the flask for introducing dry hydrogen chloride. Any excess of hydrogen chloride was removed through an exhaust tube, in the side arm of the flask opposite to the one containing the inlet, attached to an aspirator pump. After the introduction of hydrogen chloride gas for two hours, followed by cooling in the refrigerator, the precipitate which had formed was filtered off and crystallized once from water to give 6 to 8 g. of white crystals, m. p. 254°. Dilution of the filtrate with water to twice its volume and then standing overnight in the refrigerator gave more crystals, which when crystallized twice from water weighed 6 to 8 g. and melted at 175°.

The first crystals produced a fluorescence when heated with resorcinol and sulfuric acid, but there was no color

(1) Present address, Tennessee Eastman Corporation, Kingsport, Tennessee.

(2) Present address, Trojan Powder Company, Allentown, Penna.

(3) For the previous publication, see *J. Org. Chem.*, 6, 902 (1941).

(4) Coppadoro, *Gazz. chim. ital.*, 32, II, 332–339 (1902).

(5) Buehler, Decuel and Evans, *J. Org. Chem.*, 6, 216 (1941).

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with ferric chloride, no precipitate with alcoholic silver nitrate, no indication of the presence of a dioxane ring with phloroglucinol and sulfuric acid, and attempts to esterify with several alcohols were unsuccessful.

Anal. Calcd. for $C_8H_8O_3$: C, 64.00; H, 4.03; neut. equiv., 150. Found: C, 63.94, 63.68; H, 4.24, 4.14; neut. equiv. (indirect), 151, 150.

(a) **4-Methoxyphthalide.**—The hydroxyphthalide, 3 g., was treated in the usual manner with an excess of 10% sodium hydroxide solution and an excess of dimethyl sulfate. After warming for thirty minutes, the solution was acidified with hydrochloric acid and cooled. The solid, which separated, was crystallized three times from water to give 1.3 g., m. p. 127°.

Anal. Calcd. for $C_9H_8O_3$: C, 65.85; H, 4.91; OCH_3, 18.91; mol. wt., 164. Found: C, 65.58, 65.75; H, 4.80, 4.67; OCH_3, 18.54, 18.55; mol. wt. (cryoscopic, benzene), 166, 166.

(b) **4-Ethoxyphthalide.**—4-Hydroxyphthalide, 2 g., in 100 cc. of 10% sodium hydroxide solution was treated with 5 cc. of diethyl sulfate in the usual manner. The product, thrice crystallized from ethanol–water, weighed 1.8 g., m. p. 170°.

Anal. Calcd. for $C_{10}H_{10}O_3$: C, 67.40; H, 5.66; neut. equiv., 178. Found: C, 67.52, 67.40; H, 5.72, 5.60; neut. equiv. (indirect), 179, 179.

(c) **4-Acetoxyphthalide.**—The hydroxyphthalide, 2.3 g., was acetylated by the method of Pratt and Robinson[6] in which it was mixed with 2.5 g. of potassium carbonate and 6.4 cc. of acetic anhydride. When the first reaction had subsided, 1.3 g. more of potassium carbonate and 5 cc. more of acetic anhydride were added. After thirty minutes the mixture was diluted with approximately 100 cc. of water, potassium carbonate was added in slight excess and then the solution was acidified with hydrochloric acid. Cooling produced crystals, which when crystallized three times from water gave 1.4 g., m. p. 96–97°.

Anal. Calcd. for $C_{10}H_8O_4$: C, 62.50; H, 4.20. Found: C, 62.50, 62.54; H, 4.50, 4.48.

II. Oxidation of 4-Methoxyphthalide

3-Methoxyphthalic Acid.—4-Methoxyphthalide, 2 g., in 200 cc. of *N* potassium hydroxide solution was heated to 60–70° for one hour and then potassium permanganate solution (2 g. in 200 cc. of water) was added gradually during one and one-half hours. The reaction mixture was held at 75° for another hour and one-half, after which the excess permanganate was removed with sodium bisulfite. Filtration removed the manganese dioxide and the filtrate, upon being acidified with hydrochloric acid and evaporated to one-third its volume, was extracted with ether. The solid obtained on evaporation was taken up in water and the solution was made basic with sodium bicarbonate and then filtered. The filtrate was again acidified, evaporated to dryness, and the residue was leached with ether. Evaporation gave a product which was crystallized twice from benzene–ethanol solution (10:1), norite having been used the first time, to yield 0.5 g., m. p. 167–168° (Bentley, Robinson and Weizmann[7] give 173–174°).

Anal. Calcd. for $C_9H_8O_5$: C, 55.11; H, 4.10. Found: C, 55.11, 55.34; H, 4.29, 4.22.

Dimethyl 3-Methoxyphthalate.—A solution of the acid, 1 g. in 10 cc. of ethanol and 140 cc. of ether was cooled to 5° and diazomethane was added until a yellow color appeared. The ester was recovered in the usual manner, washed with sodium bicarbonate solution, then with water and finally crystallized from ethanol several times by the addition of water. The pure product, 0.8 g., melted at 73–74° (Onnertz[8] gives 71°).

Anal. Calcd. for $C_{11}H_{12}O_5$: C, 58.92; H, 5.39. Found C, 59.40, 59.52; H, 5.32, 5.40.

III. Synthesis of 4-Hydroxyphthalide

3-Hydroxy-4,6-dibromobenzoic Acid (II).—This acid was prepared by the method of Robertson.[9] Sixty-nine g. (0.5 mole) of *m*-hydroxybenzoic acid dissolved in a minimum amount of glacial acetic acid at 50° was treated with 77 cc. (1.5 moles) of bromine and the solution was allowed to stand at 50° for two hours. Cooling in the refrigerator gave crystals, which when crystallized from water amounted to 36 g. Three additional crystallizations from water gave a product melting at 198–199° (Robertson gives 201–202°).

Anal. Calcd. for $C_7H_4Br_2O_3$: Br, 54.01. Found: Br, 53.93, 53.98.

3-Methoxy-4,6-dibromobenzoic Acid (V).—The acid, 10 g., was dissolved in 10% sodium hydroxide solution of such an amount that the resulting solution was decidedly alkaline. Dimethyl sulfate in excess was added in the customary manner over a half hour period. About 10 cc. of 25% sodium hydroxide solution was then introduced and the solution was boiled for fifteen minutes. Acidification and cooling in the refrigerator gave a white, gelatinous mass. Solution in the minimum amount of boiling methanol, followed by the addition of water of an amount just short of that necessary to cause precipitation at the boiling point, and then slow cooling yielded white, fluffy crystals. Repetition of the above process twice more gave 6 g. (57%) of the acid, m. p. 205° (Hodgson and Beard[10] give 202–203°).

Anal. Calcd. for $C_8H_6Br_2O_3$: Br, 51.57; neut. equiv., 310. Found: Br, 51.34, 51.34; neut. equiv., 301, 304.

4-Hydroxy-5,7-dibromophthalide (III).—The dibromo acid, 26.8 g., dissolved in 250 cc. of methylal, was treated with 400 cc. of concentrated hydrochloric acid and 12 cc. of concentrated sulfuric acid. Hydrogen chloride was bubbled through this solution at 50–55°, with stirring, for six hours, after which the reaction mixture was diluted to two liters with water and cooled. The white crystalline product which formed was crystallized three times as described above by solution in the minimum amount of methanol followed by the addition of water. Final product, 16.9 g. (60%), m. p. 146°, gave a fluorescence with resorcinol and sulfuric acid, but it reacted negatively toward ferric chloride and alcoholic silver nitrate.

Anal. Calcd. for $C_8H_4Br_2O_3$: Br, 51.90. Found: Br, 52.18, 52.00, 51.86.

4-Hydroxyphthalide (IV).—The dibromophthalide, 1 g., in absolute ethanol with 0.5 g. of Raney nickel was shaken with hydrogen at 150–200° and 500 lb. pressure for three hours. The product recovered on evaporating the ethanol was crystallized twice from water to give 0.2 g. (41%), m. p. 254°. A mixed melting point with the original condensation product showed no depression.

Anal. Calcd. for $C_8H_6O_3$: C, 64.00; H, 4.03. Found: C, 63.78, 63.99; H, 4.35, 4.32.

Summary

At room temperature one of the products of the condensation of formaldehyde and *m*-hydroxybenzoic acid in acid medium is 4-hydroxyphthalide.

Although the structure of this phthalide may be inferred by indirect means, it has been established by oxidative and synthetic methods.

KNOXVILLE, TENNESSEE RECEIVED DECEMBER 9, 1943

(6) Pratt and Robinson, *J. Chem. Soc.*, **127**, 1184 (1925).
(7) Bentley, Robinson and Weizmann, *ibid.*, **91**, 110 (1907).
(8) Onnertz, *Ber.*, **34**, 3747 (1901).
(9) Robertson, *J. Chem. Soc.*, **81**, 1483 (1902).
(10) Hodgson and Beard, *ibid.*, **127**, 880 (1925).

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY, BUREAU OF AGRICULTURAL AND INDUSTRIAL CHEMISTRY, AGRICULTURAL RESEARCH ADMINISTRATION, UNITED STATES DEPARTMENT OF AGRICULTURE]

Isolation of Partheniol, Parthenyl Cinnamate, and Other Constituents from Guayule Resin[1]

BY E. D. WALTER

In the program conducted in this Laboratory on the isolation and improvement of quality of rubber from guayule, *Parthenium argentatum* Gray, retting by aerobic microbiological decomposition to reduce the resin content received considerable attention. For the retting experiments it was of interest to know the chemical constituents of the resin and whether they were altered by retting. This paper describes some of the constituents isolated from the acetone extracts (considered to be resin) of the whole shrub, the foliage, the rubber from the unretted and the retted shrub and also from the resin exuded from the shrub.

A crystalline ester, which hyrolyzes to give cinnamic acid, and a crystalline sesquiterpene alcohol were obtained from the exuded resin and from an acetone extract of the rubber. Since the literature reveals no compounds identical with the ester or the alcohol, the name *partheniol* is proposed for the sesquiterpene alcohol and *parthenyl cinnamate* for the ester. Other constituents were obtained, in small amounts, which have not been definitely identified.

In 1911 Alexander[2] investigated the acetone-soluble constituents and ethereal oils derived from the guayule plant. He obtained an acid melting at 119°, which he thought belonged to the cinnamic series, and mentioned a private communication from R. Weil, who said he had found cinnamic acid in the saponification products of guayule resin. By prolonged steam distillation of the acetone extract of guayule wood, Alexander also obtained a crystalline substance melting at 127–28°, which he thought was a sesquiterpene alcohol. By distillation of the ethereal oils, he obtained two fractions. The first was characterized as pinene and the second was thought to be a sesquiterpene, $C_{15}H_{24}$, but efforts to identify it with any known sesquiterpene failed. Alexander mentioned that his sesquiterpene alcohol changed to a liquid on long standing. This tendency was also observed with *partheniol* and seems to be characteristic of the sesquiterpene tertiary alcohols described by Simonsen[3] under alcohols of unknown constitution, such as cedrol and ledol.

Experimental

Parthenyl Cinnamate.—The sticky balsam-like exudate from injured roots and bark of two-year old shrubs was collected with a penknife. The material was dissolved in ether and filtered, and the ether evaporated. At this stage the product resembled Canada balsam in appearance and had $n^{20}D$ 1.537, acid number 0.94, saponification number 34.5, iodine number 150. When 80% ethanol was added to this material until turbidity appeared and then allowed to stand for several days, a white crystalline substance separated. Recrystallization from acetone gave tetragonal crystals (Fig. 1), melting at 125–126°, with a yield of about 20% of the whole resin. This substance, named *parthenyl cinnamate*, is insoluble in water but soluble in organic solvents. Saponification of this substance with alkali in ethanol solution yields *partheniol* and cinnamic acid.

Anal. Calcd. for $C_6H_5CH{=}CHCO_2C_{15}H_{25}$: C, 81.81; H, 9.09; mol. wt., 352. Found: C, 81.97, 81.97; H, 8.97, 8.92; mol. wt. (Rast), 353 (saponification equivalent, 354); $[\alpha]^{24}D$ 61.6° ($CHCl_3$, c = 4.752).

This substance also was isolated from concentrated acetone extract of guayule rubber, supplied by the Rubber Laboratory, Navy Yard, Mare Island, California. After the extract had stood for about a month, crystals of parthenyl cinnamate (Fig. 1) were found throughout the sticky mass. On centrifuging, the yield of crystals contaminated with mother liquor was about 20% of the total. Pure crystals were obtained by clarification with Nuchar followed by recrystallization from acetone solution, the yield being about 5% of the extract.

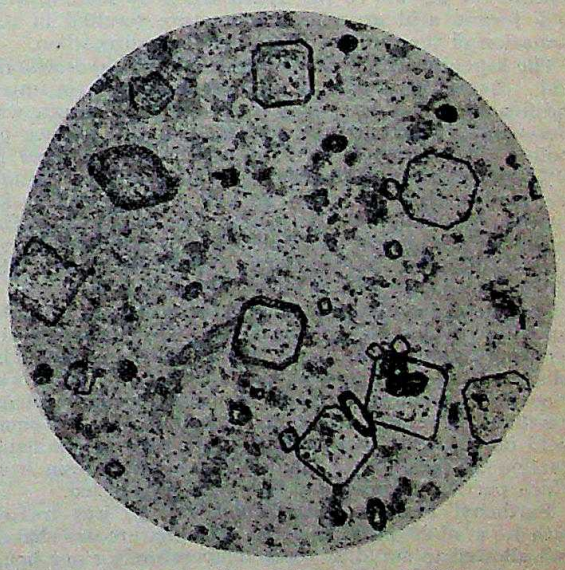

Fig. 1.—Parthenyl cinnamate (×30).

Partheniol.—The crystalline ester (0.56 g.) was saponified with 25 cc. of a saturated solution of potassium hydroxide in 95% ethanol. The excess alcohol was distilled, and the mixture was diluted with water and extracted with petroleum ether. The petroleum ether was removed, and the residue, when heated on the steam-bath in a beaker covered with a watch glass, yielded long silky crystals subliming and festooning the inside of the beaker. Repeated tufts of crystals were collected over a period of several days. The resublimed crystals (Fig. 2) melted at 131°; yield, 0.06 g. of partheniol from 0.56 g. of ester. It had a delicate terpene odor and was slightly soluble in hot water and very soluble in organic solvents. It may

(1) Natural Rubber from Domestic Sources: Paper No. 1. Not copyrighted.

(2) P. Alexander, *Ber.*, **44**, 2320–2328 (1911).

(3) J. L. Simonsen, "The Terpenes," Cambridge University Press, London, 1932, Vol. II, pp. 585–596.

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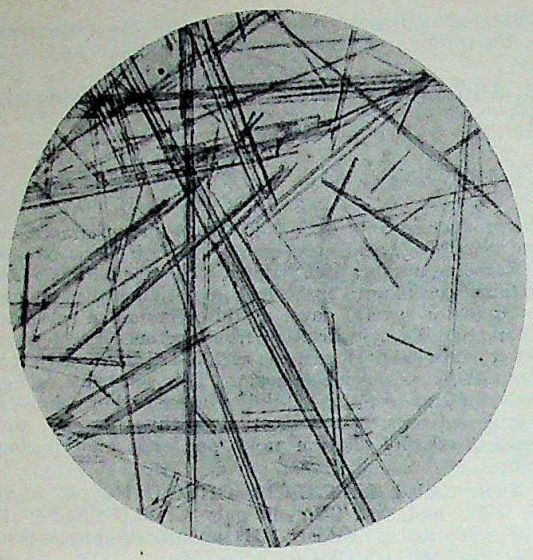

Fig. 2.—Partheniol (×100).

be obtained by steam distillation of the saponification mixture and crystallization in the aqueous distillate.

Anal. Calcd. for $C_{15}H_{26}O$: C, 81.08; H, 11.71; hydroxyl, 7.65; mol. wt., 222. Found: C, 81.17, 81.48; H, 11.39, 11.10; hydroxyl, 7.62, 7.65; mol. wt. (Rast), 233; $[\alpha]^{24}D$ 88.7 ($CHCl_3$, c = 1.566).

Attempts to prepare the phenylurethan or the 3,5-dinitrobenzoate were unsuccessful. An attempt to dehydrate the alcohol to the hydrocarbon by shaking with 90% formic acid at room temperature resulted in the formation of the formate instead of the hydrocarbon.

The saponified fraction was acidified with hydrochloric acid. A tarry substance, as yet uncharacterized, separated and floated. This was partly filtered, and the filtrate was concentrated until crystals appeared on the surface on cooling. The crystals were separated and dissolved in 50% ethanol and clarified with Nuchar. When recrystallized and dried, they melted at 133°. The phenacyl derivative was prepared, and this melted at 140.5°. The conclusion that it was cinnamic acid was confirmed by an X-ray diffraction pattern from the powdered crystals, which agreed with that of known cinnamic acid.

Partheniol and cinnamic acid also were isolated from the saponification products of the acetone extracts of the rubber from retted shrubs, from whole shrubs, and from the foliage. The yield of partheniol from the rubber was about 2.5%, from the shrub about 2%, and from the foliage less than 1%, respectively, of the acetone extract. A small yield of partheniol was isolated from the unsaponifiable fraction of the mother liquor of the exuded resin from which parthenyl cinnamate had been crystallized.

Parthenyl Formate.—Partheniol, 0.7 g., was treated with 1.5 g. of 90% formic acid. The mixture was shaken and allowed to stand at room temperature for one hour. The acid was neutralized with sodium hydroxide, and the ester was extracted with ether. The alkali was removed by shaking the mixture with water and draining it off in a separatory funnel. The ether solution was dried with calcium chloride, and then the ether was evaporated. The product was a brown liquid, yield 0.6 g.; d^{25} 0.941; b. p. 215° (dec.) at 755 mm.; $n^{25}D$ 1.503.

Anal. Calcd. for $HCO_2C_{15}H_{25}$: C, 76.80; H, 10.40; mol. wt., 250. Found: C, 76.65, 76.49; H, 10.11, 9.93; mol. wt. (saponification equivalent), 250.

Crystallographic Optical Properties

When crystallized from the concentrated acetone extract from guayule rubber parthenyl cinnamate (Fig. 1) appears as tetragonal tablets and bipyramids. In convergent polarized light (crossed nicols), uniaxial interference figures are common. When crystallized from 80% ethanol the crystals appear more fragmented but the same interference figures are observed. The optic sign is positive. On fragments showing a well-centered uniaxial figure, $n\omega$ = 1.550. On fragments showing red interference color, $n\epsilon$ > 1.64 (the substance was soluble in the higher index liquids available).

Sublimed crystals of partheniol appear as very long orthorhombic lathlike prisms (Fig. 2). In parallel polarized light (crossed nicols) the extinction is parallel; the elongation is negative. All crystals extinguish rather sharply and no clear interference figures are found in convergent polarized light. Lengthwise $n\alpha$ = 1.538; across the elongation $n\gamma$ = 1.590; $n\beta$ = indet.

Wax-like Substance.—The air-dried foliage (1500 g. of leaves and flowering stems) was ground in a Ball and Jewell mill to $^1/_{16}$-inch size and extracted with warm acetone in a Soxhlet type extractor for thirty-two hours. The extract was cooled before being concentrated and on standing overnight deposited fine crystalline material. Recrystallization from either ethanol or acetone gave tiny white crystals melting at 76°; yield, 3.73 g. or about 0.25% of the foliage or about 3 to 4% of the acetone extract (resin). It was soluble in organic solvents, but insoluble in water and in concentrated sulfuric acid. It dissolved slowly in fuming sulfuric acid, forming a brown solution. It did not absorb bromine.

Anal. Found: C, 80.18; H, 13.25; saponification number, 74.4; mol. wt. (Rast), 597.

The same substance was obtained in lower yields from acetone extracts of the whole shrub and from rubber from both retted and unretted shrubs. Attempts to identify it with any known substance have not been successful.

Volatile Oil.—Steam distillation of acetone extract of guayule rubber gave a volatile oil, $n^{25}D$ 1.4938, $[\alpha]^{25}D$ −17.92°, b. p. 244–245° at 750 mm. Attempts to prepare a nitrosochloride or a bromide of this material failed. It is probably a mixture of sesquiterpenes.

Products of Vacuum Distillation of Acetone-Extracted Resin.—Distillation of 650 g. of resin in a Fenske column yielded about 80 g. of liquid between 28° and 17 mm. and 162° and 26 mm. A greenish solid was collected between 170° and 25 mm. and 202° and 4 mm. The major part of this fraction proved to be cinnamic acid.

The liquid fraction was redistilled in a short Fenske column at a pressure of about 1 mm. No constant boiling temperature was attained, but cuts were made between 70 and 78°, 78 and 81°, and 82 and 90°. The lower boiling fraction had $n^{24}D$ 1.4850 and $[\alpha]^{22}D$ −10.5° (1-dm. tube). The intermediate fraction had $n^{24}D$ 1.4952 and $[\alpha]^{22}D$ −9.17° (1-dm. tube); b. p. 244–245° at 755 mm. The higher boiling fraction had $n^{24}D$ 1.4995 and $[\alpha]^{22}D$ −6.84; b. p. 246–247° at 755 mm. *Anal.* of the higher boiling fraction: Calcd. for $C_{15}H_{24}$: C, 88.23; H, 11.76; found: C, 87.59, 87.40; H, 11.17, 11.09. Since no partheniol was obtained in these distillates and cinnamic acid was obtained, it appears that the alcohol was dehydrated in the process and appeared in these fractions as the sesquiterpene, $C_{15}H_{24}$, the higher boiling fraction being the least contaminated.

Discussion

Since parthenyl cinnamate, partheniol, and cinnamic acid were isolated from the whole shrub, from the foliage, and from rubber from both the retted and the unretted shrub, it is obvious that the acetone extracts from all of these are qualitatively similar. The foliage extract, of course, contains more chlorophyll and more wax-like material than that from the whole shrub or

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from the rubber. No wax-like material was found in the exuded resin, and since this is practically free of chlorophyll it might be considered as the true guayule resin. About 20% of the exuded resin was parthenyl cinnamate. The acetone extract of the rubber also yielded roughly 20% of crude parthenyl cinnamate.

Acknowledgment.—The author is indebted to the Rubber Laboratory, Navy Yard, Mare Island, California, for a supply of acetone extract of guayule rubber and to Dr. C. L. Ogg and assistants of the Microanalytical Laboratory for the analyses reported.

Summary

1. *Partheniol*, a new sesquiterpene alcohol, and *parthenyl cinnamate* were isolated from guayule resin, and some of their properties, including crystallographic optical properties, are described.

2. A crystalline waxlike substance and several fractions of volatile oils, probably sesquiterpenes, were prepared from acetone extracts of whole shrub, guayule foliage, and guayule rubber.

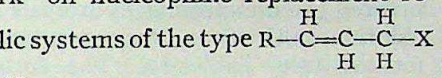
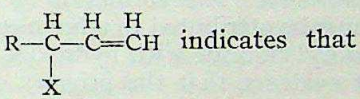
3. Retting of the shrub appears to make no change in the relative proportions of the constituents isolated from the resin.

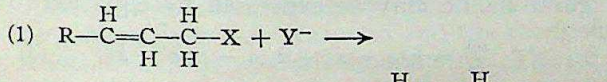
PHILADELPHIA, PA. RECEIVED DECEMBER 13, 1943

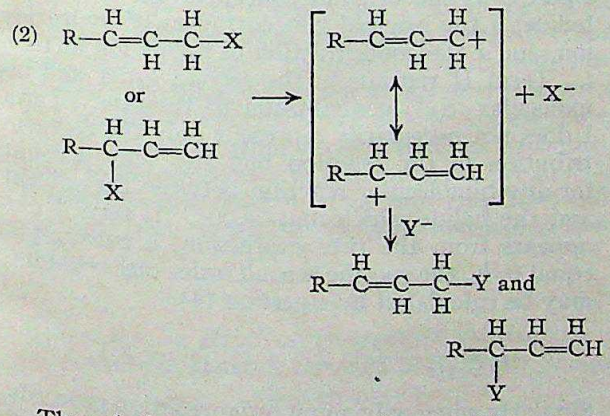
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

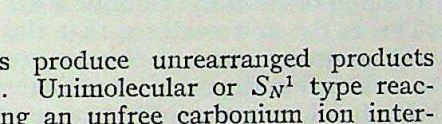
Allylic Rearrangements. XIV. The Hydrolysis of Butenyl Chlorides[1]

BY WILLIAM G. YOUNG AND LAWRENCE J. ANDREWS

Recent work[2] on nucleophilic replacement reactions of allylic systems of the type  or  indicates that bimolecular or S_N2 reactions produce unrearranged products (Equation 1). Unimolecular or S_N1 type reactions, involving an unfree carbonium ion intermediate, lead to a mixture of allylic isomers (Equation 2)

(1) 

(2) 

The relative contributions of types (1) and (2) in a given reaction are readily influenced by the experimental conditions. With this in mind it was desirable to examine critically the apparently conflicting reports in the literature concerning the hydrolysis of alkenyl halides.[3] For example, halides of the type are reported to give primary alcohol, mixtures of alcohols or the pure allylic isomer,  . Although reaction (1) would account for the production of pure normal product and reaction (2) would give a mixture due to the formation of a resonating carbonium ion intermediate, neither (1) nor (2) should give a pure secondary alcohol from a pure primary halide.

The present investigation has been undertaken to show that under controlled conditions it is possible to account for the products of hydrolysis of the butenyl chlorides[4] in terms of the mechanisms given above. Reaction conditions were varied from those favorable to S_N1 type hydrolysis to those suitable for a bimolecular type (S_N2) reaction of the organic halide with hydroxide ion. From a consideration of the composition of the alcohols produced in these reactions (Table I) it was possible to compare the relative contributions of the S_N1 and S_N2 type processes to the hydrolysis of the two halides. The correctness of the estimated contributions of the mechanisms to these hydrolyses has been demonstrated by an investigation of the kinetics of the reactions.

The Products of Hydrolysis of the Butenyl Chlorides.—The reactions with silver oxide were studied to determine the composition of

(1) This paper was presented before the Division of Organic Chemistry of the American Chemical Society, Memphis, April, 1942.

(2) (a) (XIII) Roberts, Young and Winstein, THIS JOURNAL, **64**, 1725 (1942); (b) Hughes, *Trans. Faraday Soc.*, **37**, 603 (1941).

(3) (a) Claisen and Tietze, *Ber.*, **59**, 2344 (1926). (b) Claisen, *J. prakt. Chem.*, [2] **105**, 65 (1922). (c) Prévost, *Ann. chim.*, [10] **10**, 113 (1928). (d) Meisenheimer and Link, *Ann.*, **479**, 211 (1930). (e) Petrov, *J. Gen. Chem.* (U. S. S. R.), **11**, 713 (1941).

(4) In order to avoid complications arising from thermal rearrangement of the starting material the pure primary and secondary butenyl chlorides have been used rather than the corresponding bromides.

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TABLE I

THE COMPOSITION OF BUTENOLS FROM THE HYDROLYSIS OF BUTENYL CHLORIDES[a,b]

Hydrolysis medium	Chloride used	Time of reaction, hr.	Composition of products % secondary alcohol		% primary alcohol		Yield,[c] %
Silver hydroxide suspended in water	Primary	1.5	54.7	54.8	45.3	45.2	57
		1.5	54.9		45.1		60
	Secondary	1.5	67.0	66.2	33.0	33.8	53
		1.5	65.5		34.5		72
0.5 *N* aqueous sodium carbonate; initial (OH^-) = 10^{-2} *N*	Primary	130	45.0		55.0		67
		49	45.0		55.0		64
	Secondary	120	65.2		34.8		65
0.8 *N* aqueous sodium hydroxide; initial (OH^-) = 0.8 *N*	Primary	123	39.9		60.1[d]		73
	Secondary	121	62.0		38.0		68
0.5 *N* solution of sodium carbonate in 45 volume % aqueous ethanol	Primary	96	31.8		68.2[d]		57
	Secondary	97	60.9		39.1		43

[a] All reactions were carried out at room temperature. [b] The designations primary and secondary are used for the crotyl and methylvinylcarbinyl radicals, respectively. [c] Yields are based on butenyl chloride assuming complete reaction. [d] This crotyl alcohol contains some *cis* isomer.

alcohols to be expected from the solvolytic (S_N1) type reaction. In this case both chlorides gave a predominance of secondary alcohol, 55% from the primary chloride and 66% from the secondary chloride. It might be expected that the same mixture of alcohols should be obtained from both chlorides in an S_N1 type process. This difference in composition of alcohols arising from the unfree carbonium ion[2a] probably should be attributed to the polarizing influence of the chloride ion on the carbon atom from which it is being removed rather than to contributions of a bimolecular type. The low solubility of silver oxide would leave little opportunity for a bimolecular reaction with hydroxide ion, and the rate of reaction was far too rapid to allow for bimolecular reaction of the organic halide with solvent.

The other experiments were designed to increase the opportunity for a bimolecular reaction with hydroxide ion either by raising the hydroxide ion concentration or by decreasing the solvating power of the medium. In every case the composition of the butenols from the secondary chloride was close to that obtained in the runs with silver hydroxide. Aqueous sodium carbonate gave 65% secondary alcohol; aqueous sodium hydroxide gave 62% secondary alcohol. It thus appeared that the secondary chloride was not affected by conditions designed to promote the S_N2 reaction and instead reacted by an S_N1 process The primary chloride responded readily to conditions favoring the bimolecular reaction giving larger amounts of unrearranged product than obtained with silver oxide.

Additional evidence that a bimolecular reaction was being brought into play during the hydrolysis of the primary chloride arose through the fact that the crotyl chloride used must have contained some *cis* isomer. The S_N1 type hydrolysis of either the primary or the secondary chloride gave only *trans*-crotyl alcohol from the resonating carbonium ion. Similarly it has been observed that only *trans*-crotyl alcohol is formed when the secondary alcohol is rearranged by strong acid to produce primary alcohol by means of the intermediate carbonium ion.[5] However, when the conditions favored the bimolecular hydrolysis of the primary chloride, both *cis* and *trans* primary alcohols were formed (see Table I). The formation of *cis*-crotyl alcohol must be attributed to a bimolecular reaction of *cis*-crotyl chloride with hydroxide ion. This is the first evidence that the primary chloride contains some of the *cis* isomer[6]; however previous investigators did not prepare their chloride by chlorination of butene mixtures.

The Rate Expressions for Organic Halide Hydrolysis.—The rate of hydrolysis of an organic halide may be expressed by equation (3)

$$\frac{dx}{dt} = k_1(a - x) + k_2(a - x)(b - x) \qquad (3)$$
$$\text{I} \qquad \text{II}$$

where a is the original concentration of organic halide, b the original concentration of hydroxide ion, and x the concentration of halide ion at time t. Term II represents the second order and bimolecular (S_N2) contribution to the rate. Term I does not necessarily represent only the S_N1 contribution to the reaction but also may account for any bimolecular reaction between the solvent and the halide which may occur. If term I disappears from the rate expression, a constant κ_2 equal to k_2, the specific second order rate constant, may be calculated by equation (4).

$$\kappa_2 = \frac{1}{t(a - b)} \ln [b(a - x)]/[a(b - x)] \qquad (4)$$

Similarly when only a first order reaction proceeds, κ_1 equal to k_1, the specific first order rate constant, is calculated by equation (5).

$$\kappa_1 = \frac{1}{t} \ln \frac{a}{a - x} \qquad (5)$$

(5) Young, Warner and Andrews, unpublished work.

(6) Gredy, *Bull. soc. chim.*, [5] 2, 1029 (1935), found only the *trans* isomer by measurement of the Raman spectrum of crotyl chloride prepared from methylvinylcarbinol and phosphorus trichloride.

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In the event that first and second order reactions occur simultaneously values calculated for κ_1 and κ_2 during a run will show serious drifts.

Kinetic Studies of Butenyl Chloride Hydrolysis.—To verify the assumptions that the secondary chloride was hydrolyzed only by the S_N1 type reaction while the primary chloride could react by both S_N1 and S_N2 processes the kinetics of the hydrolysis of the butenyl chlorides were studied. The rate runs were made at 25.00° using dilute solutions of the halide and sodium hydroxide in approximately fifty volume per cent. aqueous ethanol.

As was expected, the rate of reaction of methylvinylcarbinyl chloride was independent of hydroxide ion over a range of 0.0 to 0.2 *N* hydroxide ion concentration. A typical run is summarized in Table II. During any given run using primary chloride in the presence of hydroxide ion values of κ_1 drifted downward while those of κ_2 drifted upward. This indicates that both first and second order reactions contribute to the total rate as was expected. Values of k_1 and k_2 were obtained by plotting x against t to obtain values of dx/dt at any time t. A plot of $(dx/dt)/a - x$ against $b - x$ gives a straight line according to equation (3). The slope of this line is k_2, and the intercept at $b - x$ equals zero is k_1. The values of k_2 and k_1 obtained from several runs in which the halide and sodium hydroxide concentrations were varied are in good agreement. The small variations in the rate constants may be the result of salt effects. The values of k_1 are also in good agreement with that obtained from a run in which no sodium hydroxide was used and the rate constant was calculated from equation (5). The rate constants for the hydrolysis of the primary and secondary chlorides are summarized in Table III.

It appears that the primary chloride reacts by a bimolecular process much more readily than does the secondary chloride. To demonstrate further this difference in reactivity of the primary and secondary chlorides toward S_N2 type replacements a few rate runs were carried out with alcoholic sodium ethoxide in a manner similar to that previously described.[2a] The rate constants calculated from equation (4) are summarized in Table IV.

TABLE II

HYDROLYSIS OF METHYLVINYLCARBINYL CHLORIDE IN A 50 VOLUME % AQUEOUS ETHANOL SOLUTION OF SODIUM HYDROXIDE

Time, hours	(Halide) = a x	$a - x$	(OH$^-$) = b $b - x$	k_1
0	0.00000	0.07165	0.05080	
2	.00715	.06450	.04365	0.0450
4½	.01360	.05805	.03720	.0432
7½	.02605	.05100	.03015	.0433
11	.02755	.04410	.02325	.0426
			Mean[a]	.0437

[a] Mean actually based on eleven observations.

TABLE III

RATE CONSTANTS FOR THE HYDROLYSIS OF BUTENYL CHLORIDES IN 50 VOLUME % AQUEOUS ETHANOL AT 25°

Halide	Halide concn.	OH$^-$ concn.	k_1 hours^{-1}	k_2 hours^{-1} g. mole^{-1} l.
Secondary	0.1262	0.0000	0.0411	..
Secondary	.07165	.05080	.0437	..
Secondary	.04855	.05140	.0470	..
Secondary	.06902	.2143	.0461	..
Primary	.1224	.0000	.0532	..
Primary	.09375	.05140	.0525	1.16
Primary	.09913	.05140	.0511	1.11
Primary	.08941	.1024	.0480	1.05

TABLE IV

THE REACTION OF BUTENYL CHLORIDES IN ALCOHOLIC SODIUM ETHOXIDE SOLUTION

Butenyl chloride	Temp., °C.	(Butenyl chloride) = a a	(NaOEt) = b b	κ_2 hours^{-1} g. mole^{-1} l.
Secondary	40.00	0.1984	0.2110	0.0225
Secondary	40.00	.1984	.0937	.0276
Secondary	25.00	.1979	.2073	.00363
Primary	25.00	.2051	.2694	.201

At 25° the ratio of κ_2 for the primary chloride to that of the secondary chloride is 55/1. The effect of halving the sodium ethoxide concentration in the runs at 40° with the secondary chloride was to cause a 23% increase in the rate constant. This may be due to salt effects.

The Nature of the Solvolytic Reactions of the Butenyl Chlorides.—It is interesting to note that the first order constant for the hydrolysis of the primary chloride ($k_1 = 0.0532$) is slightly higher than that for the secondary chloride ($k_1 = 0.0411$). Similarly the first order constant for the solvolysis of the primary chloride in absolute ethanol at 25° ($\kappa_1 = 2.20 \times 10^{-4}$ hr.$^{-1}$) was found to be of the same magnitude as that for the secondary chloride at 40° ($\kappa_1 = 2.11 \times 10^{-4}$ hr.$^{-1}$). These facts are contrary to the usual observation that primary chlorides react much more slowly by an S_N1 type process than do secondary chlorides. It seemed quite possible, therefore, that the first order reaction of the primary chloride might be in part a bimolecular reaction with solvent giving rise to normal product, as represented by equation (6).

$$\begin{array}{l} R{-}\underset{\displaystyle H}{\underset{|}{O}} + Cl{-}CH_2{-}CH{=}CH{-}CH_3 \longrightarrow \\ \qquad\qquad R{-}\overset{+}{\underset{\displaystyle H}{\underset{|}{O}}}{-}CH_2{-}CH{=}CH{-}CH_3 + Cl^- \end{array} \quad (6)$$

It seemed like that in alcoholic solution, which is a poorer solvating medium than water, the primary chloride solvolysis might be completely bimolecular. This was found to be true when the primary chloride was refluxed with 90% aqueous ethanol in the presence of calcium carbonate giving a product containing at least 95.6% crotyl ethyl ether. It is, therefore, probable that the formation of normal product in the hydrolysis of the

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primary chloride in dilute basic media must result, in part, from a bimolecular reaction with solvent.

The Validity of Previously Reported Work.—The present investigation has shown that methylvinylcarbinyl chloride is hydrolyzed in dilute basic media by a first order process giving rise to a mixture of alcohols. Crotyl chloride reacts by a mixed first and second order process to give mixtures of alcohols, but the relative amount of normal product may be increased by raising the base concentration. In agreement with these findings are several reports in the literature that primary or secondary allylic halides hydrolyze in dilute basic media to give alcohol mixtures.[3c,d,e] In view of the rapid thermal rearrangement of butenyl bromides it is questionable just how much significance can be attached to the quantitative results reported for allylic bromide hydrolysis. The report of Claisen and Tietze[3a] that crotyl bromide is hydrolyzed in 10% sodium carbonate solution to give only crotyl alcohol must be regarded as erroneous. The reported conversion of 1-bromo-3-methyl-2-butene to 3-methyl-1-butene-3-ol in 10% sodium carbonate[3b] involves a rearrangement from a primary to a tertiary carbon atom. The present results indicate that complete conversion from one allylic isomer to the other is not to be expected from the hydrolysis of primary and secondary allylic halides. Therefore this report will be checked in this Laboratory.

Acknowledgment.—The authors wish to express their appreciation to Dr. S. Winstein for the many helpful suggestions which he made in regard to this work.

Experimental Part

Crotyl and Methylvinylcarbinyl Chlorides.—Mixtures of the chlorides obtained from the Shell Development Corporation or prepared from the alcohols as previously described[2a] were separated by fractionation on a six foot column packed with glass helices. The secondary chloride used had the properties: b. p. 63.4–63.5° (751 mm.), n^{20}D 1.4151. The purity of the crotyl chloride samples was tested by measuring their rates of reaction with alcoholic sodium ethoxide.[2a] The sample used for rate work was prepared from methylvinylcarbinol and phosphorus trichloride and had the following physical properties: b. p. 45.2–45.4° (192 mm.), n^{20}D 1.4352, κ_2 (alcoholic sodium ethoxide) 0.201. Other samples (from the Shell Development Corporation or prepared by the reaction of the butenols with concentrated hydrochloric acid) had somewhat higher refractive indices and rate constants. The properties of the primary chloride obtained from the Shell Development Corporation mixture were: b. p. 83.8–84.0° (750 mm.), n^{20}D 1.4364, κ_2 0.225. It seems likely that the presence of *cis*-crotyl chloride in some of the samples is responsible for their varying physical properties.

The Hydrolysis of the Butenyl Chlorides in the Presence of Silver Hydroxide.—A mixture of freshly prepared silver hydroxide (258 g. or 1.1 moles), 250 ml. of water, and 100 g. (1.1 moles) of the chloride was stirred at room temperature, and the reaction flask was cooled by a water-bath. At the end of the reaction period the aqueous phase was filtered from the precipitate. The precipitate was washed several times with water, and the washings were added to the filtrate. The filtrate was distilled until the distillate no longer gave a bromine test for unsaturation. The alcohols were salted out from the distillate and dried over potassium carbonate. Analysis of the alcohol mixtures was accomplished by fractionation through a three foot Podbielniak type column. The refractive indices of samples of the pure chlorides in contact with silver chloride did not change over a long period of time nor did the pure butenols rearrange when in contact with silver residues taken from one of the runs.

The Hydrolysis of the Butenyl Chlorides in Dilute Basic Media.—In the aqueous sodium carbonate runs the hydrolysis medium was a solution of 58 g. (0.5 mole) of sodium carbonate in 2 liters of water. In the runs using aqueous ethanol 58 g. of sodium carbonate was dissolved in a solution of 1142 ml. of water and 858 ml. of 95% ethanol. In the runs with sodium hydroxide the medium contained 65 g. (1.63 moles) of sodium hydroxide in 2 liters of water. To these solutions were added 100 g. (1.1 moles) of the chloride, and the mixtures were stirred at room temperature until the halide layer had disappeared. The products from the runs in aqueous media were isolated and analyzed in a manner similar to that used in the runs with silver hydroxide. The products from the runs in aqueous ethanol were isolated by distillation from their solution and dried as before. The ethanol and the constant boiling mixtures of ethanol and the ethyl ethers of the primary and secondary chlorides[7] were removed from the butenols by distillation through a three foot column packed with glass helices. When all of the low boiling material was removed, the column was washed down with 50 ml. of ether. Fractionation of the combined boiler residues and ether washings was carried out on the three foot column of the Podbielniak type.

Properties of the Butenols Prepared from the Butenyl Chlorides.—The methylvinylcarbinol produced in these reactions had the following properties: b. p. 97°, n^{25}D 1.4125, m. p. of 3,5-dinitrobenzoate 54°. The crotyl alcohol obtained from the hydrolysis of methylvinylcarbinyl chloride and that obtained from the hydrolysis of crotyl chloride in the presence of silver hydroxide or in aqueous sodium carbonate solution appeared to be predominantly the *trans* isomer. Its properties were as follows: b. p. 121°, n^{25}D 1.4270, m. p. of 3,5-dinitrobenzoate 70.5°. The crotyl alcohol isolated from the reaction of crotyl chloride with aqueous sodium hydroxide and with an aqueous ethanol solution of sodium carbonate always distilled over a range of 121–122°. The refractive index of material taken at the end of these distillations was high. A sample of such material of n^{25}D 1.4302 gave a 3,5-dinitrobenzoate which melted from 54–56°. These properties indicated that this sample contained an appreciable quantity of *cis*-crotyl alcohol. The properties of *cis*-crotyl alcohol which had been prepared in this Laboratory by other methods[8] were b. p. 121°, n^{25}D 1.4330, m. p. of 3,5-dinitrobenzoate 54–56°.

Rates of Reaction of Butenyl Chlorides with 50 Volume % Aqueous Ethanol Solutions of Sodium Hydroxide.—To a 100-ml. volumetric flask was added 50 ml. of a standardized aqueous solution of sodium hydroxide and enough anhydrous ethanol to fill the flask to within about 0.5 ml. of the mark. This solution was brought to temperature in the thermostat, and the butenyl chloride was added to the mark by means of a weight pipet. Aliquot portions were withdrawn from time to time and titrated with alcoholic hydrogen chloride or in runs where no sodium hydroxide was used with aqueous sodium hydroxide to the phenolphthalein end-point.

Rate of Conversion of Butenyl Chlorides to Ethyl Ethers.—To a 100-ml. volumetric flask was added the proper volume of a standardized solution of sodium ethoxide in absolute ethanol. The flask was filled to within 5 ml. of the mark with absolute ethanol, and a 2-ml. sample of the organic halide was added from a weight pipet. The flask was filled to the mark with absolute ethanol, shaken and immersed in the thermostat. Aliquot portions were removed from time to time and analyzed as described above. All liquids were brought to thermostat temperature before they were mixed.

(7) Lépingle, *Bull. soc. chim.*, [4] **39**, 864 (1926).

(8) Young and Siegel, unpublished work.

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The Solvolysis of Crotyl Chloride in 90% Aqueous Ethanol.—A mixture of 75 g. (0.83 mole) of crotyl chloride, 200 ml. of absolute ethanol, 20 ml. of water, and 95 g. of calcium carbonate was stirred and refluxed on an oil-bath (85°) for one hundred hours. The calcium carbonate was filtered out and washed with 50 ml. of ethanol, and the washings were added to the filtrate. The alcoholic solution of the product was added to 1.5 liters of water. The mixture was extracted with a total of 400 ml. of carbon disulfide and dried briefly over potassium carbonate. Fractionation of this material was carried out on the three foot Podbielniak type column. Fractions containing other than carbon disulfide, alcohol and water were

Fr. 1	1.9 g.	48.0–76.0° (uncor.)	$n^{20}D$ 1.5030
Fr. 2	2.0 g.	76.0–98.6°	$n^{20}D$ 1.4010
Fr. 3	24.9 g.	98.6–99.0°	$n^{20}D$ 1.4049 (crotyl ethyl ether)

It was estimated that not more than 1.2 g. of methylvinylcarbinyl ethyl ether (b. p. 77.6°, $n^{21}D$ 1.3751)[2a] out of a total of 27.6 g. of ether was formed in this reaction. The yield of ether was 33%.

Summary

The hydrolysis of crotyl and methylvinylcarbinyl chlorides has been studied using a variety of experimental conditions designed to produce different ratios of S_N1 and S_N2 replacement reactions, and the compositions of butenols from these reactions have been determined. The secondary chloride appears to react only by the S_N1 type process to give a mixture of allylic isomers while the primary chloride responds readily to changes in experimental conditions, giving relatively larger amounts of normal product as the medium becomes more suitable for a bimolecular reaction.

Kinetic studies of the reaction of the isomeric chlorides in dilute solutions of sodium hydroxide in aqueous ethanol showed that the secondary chloride reaction rate was independent of hydroxide ion; the primary chloride, however, showed both first and second order kinetics. Evidence was obtained that the first order reaction of the primary chloride is in part a bimolecular reaction with solvent.

LOS ANGELES, CALIFORNIA RECEIVED SEPTEMBER 7, 1943

[CONTRIBUTION FROM THE NUTRITIONAL RESEARCH DEPARTMENT, ABBOTT LABORATORIES]

The Hydrolysis of Pantothenate: A First Order Reaction.[1] Relation to Thiamin Stability

BY DOUGLAS V. FROST AND FLOYD C. MCINTIRE

A rapid polarimetric method for following the hydrolytic decomposition of pantothenate in aqueous solution was described recently in a paper from this Laboratory.[2] Reaction rate analyses applied to the data of this earlier publication clearly show that at the temperature studied, 60°, pantothenate hydrolysis follows the pattern of a first order reaction with respect to pantothenate concentration. The effect of varying *p*H at that temperature demonstrates that pantothenate stability is good in the *p*H range 5.5–7, but that hydrolysis proceeds at an increasing rate with increase in acidity below *p*H 5.5. The present study deals with the temperature variation of the rate of pantothenate destruction at constant *p*H.

Procedure.—A *p*H of 3.7–4.0 was chosen since the formation of pantoyl lactone is rapid and complete in this range.[2] The specific rotation of 1% calcium pantothenate at *p*H 3.8 was found to be +24.2°. A standard reference curve was therefore plotted from −27.5 to +24.2° and estimations of residual pantothenate were made as previously described.[2]

Two solutions of 1% calcium pantothenate, one buffered with 3% monosodium phosphate, the other unbuffered, were studied in parallel. Addition of small amounts of concentrated hydrochloric acid was required at the start and from time to time during the experiments to maintain a *p*H of 3.8 as closely as possible. Since the necessary additions of acid were small, no corrections were made for dilution. The various temperatures of reaction were maintained constant within 0.5°. Samples were withdrawn from the reaction vessels to make the rotation measurements.

The results obtained are shown in Table I.

Discussion.—When the logarithm of the concentration of pantothenate was plotted against time, straight lines, characteristic of a first order reaction, were obtained at each of the temperatures studied. The values of k in Table I have therefore been calculated using the standard first order equation.

The rate of destruction of pantothenate was slightly greater in the buffered solutions than in the unbuffered ones. The effect of phosphate buffer, as well as other substances, in catalyzing pantothenate destruction is more pronounced at higher *p*H,[2] than at the relative low *p*H of this study. The values for the unbuffered and buffered solutions in this case are close enough to serve as a partial check against one another.

In Table II the average values for k at different temperatures are shown, together with a calculation of the half-life period for each. When the values for log k are plotted against $1/T$, the results are seen to follow the Arrhenius equation in yielding a straight line, as shown in Fig. 1. From the slope of this line an activation energy of 19,000 ± 1000 cal. may be calculated. By extrapolation of the data the value for the half-life at 0° is found to be 6030 days, while at 110 and 120° it is 0.174 and 0.096 day, respectively.

Studies also were made to determine whether

(1) Reported in part before the American Chemical Society at Pittsburgh, Pa., September 9, 1943.

(2) D. V. Frost, *Ind. Eng. Chem., Anal. Ed.*, **15**, 306 (1943).

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TABLE I

TEMPERATURE VARIATION OF RATE OF DESTRUCTION OF PANTOTHENATE

Original solutions at each temperature contained 1% calcium pantothenate, $Ca(Pa)_2$, corresponding to 21 millimoles per liter. Solutions had $\alpha^{25}D$ of +24°, *p*H of 3.7–4.

		Buffered[a]			Unbuffered		
Temp., °C.	Time, days	$\alpha^{25}D$	Concn. $Ca(Pa)_2$, millimoles per liter	k,[b] $days^{-1}$	$\alpha^{25}D$	Concn. $Ca(Pa)_2$, millimoles per liter	k,[b] $days^{-1}$
100	0.083	+16	17.75	2.38	+15.7	17.5	2.18
100	0.25	+ 3	12.2	2.17	+ 4.5	13	1.92
75	6	−23	1.68	0.42	−22	2.1	0.384
55	9	− 5.5	8.8	.0965	− 3.5	9.65	.0864
55	15	−12	6.1	.0823	−10.5	6.71	.075
39	9	+18	18.5	.0143	+19.5	19.26	.0106
39	15	+13.5	16.5	.0159	+17.5	18.4	.0087
39	21	+12	16	.0125	+14	16.8	.0106
39	29	+ 8	14.3	.0133	+ 9	14.7	.0123
39	42	+ 2	11.9	.0135	+ 4	12.7	.0119
39	60	− 4	9.45	.0133	− 3	9.87	.0126
39	90	− 9	7.35	.0117	− 5	9.03	.0094
39	107	−15.5	5.5	.0125	−13.5	5.56	.0124
39	121	−17.5	3.88	.0134	−14	5.35	.0113
23	15	+21.7	20	.00325	+23.2	20.6	.001280
23	29	+19	18.9	.00359	+20	19.3	.00290
23	42	+17	18.1	.00352	+17.5	18.3	.00327
23	60	+15.5	17.4	.00311	+15	17.2	.00332
23	90	+14	16.8	.00248	+14	16.8	.00248
23	121	+10.5	15.3	.00267	+10.5	15.3	.00261
10	42	+22.5	20.4	.000704	+24	21	.....
10	60	+22.2	20.2	.000654	+23	20.5	.000401
10	107	+22	20	.000455	+22	20.0	.000455
10	121	+22	20	.000402	+22	20.0	.000402

[a] Buffered solutions contained 3% monosodium phosphate. [b] Constants calculated by formula $K = 2.303/t \log C_0/C$.

the rate of pantothenate destruction at *p*H 3.7–4 depended on the buffer used. Buffers tried were 3 and 6% glycine, 3 and 6% β-alanine, 2 and 5% nicotinamide and 3% acetic acid. In all cases the amounts of destruction at 39° over a period of ninety days were about equal. Thus the rate of destruction in this acid range appears to be independent of the type of buffer.

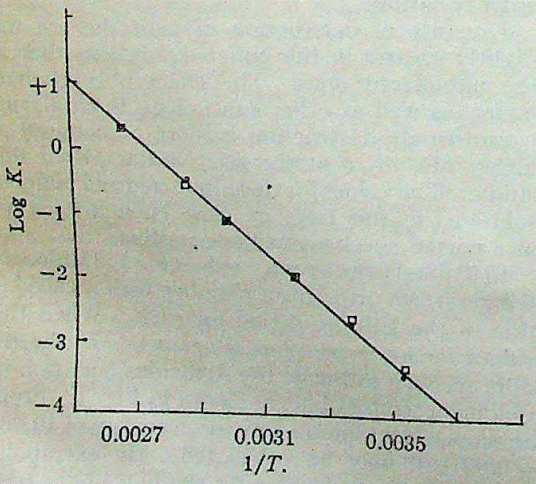

Fig. 1.—The temperature variation of the rate of hydrolysis of pantothenate: O, rate of hydrolysis unbuffered; □, rate of hydrolysis buffered with 3% monosodium phosphate.

TABLE II

SUMMARY OF VELOCITY CONSTANTS AT VARIOUS TEMPERATURES IN DECOMPOSITION OF PANTOTHENATE

	Buffered		Unbuffered	
Temp., °C.	k, ave.	half-life, days	k, ave.	half-life days
100	2.28	0.304	2.05	0.338
75	0.42	1.7	0.384	1.8
55	.0894	7.8	.0811	8.5
39	.0137	50.6	.0111	62.4
23	.00310	224	.0027	257
10	.000554	1250	.00042	1650

Relative Stability of Pantothenate and Thiamin.—A solution of 0.1% thiamin hydrochloride in 3% monosodium phosphate was divided into several equal parts. The separate parts were adjusted to various *p*H values by the addition of small amounts of hydrochloric acid or sodium hydroxide. A 1% solution of calcium pantothenate was treated in like manner. The separate solutions were filtered, sealed in ampoules and immediately placed in an autoclave for fifteen minutes at 15 lb. pressure. The amounts of thiamin and pantothenate remaining after removal from the autoclave were determined by the thiochrome and rotation methods, respectively.

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Figure 2 shows the percentage of original pantothenate and thiamin remaining at each *p*H studied. The maximum shift in *p*H during autoclaving was 0.2 unit. The point at which the two curves cross, *p*H 4.6, represents the condition under which destruction of the two compounds is equally rapid. In other experiments using somewhat different conditions some variation in the slope of the curves and in the point at which they cross has been noted. In general, however, the latter point falls in the *p*H range 4.5–4.8.

That stability of thiamin is favored by acid conditions has been known for some time.[3,4] More recently the thermal decomposition of thiamin was shown to be a first order reaction at a number of different acidities.[5] Reports have since appeared that the type of buffer used has a large effect on the rate of this decomposition at different acidities.[6,7]

In contrast to this, stability of pantothenate has been shown to be largely independent of the presence or type of buffer at *p*H 3.7–4. Other studies, however, have confirmed the earlier indications that buffer substances cause significant increases in the rate of destruction in the *p*H range 4–7. The positive effect of nicotinamide or phosphate in hydrolysis of pantothenate is most apparent in the range in which pantothenate is normally most stable, *i. e.*, *p*H 5–7.

Destruction of thiamine appears from the facts at hand to be considerably more complicated than that of pantothenate. Rate of hydrolysis of pantothenate is chiefly a function of *p*H, but may be catalyzed by the presence of electrolytes. Destruction of thiamin, however, appears to be subject to many influences other than *p*H and may even be inhibited by presence of certain compounds.

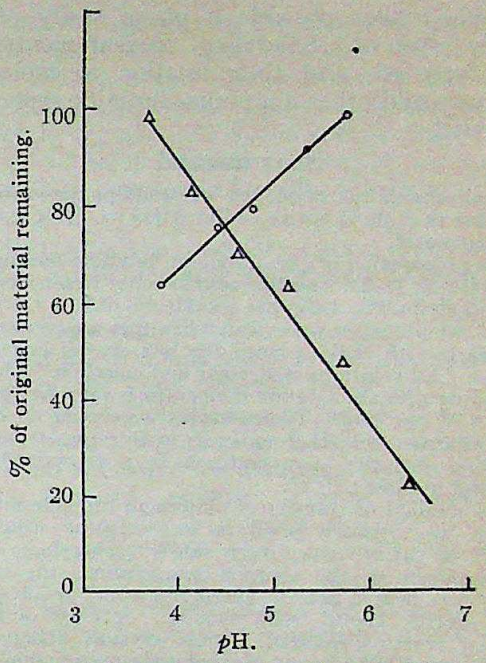

Fig. 2.—Relative rates of destruction of calcium pantothenate and thiamin hydrochloride in acid solution: O, 1% solution of calcium pantothenate; △, 0.1% solution of thiamin hydrochloride. All solutions were run in an autoclave at 15 lb. pressure for fifteen minutes.

(3) H. C. Sherman and G. W. Burton, *J. Biol. Chem.*, **70**, 639 (1926).

(4) B. C. Guha and J. C. Drummond, *Biochem. J.*, **23**, 880 (1929).

(5) A. Watanabe, *J. Pharm. Soc. Japan*, **59**, 52 (1939).

(6) B. W. Beadle, D. A. Greenwood and H. R. Kraybill, *J. Biol. Chem.*, **149**, 339 (1943).

(7) F. C. McIntire and D. V. Frost, Abstracts 106th meeting Amer. Chem. Soc., Pittsburgh, Sept. 1943, p. 63.

Summary

Hydrolysis of pantothenate in acid solution follows a first order relation with respect to pantothenate concentration.

The activation energy of the reaction has been measured to be 19,000 cal., corresponding to an increment per 10° of 2.6.

The contrasting effect of acidity on rate of hydrolysis of thiamin and pantothenate has been studied and discussed.

NO. CHICAGO, ILLINOIS RECEIVED NOVEMBER 8, 1943

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

The Solubility of Aluminum Bromide in *n*-Butane

BY JULIUS D. HELDMAN[1] AND CARL D. THURMOND

Aluminum bromide exists as the dimer in the crystal, in the molten salt, in solution in non-basic solvents, and in the vapor phase over a wide range of conditions. Although it forms highly polar double salts and complexes with organic bases, it would be expected to show normal solubility characteristics in non-polar, inert solvents, of which the paraffin hydrocarbons are good examples.

It has been shown that pure, dry aluminum bromide exerts no catalytic influence on the butanes[2] or *n*-heptane,[3] even though in the presence of a "promoter" (a hydrogen halide or substance capable of producing hydrogen bromide by reaction with the salt) aluminum bromide acts as a catalyst for paraffin conversions, notably isomerization.[2,3,4]

The stability of *n*-butane in dry aluminum

(1) National Research Fellow in Chemistry, 1942–1943.

(2) Leighton and Heldman, THIS JOURNAL, **65**, 2276 (1943).

(3) Sensel, Dissertation, Western Reserve University, Cleveland, Ohio, 1938.

(4) See Egloff, Hulla and Komarewsky, "Isomerization of Pure Hydrocarbons," Reinhold Publishing Corporation, New York, N. Y., 1942, Chapter I and Tables, pp. 218, *et seq.*

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bromide makes possible a phase study of the binary system. Solubility measurements are here reported, and their relation to molecular structure and other aluminum bromide systems is discussed.

Experimental

The hydrocarbon employed was Phillips pure *n*-butane of better than 99% purity, sulfur 0.005 wt. % or less, free of unsaturates.

The preparation of the aluminum bromide and method of obtaining sealed solution sample tubes were essentially those described by Leighton and Heldman.[2]

The sample tubes were heated in either a water or glycerol bath with shaking until the last crystal had disappeared. All solutions were clear and colorless. The rate of heating near the solution temperature was never greater than 0.2° per min. Temperatures were read on one of two calibrated 0.1° thermometers, with ranges 0–50° and 50–100°. Solution temperatures were reproducible to 0.3° and usually to 0.2°.

The method of transfer of aluminum bromide into the sample tubes usually produced large crystals which dissolved in the *n*-butane very slowly. Therefore, before measurement of the solution temperature, the sample tubes were heated until all the bromide had dissolved and then quickly cooled, with shaking. A mass of finely-divided crystals resulted. These crystals dissolved so readily upon subsequent heating that presumably there was equilibrium between the solid and liquid phases at all times.

Because of the high vapor pressures of *n*-butane at the temperatures measured, the vapor volume in each sample tube at the solution temperature was estimated, in order to apply a correction. The lack of uniformity in tube size and therefore vapor volume arises from the fact that the vacuum distillation of the aluminum bromide into the many tubes sealed to the manifolds used is not easily controllable; consequently some larger tubes received less of a bromide charge than some of the smaller ones. For the same reason, the spacing of the experimental points is somewhat fortuitous, and the rather frequent close duplication of composition inherent in the sampling method.

Samples were analyzed by weighing the sealed tube and contents, freezing in liquid air and either heating the tip to suck in the glass and reaming out the opening or merely breaking open the tube, washing out the contents, and weighing the glass parts. The aluminum bromide was calculated by difference from the tare of the glass and the known weight of *n*-butane introduced.

The butane from one tube, which had been brought to its solution temperature of 67.0° twice and then purposely set aside to stand at room temperature for fifteen days, was analyzed in a dew pressure apparatus and found to be over 98% *n*-butane. Considerable isomerization would be expected if traces of water or hydrogen bromide had been present.[2,5]

Results

In Table I are given the solution temperatures and composition of the mixtures examined. The moles of aluminum bromide are calculated on the basis of the formula Al_2Br_6. The actual moles of *n*-butane in the liquid phase have been calculated by subtracting from the total butane charge the estimated moles of vapor. This quantity was approximated using the vapor pressure of *n*-butane at the solution temperature[6] and the estimated vapor volume, assuming both the perfect gas equation and Raoult's law to be valid for the system. Neither of the assumptions hold strictly, but the former can introduce no important error. The deviation from Raoult's law could have been estimated from the solubility curve and a second-order approximation of the vapor pressure made, but this procedure is not justified by the accuracy of the results.

The internal consistency of the results points to an accuracy of about 1 or 2% in determining the composition of the mixtures. If we arbitrarily fix the maximum error arising in calculating the moles of liquid *n*-butane on the above assumptions as one-fourth of the estimated moles of *n*-butane vapor, the accuracy of the calculated moles of liquid *n*-butane is usually 0.25 to 2%, and, in a few cases, 3 to 5%. The possible error in mole fraction derived from this arbitrary basis is, in general greater than the scattering of the experimental points indicates, except for the

TABLE I

SOLUTION TEMPERATURES OF ALUMINUM BROMIDE–*n*-BUTANE MIXTURES

t, °C.	Est. vapor vol., cc.	Est. moles n-C_4H_{10} in vapor $\times 10^4$	Moles liq. n-C_4H_{10} $\times 10^2$	Moles Al_2Br_6 $\times 10^2$	Mole fraction Al_2Br_6
A. 2.503×10^{-2} moles n-C_4H_{10} added					
28.3	2	2.1	2.482	0.131	0.0501
32.2	2	2.3	2.480	.161	.0609
38.8	2	2.6	2.477	.238	.0874
39.2	2	2.6	2.477	.243	.0893
46.7	2	3.0	2.473	.364	.128
48.6	2	3.2	2.471	.400	.139
B. 2.134×10^{-2} moles n-C_4H_{10} added					
53.4	1	1.7	2.117	0.475	0.183
C. 1.067×10^{-2} moles n-C_4H_{10} added					
43.2	3	4.2	1.025	0.124	0.108
48.7	3	4.8	1.019	.172	.144
51.4	2	3.3	1.034	.203	.164
57.6	2	3.3	1.034	.312	.232
64.1	2	3.3	1.034	.494	.323
67.0[a]	2	3.3	1.034	.599	.367
67.8	2	3.3	1.034	.653	.387
71.1	3	5.0	1.017	.770	.431
71.7	7	11.3	0.954	.830	.465
72.7	5	8.0	.987	.841	.460
74.1	9	14.7	.920	.902	.495
77.2	2	2.8	1.039	1.367	.568
79.8	10	13.3	0.934	1.373	.595
80.9	2	2.6	1.041	1.838	.639
81.4	7	9.1	0.976	1.635	.628
82.5	9	11.7	0.950	1.674	.638
84.3	1	1.1	1.056	3.333	.759
86.3	7	5.8	1.009	3.200	.761
89.9	3	1.9	1.048	5.10	.830
D. No n-C_4H_{10} added					
97.5					1.000

[a] Set aside for fifteen days after measurements and analyzed; *vide supra*.

(5) Montgomery, McAteer and Franke, THIS JOURNAL, 59, 1768 (1937); papers presented before the Petroleum Division of the American Chemical Society, Part I, Baltimore meeting, April 3–7, 1939, p. M-1.

(6) Sage, Webster and Lacey, *Ind. Eng. Chem.*, 29, 1188 (1937).

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measurement at 84.3°, which is not consistent with the rest and is presumably in error in some way.

Although it would have been desirable to obtain measurements at even greater concentrations of aluminum bromide than the highest reported here, the techniques employed do not lend themselves to the handling of the larger amounts of bromide necessary.

Discussion

The usual plot of the logarithm of the solubility expressed in mole fraction of aluminum bromide (as Al_2Br_6) *vs.* the reciprocal of the absolute temperature is shown in Fig. 1. All of the points, with the single exception noted, fall close to a smooth curve of the reverse S type commonly encountered when the solvent and solute have different internal pressures.[7]

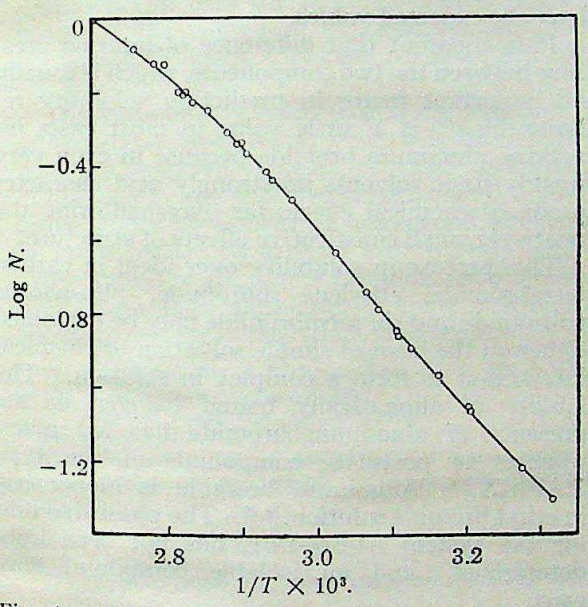

Fig. 1.—Solubility of aluminum bromide in *n*-butane (N = mole fraction Al_2Br_6).

Kendall, Crittenden and Miller[8] and Kaveler and Monroe[9] have reported a phase change in aluminum bromide just above 70° on the basis of solubility measurements. In the present case there is no change in slope of the solubility curve near 70°, nor was any change in aluminum bromide at that temperature visually observed, even with very slow heating and cooling. Kendall, *et al.*,[8a] and Crittenden[8b] claim to have authenticated the existence of two crystalline modifications of aluminum bromide by "thermal analysis" of the pure salt. No cooling curve data were presented, however. We have taken several cooling curves with pure aluminum bromide and have found them noteworthy only in the check on the melting (freezing) point obtained with the thermocouple and with the thermometer in the solubility work. Otherwise the cooling curves are completely regular. Also, the specific heat[10] and volume[11] of solid aluminum bromide are apparently smooth monotonic functions of the temperature.

Furthermore, the solubility curves from which Kendall, Crittenden and Miller, and Kaveler and Monroe, infer a phase change in aluminum bromide show no discontinuities near 70°, nor has Isbekow,[12] who has reported thermal analyses of some of the same systems, found any irregularities near 70°. Indeed, a re-plot of their data in terms of log N *vs.* $1/T$, Fig. 2, clearly shows that there is no necessity for assuming two modifications of aluminum bromide. One of the systems on which Kendall, Crittenden and Miller base their conclusions, PBr_3–Al_2Br_6, actually shows a small decrease in negative slope starting near 70°, and the internal consistency of the data for any of the systems is not great enough to justify postulating a discontinuity. It should be noted that the carbon tetrabromide used by Isbekow melted 1.9° higher than that of Kendall, *et al.*, whereas his arsenic tribromide melted 0.8° lower.

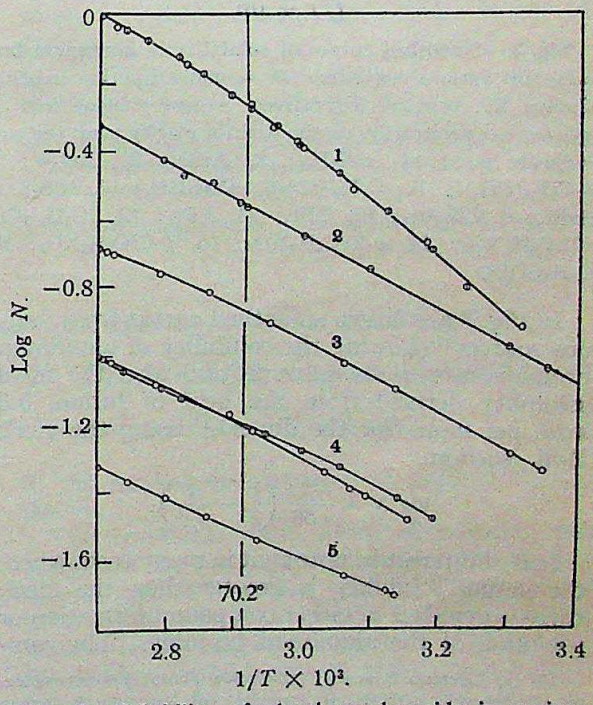

Fig. 2.—Solubility of aluminum bromide in various solvents (N = mole fraction Al_2Br_6): Curve 1, $AsBr_3$; 2, CS_2, add 1/3 to log N; 3, $SnBr_4$, add 2/3 to log N; 4, CBr_4, add 1 to log N; 5, PBr_3, add 1 1/3 to log N; ○, Kendall, Crittenden and Miller; ⊖, Kaveler and Monroe; ⊙, Isbekow.

(7) Hildebrand, "Solubility of Non-Electrolytes," Reinhold Publishing Corporation, New York, N. Y., 1936, p. 170.

(8) (a) Kendall, Crittenden, and Miller, THIS JOURNAL, **45**, 963 (1923); (b) Crittenden, Dissertation, Columbia University, New York, 1922.

(9) Kaveler and Monroe, THIS JOURNAL, **50**, 2421 (1928).

(10) Fischer, *Z. anorg. allgem. Chem.*, **200**, 332 (1931).

(11) Klemm, Tilk and Muellenheim, *ibid.*, **176**, 11 (1928).

(12) Isbekow, *ibid.*, **143**, 80 (1925).

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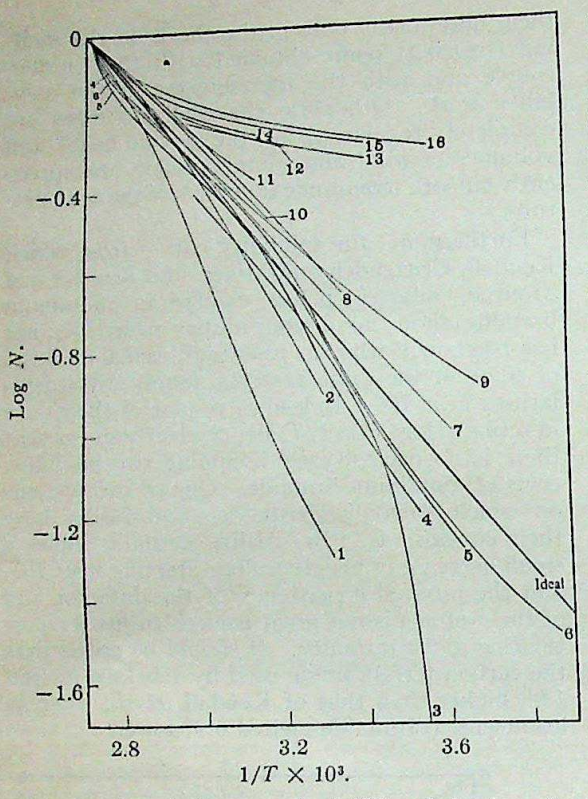

Fig. 3.—Smoothed curves of solubility of aluminum bromide in various solvents (N = mole fraction Al_2Br_6). Curves for benzene derivatives, except toluene and *p*-xylene, are arbitrarily terminated for clarity near the convergence point: 1, *n*-C_4H_{10}; 2, $AsBr_3$; 3, C_6H_6[13f]; 4, *p*-$C_6H_4(CH_3)_2$; 5, C_6H_6[13a]; 6, $C_6H_5CH_3$; 7, CS_2; 8, $SnBr_4$; 9, $C_2H_4Br_2$; 10, CBr_4; 11, PBr_3; 12, $(C_6H_5)_2CO$; 13, $C_6H_5NO_2$; 14, *p*-$BrC_6H_4NO_2$; 15, *p*-$ClC_6H_4NO_2$; 16, C_6H_5COCl.

In Fig. 3 are drawn smoothed curves from various sources[13] showing the solubility of aluminum bromide in various solvents and also the ideal solubility derived from the heat of fusion, 5.5 kcal. per mole (for the dimer),[14] using the van't Hoff isochore

$$\log N = \frac{-Lf}{4.58}\left(\frac{1}{T} - \frac{1}{Tm}\right) \qquad (1)$$

It is of interest to note that in many cases where the actual solubility is greater than the ideal, there is evidence of either compound formation or solvation of the aluminum bromide. The compounds with nitrobenzene and its derivatives are well known.[13d,15]

Benzene and its analogs give curves that are particularly interesting and somewhat puzzling, being of the unreversed S type, which is extremely uncommon in solubility work. The molecular state of aluminum bromide in benzene is that of the monomer (probably $AlBr_3 \cdot C_6H_6$) in very dilute solution and essentially the dimer at ordinary concentrations.[13f,16] The reported existence of an unstable solid compound $AlBr_3 \cdot C_6H_6$[13f] and the lack of agreement between the solubility data of Menschutkin and Plotnikow and Gratsianskiĭ indicate that the curvature may be due to non-equilibrium conditions with respect to the solid phase in Menschutkin's work.

The deep color of concentrated solutions of aluminum bromide in carbon disulfide leads us to believe that here solvation is increasing solubility over the expected values.

It is apparent that difference of internal pressure between the two components, which is usually an important factor in predicting solubility relationships,[17] is of little value in most cases involving aluminum bromide because in even very weakly basic solvents its strongly acid character produces chemical effects far overshadowing the relatively small constitutive effects of structure.

The increase in solubility over ideal in carbon tetrabromide, ethylene dibromide, phosphorus tribromide and tin tetrabromide may be explained either on the basis of simple solvation or chemical interaction to form a complex in solution. The lability of aliphatically bound halogen in the presence of aluminum bromide has led many workers to postulate compounds of the type $RAlBr_3X$.[18] Aluminum bromide is monomeric in ethyl bromide solution.[19,20] The phase diagram for the system Al_2Br_6–PBr_3 has not been fully determined,[8] and an isolable compound may exist.

In the case of *n*-butane, in which the solubility of aluminum bromide is much less than the ideal, a calculation based on the equation given by Hildebrand[21]

$$RT \ln \gamma_1 = V_1\left(\frac{N_2V_2}{N_1V_1 + N_2V_2}\right)^2\left[\left(\frac{\Delta E_1}{V_1}\right)^{1/2} - \left(\frac{\Delta E_2}{V_2}\right)^{1/2}\right]^2 \qquad (2)$$

is of interest. We can estimate the energy of vaporization of aluminum bromide at 25° from the heat of vaporization at the boiling point, 12.0 kcal. per mole at 255°, and ΔC_p of vaporization =

(13) (a) Reference 8, arsenic tribromide, phosphorus tribromide, tin tetrabromide, carbon tetrabromide; (b) Reference 9, carbon disulfide; (c) Reference 12, arsenic tribromide, carbon tetrabromide; (d) Menschutkin, *Chem. Zentr.*, **14**, 164 (1910), nitrobenzene, benzophenone, benzoyl chloride, *p*-chloronitrobenzene, *p*-bromonitrobenzene, ethylene bromide; (e) *ibid.*, **14**, 167 (1910), benzene, toluene, *p*-xylene; (f) Plotnikow and Gratsianskiĭ, *Mem. Inst. Chem. Acad. Sci. Ukrain. S. S. R.*, **5**, 213 (1939), benzene.

(14) The data of Kablukow [*C. A.*, **3**, 870 (1909)] lead to the value 5.58 kcal; two determinations by Fischer[10] give values of 5.1₂ and 5.5₃ kcal. The weighted average is here taken as 5.5 kcal. Any value between 5 and 6 kcal. will not affect the qualitative conclusions to be drawn.

(15) Mezhenif and Turov, *Mem. Inst. Chem. Acad. Sci. Ukrain. S. S. R.*, **5**, 98 (in English) (1938).

(16) (a) Plotnikow, Sheka and Yankelewich, *ibid.*, **4**, 382 (in German) (1938); (b) Ulich, *Z. physik. Chem.*, Bodenstein Festband, 423 (1931); (c) Ulich and Nespital, *Z. Elektrochem.*, **37**, 559 (1931).

(17) See reference 7, Chapters III, V, VI.

(18) See for example Brejevna, Roginsky and Schilinsky, *Acta Physicochim. U. R. S. S.*, **6**, 744 (1937); **7**, 201 (1938).

(19) (a) Konowaloff and Plotnikow, quoted in Walden, "Molecular-grossen von elektrolyten," T. Steinkopff, Dresden, 1923, p.207.

(20) Wertyporoch, *Ber.*, **64B**, 1361 (1931).

(21) Ref. 7, p. 72.

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-18 cal. per deg. mole,[22] giving the heat of vaporization at 25° as 16.14 kcal. per mole. Subtraction of RT leaves the energy of vaporization, 15.55 kcal. per mole. It must be emphasized at the outset, however, that the uncertainty in ΔC_p leaves a margin of about 1.5 kcal. per mole in ΔE, which will be reflected in the calculation based on equation (2).

From the density of solid aluminum bromide at 25°, 3.01, and the coefficient of cubical expansion, 2.83×10^{-4},[11] the molal volume at 100° is calculated as 181 cc. At that temperature, the molal volume of the liquid is 203 cc.[23] Assuming the same percentage increase in volumes on melting the solid at 25 and 100°, we find the molal volume of molten aluminum bromide at 25° to be 198 cc. The possible error in this value can be at most 10 cc. and will not affect the conclusions to be drawn.

Hildebrand lists the required constants for *n*-butane,[24] the energy of vaporization and molal volume at 25° being 4.44 kcal. per mole and 102.0 cc., respectively.

The value of $\ln\gamma$ calculated from equation (2) on the above bases is 1.4, which is to be compared with the observed value of 1.3, taken as the ratio of the ideal to the observed (extrapolated 3°) solubility. The agreement is quite good and could be made perfect by a slight lowering of $-\Delta C_p$ of vaporization of aluminum bromide. We conclude that solutions of aluminum bromide in *n*-butane are quite regular in the Hildebrand sense.[25]

(22) Fischer and Rahlfs, *Z. anorg. allgem. Chem.*, **205**, 1 (1932). The value of $-\Delta C_p$ is surprisingly large.

(23) Biltz and Voight, *ibid.*, **126**, 39 (1923).

(24) Hildebrand, ref. 7, p. 104.

(25) Other effects, such as deviations from random mixing in solution [Rushbrooke, *Proc. Roy. Soc.* (London), **166A**, 294 (1938); Kirkwood, *J. Phys. Chem.*, **43**, 97 (1939)], and a size effect due to dimerization of the solute, which can be applied in this case [Fowler and Rushbrooke, *Trans. Faraday Soc.*, **33**, 1272 (1937)], are quite small in comparison to the Hildebrand term for regular solutions.

The system Al_2Br_6–$AsBr_3$ is apparently normal. There is good evidence for the lack of compound formation.[26]

We have throughout written aluminum bromide as the dimer Al_2Br_6. It seems to us that this is logical in view of our knowledge of its molecular state when no chemical reaction has occurred. To write it as $AlBr_3$ would be analogous to using the formula I for liquid iodine or iodine in solution. The fact that in both cases a reaction with certain solvents may occur renders it even more important to compare such solutions with others on the basis of the ideal solution, in which Al_2Br_6 (or I_2) is certainly the true molecular formula.

Summary

The solubility of aluminum bromide in *n*-butane has been measured from 28.3° to the melting point of the salt, 97.5°.

There appears to be no convincing evidence for a phase transformation in aluminum bromide near 70°, as has been reported by other workers.

The difference between the actual and ideal solubility of aluminum bromide in *n*-butane is predicted by Hildebrand's equation relating solubility to internal pressure differences. The system is regular in the Hildebrand sense.

The solubility relationships of aluminum bromide in other solvents have been briefly discussed.

(26) Yankelewich and Sheka, *Mem. Inst. Chem. Acad. Sci. Ukrain. S. S. R.*, **5**, 81 (in English) (1938).

BERKELEY, CALIFORNIA RECEIVED NOVEMBER 2, 1943

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

Acid–Base Studies in Gaseous Systems. I. Precise Dissociation Measurements

BY HERBERT C. BROWN,[1] MODDIE D. TAYLOR AND MELVIN GERSTEIN

The rarity of simple reversible organic reactions has always been a major difficulty in the development of rational chemical theories. Because of this scarcity, the effects of structure and of substituents upon chemical behavior have been investigated largely by means of competitive reactions and reaction rate studies. Work with irreversible systems and the interpretation of the results thus obtained, however, involve great difficulties and uncertainties. Although much ingenuity has been displayed in overcoming such obstacles, and although modern physical methods for examining molecular structure have been of great service, simple reversible reactions, were they available, would still play an important role in the further development of organic chemical theory.

The reversible dissociation of addition compounds in the vapor phase has been the object of several studies in recent years.[2] These dissociations of the type $B{:}A^3 \rightarrow B{:} + A$ are simple reversible reactions are representative of a large class, the study of which should yield much valuable information. In studies of such dissociations, it is possible to make quantitative measurements from

(1) Present address: Department of Chemistry, Wayne University, Detroit, Mich.

(2) (a) Schlesinger, Flodin and Burg, THIS JOURNAL, **61**, 1078 (1939); (b) Davidson and Brown, *ibid.*, **64**, 316 (1942); (c) Brown and Adams, *ibid.*, **64**, 2557 (1942); (d) Laubengayer and Finlay, *ibid.*, **65**, 887 (1943).

(3) The formula of the addition compound is frequently written $B^+{:}^-A$ in order to indicate the formal charges on the bonding atoms. Since there is no evident advantage in this more complex symbolism, the simpler version will be here employed.

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which the thermodynamic quantities ΔF, ΔH and ΔS readily may be determined. The substituents in A and in B may be widely varied, and the effects of such variations on ΔF, ΔH and ΔS may then be compared. Thus it is possible to compare a particular change of the substituents in A with a similar change of the substituents in B. Moreover, the substituents in both A and B may be kept constant while the bonding atoms are varied. By comparisons of the results thus obtained, the "electrical" effects of substituent groups and the dependence of these effects on the nature of the bonding atoms may be distinguished from the "steric" effects. It is evident that the quantitative data secured from an investigation of the dissociative characteristics of a selected series of compounds offer important possibilities for broadening our understanding of the specific influences of substituent groups in organic chemistry.

The interest of such studies is considerably heightened by Lewis' suggestion that such dissociations are typical acid–base reactions.[4] The ionization of organic acids and bases in suitable solvents has hitherto been one of the few simple reversible reactions available to workers in theoretical organic chemistry. The conclusions drawn from the study of such ionizations have, however, always been open to the objection that the results may be greatly affected by complex solvent effects, the importance of which cannot yet be estimated. If Lewis' interpretations of the dissociation reaction, $B:A \rightarrow B: + A$, can be shown to be correct, the effect of structure on acid and base strength may be determined by observations made on the vapor phase, where the complexities inherent in solution work are absent. The accumulated data from solution studies may then be reëxamined in order to determine whether the customary neglect of the solvent has led to serious errors.

For these reasons, it has seemed desirable to initiate a series of studies on the dissociation of selected addition compounds in the gas phase. It was decided early that in order to derive the maximum value from the experimental data, the limits of accuracy of the measurements should be set as high as practical. The following limits were tentatively fixed: the dissociation constants should be accurate to 1–2%; the heat of dissociation should be correct to 0.1% (0.1–0.2 kcal.). The technique finally developed, and described in the present paper, is both simple and accurate—it is easily reliable to these limits. The results obtained by the application of this technique to specific problems will be discussed in later papers of this series.

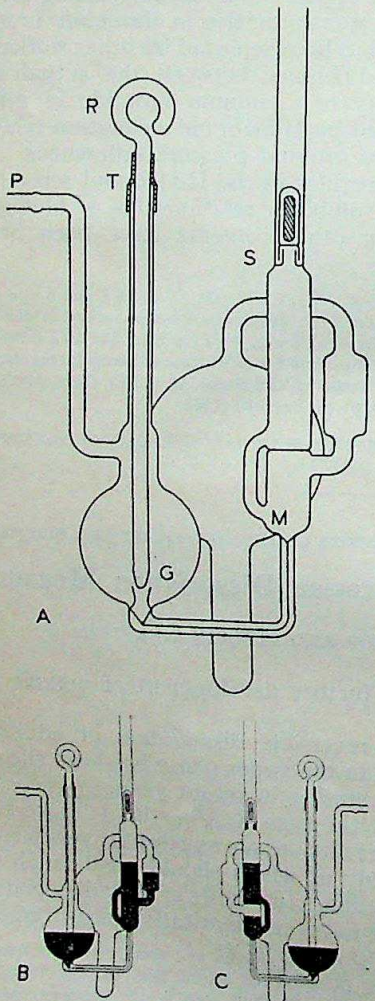

Fig. 1.—Dissociation tensimeter: A, diagram illustrating construction; B, mercury in position to read low pressures (below 20 mm.); C, mercury in position to read dissociation pressures (20–100 mm.).

The Apparatus

The apparatus used for studying the dissociations (the "dissociation tensimeter") is shown in Fig. 1.

The volumes of the two dissociation tensimeters (*ca.* 260 ml.) were matched to within 1 part in 2000. This was accomplished by comparing the pressure exerted by a given volume of gas transferred from one tensimeter to the other. Minor changes in the volumes of the tensimeter were made by adjusting the zero marks to which the mercury in the manometer was raised.

The mercury manometer was constructed of 25-mm. tubing and designed as shown to bring the upper mercury meniscus directly above the lower (Fig. 1-C). In this way the height of the mercury column could be accurately measured as a single vertical distance to within 0.01 to 0.02 mm. with the aid of a Gaertner micrometer slide (range, 100 mm.) carrying a short focus telescope. Pressures below 20 mm. could not be measured in this way. By allowing the mercury to rise in the manometer until the two menisci were side by side (Fig. 1-B), pressures below 20 mm. (*e. g.*, saturation pressure) could be read with an ordinary cathetometer with somewhat poorer precision ($\pm$0.04 mm.).

Mercury was brought into the evacuated manometer M by raising the rod R (Fig. 1-A), thus opening the ground glass closure G between the reservoir and the manometer. The mercury was lowered by connecting the mercury reservoir to a pump at the point P while the rod was lifted. The necessary vertical movement of the rod was obtained by using thin gum rubber tubing for the closure at the point T. The mercury vapor seal S was introduced to

(4) Lewis, *J. Franklin Inst.*, **226**, 293 (1938).

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TABLE I

SUMMARY OF DISSOCIATION DATA FOR TRIMETHYLAMINE–TRIMETHYLBORON[a]

Detn. no.	Inital pressure,[b] mm.	Temp., °C.	Pressure, mm. Observed	Pressure, mm. Calcd.[c]	Degree of dissociation	Dissociation constant, K (atm.)	Log K_p = $-A/T + B$ A	B	ΔH	ΔS	$\Delta F_{80°}$
1	23.39	70.4	49.77	29.42	0.692	0.0601	3852	9.9978	17619	45.7	1472
		80.0	54.35	30.24	.797	.125					
		90.6	58.48	31.15	.877	.257					
		99.0	61.18	31.87	.920	.441					
		111.3	64.47	32.92	.960	.956					
2	26.12	70.4	55.14	32.85	.678	.0619	3831	9.9392	17523	45.5	1470
		83.9	61.99	34.14	.816	.162					
		88.7	64.07	34.60	.852	.223					
		96.3	67.08	35.33	.899	.371					
3	23.01	74.6	51.18	29.30	.747	.0850	3849	9.9829	17605	45.7	1482
		78.4	52.75	29.62	.781	.108					
		85.9	55.85	30.25	.846	.185					
		93.6	58.59	30.90	.896	.314					
							Average values		*17582 ± 40*	*45.6 ± 0.1*	*1475 ± 3*
4	28.13	75.7	62.25	35.93	.732	.0948	3807	9.8903	17413	45.3	1439
		85.3	67.37	36.93	.824	.188					
		91.3	70.01	37.53	.865	.275					
		95.2	71.64	37.94	.888	.352					
5	10.04	54.1	19.66	12.03	.634	.0174	3885	10.1138	17770	46.2	1440
		65.9	22.16	12.46	.778	.0449					
		71.1	23.15	12.69	.830	.0674					
		80.7	24.71	13.01	.899	.137					
5′	10.07	54.1	19.66	12.06	.630	.0170	3809	9.8738	17422	45.2	1475
		65.9	22.16	12.50	.773	.0432					
		71.1	23.15	12.69	.824	.0646					
		80.7	24.71	13.03	.893	.129					

[a] To reduce the amount of material tabulated, only every other measurement from each determination has been reported. The corresponding dissociation constants are plotted in Fig. 2. [b] Calculated to 0°. [c] Calculated from the initial pressure to the temperature, T, assuming no dissociation.

eliminate errors resulting from the evaporation of mercury into the vacuum above the upper meniscus. In operation, the plug rested in the mercury well (Fig. 1-C), beneath the surface of the oil-bath. Thus, at equilibrium, both the bulb of the tensimeter and the space above the upper meniscus were saturated with mercury vapor. Whenever materials were introduced or removed from the tensimeter, the plug was lifted with magnets to break the seal. The tensimeter was surrounded by a thermostat maintained at a temperature constant to ±0.1° for one-hour intervals, charged with clear mineral oil and provided with a plate glass window sealed with Glyptal cement to permit observation of the manometer, this cement being resistant to the bath liquid up to 160°. Its temperature was measured by means of a mercury thermometer calibrated by the U. S. Bureau of Standards.

Procedure

A sample of component A, the amount of which had been previously measured roughly in the vacuum apparatus (±0.5%), was condensed with liquid nitrogen in one of the dissociation tensimeters. The mercury was then raised into the manometer, shutting off the tensimeter from the rest of the apparatus while component B was similarly brought into the other tensimeter. The samples used were of such a size that within the tensimeter they exerted a pressure of 20–30 mm., low enough to minimize deviations from the ideal gas laws, yet high enough to maintain the desired precision of measurement.

The sizes of the two samples were adjusted until the two pressures agreed within 0.02 mm. The adjustment was conveniently made in the following manner. The ratio between the volume of the tensimeter to the bottom of the manometer (point M) and the volume from that point to

TABLE II

CALCULATED DISSOCIATION CONSTANTS

Detn. no.	Temperatures, °C. 70.0	80.0	90.0	100.0
1	0.0590	0.123	0.245	0.472
2	.0593	.123	.245	.469
3	.0582	.121	.241	.464
Av. values	*.0588 ± 0.0004*	*.122 ± 0.001*	*.244 ± 0.002*	*.468 ± 0.003*
4	.0623	.128	.254	.468
5	.0617	.129	.259	.509
5′	.0592	.122	.242	.462

the mercury seal S was known. Calculations based upon the measured excess pressure and the known vapor pressure of the compound at low temperatures permitted an accurate fraction of the total sample to be removed by simply cooling the flask to the calculated temperature and momentarily withdrawing the mercury from the manometer. After the manometer was closed, the small plug was lifted from the mercury seal and the material trapped in the space beneath it was distilled away. In working with a series of addition compounds in which one component was maintained constant (*e.g.*, the addition compounds of trimethylboron with aliphatic amines), it proved convenient always to have the constant component (trimethylboron) present in slight excess so that the adjustment could be made to the same component.

The two matched samples were then quantitatively brought together into one tensimeter by means of liquid nitrogen. To transfer the substances quantitatively (loss

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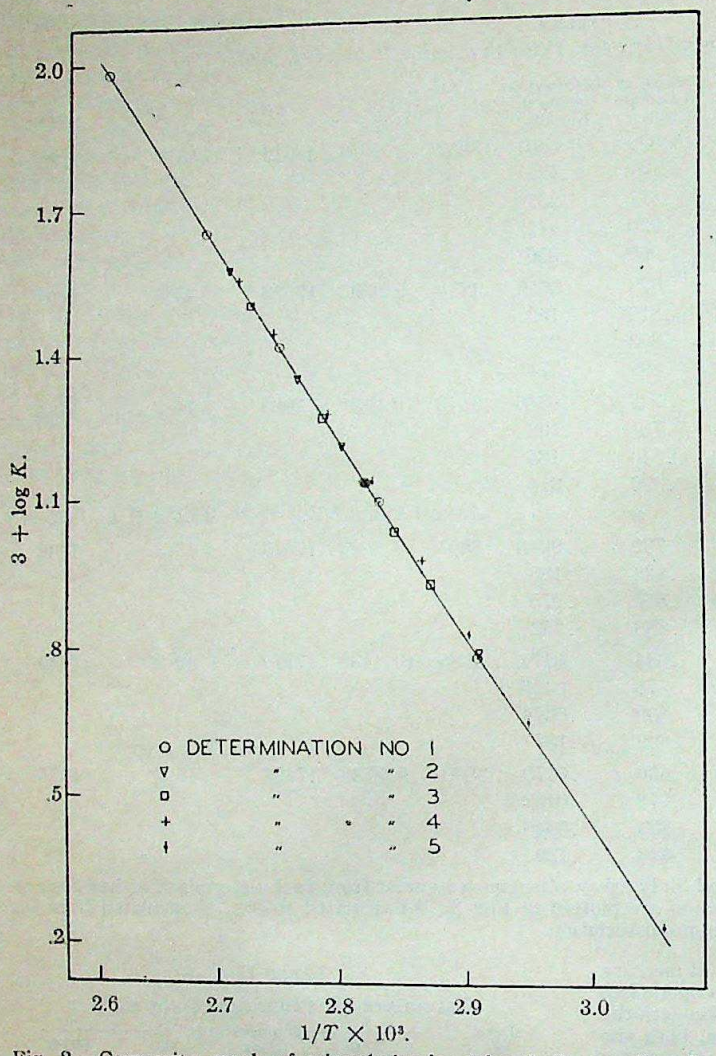

Fig. 2.—Composite graph of trimethylamine–trimethylboron dissociation data.

less than 1 part in 2000) test experiments indicated that a condensation time of close to ten minutes was necessary. Usually twenty to thirty minutes were assigned to this operation. Ordinarily the more volatile of the two components was the one transferred.

The vapor pressure of the addition compound thus synthesized from its components was measured at 0°. If this pressure agreed with that obtained for the previously prepared and purified sample of the addition compound, the heating bath was placed in position and the heating begun. The point of complete vaporization could be determined by comparison of the observed pressure with the previously measured saturation pressure. (This point could also be detected by observing the instant the glass walls of the tensimeter lost their foggy appearance and became perfectly transparent.) Usually no dissociation measurements were made for approximately 10° above this point, for the values of the dissociation constant determined near the saturation point tended to be low. The measurement of at least 8 to 10 dissociation pressures (roughly every 5°) allowed the importance of random errors in the determination of individual values to be minimized. Several check readings were also made as the bath cooled and compared with readings taken during the temperature rise in order to insure that equilibrium had been reached and to establish that no irreversible changes had occurred in the course of the experiment.

Test of Method

The reliability of the procedure described was tested by a number of studies on the dissociation of trimethylamine–trimethylboron.[5] These series of measurements were made by three different investigators who used different pairs of dissociation tensimeters and individual preparations of the components. The results are summarized in Table I (determinations 1, 2 and 3) and represented graphically in Fig. 2. To facilitate comparison between these runs, individual values of the dissociation constants for four temperatures were calculated (Table II) by means of the equation which best represented each series of measurements.[6] The agreement is excellent. The heats of dissociation calculated from these three runs agree within 0.1 kcal.; the dissociation constants agree to within 1%.

It can be shown that the value of the dissociation constant is very sensitive to small quantities of inert impurities in the components A and B used in the preparation of the addition compound. Fortunately, the nature of the addition compound and the method of its preparation offers a simple but sensitive check on the purity of the individual components and the compounds they produce. In practically all cases to which the method described is applicable, the components A and B are very volatile substances with vapor pressures of the order of 0.1 to 4 atmospheres to 0°. These components may easily be individually purified to the point where the absence of any impurities of markedly different volatility is assured. On the other hand, the addition compound B:A is, ordinarily, only slightly volatile; in most cases its saturation pressure is below 0.3 mm. at 0°. An inert impurity present to the extent of 0.2% in A would leave uncombined an equal quantity of B. If 25-mm. samples of A and B each are used, the saturation pressure of the addition compound B:A would be 0.1 mm. above the true value. A discrepancy of this magnitude is detected easily. Reactive impurities, that is, those which react with the other component to form addition compounds, are less easy to detect; their absence may be demonstrated by the constancy of the saturation pressure of the complex. That the requisite purity can be attained is indicated by the agreement between determinations 1, 2 and 3.

The effect of deviations from the perfect gas laws on the accuracy of the results remains to be considered. To obtain experimental evidence on the importance of such deviations, a run was made at a considerably lower pressure than in the three determinations already mentioned. At this low pressure the specially designed manometer and the slide cathetometer could not be used. Accordingly, the two-limb manometer and an ordinary cathetometer were used. As a check, a run was made with the same appa-

(5) Previous work on this compound and its physical properties will be described in the second paper of this series. This addition compound was selected for testing the experimental method because from its previous study, it was known that its degree of dissociation was in a moderately difficult region, $\alpha = 0.70$ to 0.95. Its study, therefore, furnished a relatively severe test of the reliability of the experimental method.

(6) The dissociation data from a number of runs were studied both by standard statistical methods and by graphical methods; the results obtained by both procedures agreed very closely. The agreement was much better than the limits of accuracy set for the results. It was, therefore, decided that the simpler graphical method should be adopted as the standard procedure for working up the experimental data.

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ratus at the usual pressure. The results are given in Tables I and II, determinations 4 and 5. It is apparent that within the lower precision of these results, there is no significant difference between the constants thus obtained and those observed in runs 1, 2 and 3. It may be concluded that the accuracy of the constants is not seriously affected by deviations from the perfect gas laws. Although errors due to this factor might be reduced by using an extrapolation procedure, the sensitivity of the dissociation data obtained in the lower pressure range to variations in the initial pressures[7] suggests that very little would be gained by recourse to such a method.

Summing up, then, it appears that the method described in this paper for measuring the dissociation of addition compounds yields dissociation data with the desired accuracy: the dissociation constants are estimated to be reliable to 2% and the heat of dissociation to 0.1%. The optimum pressure range (initial pressure of each component) is 20–30 mm. Operating below this range (*e. g.*, 10 mm.) does not noticeably affect the experimental values of the constants, but it greatly increases the probable error.

(7) Comparison of the calculated values in runs 5 and 5′ illustrates this sensitivity. In the 5′ series of calculations, 10.07 mm. was used for the initial pressure instead of the 10.04 (±0.04) actually observed.

There is little doubt that the precision of the measurements could be further improved by additional refinements. However, the uncertainty introduced by neglect of the gas law deviations suggests that higher precision is of uncertain value. Certainly, the field is so new and the questions to be answered are so many that it appears more important now to concentrate on the more urgent problems and to leave further refinements to such a time as the need for even more accurate data becomes apparent.

Summary

Accurate dissociation data of addition compounds in gaseous systems are of considerable interest and value for theoretical organic chemistry. A simple technique for precise measurement of such dissociations has been developed and tested by a series of studies on the dissociation of trimethylamine–trimethylboron. The tests indicate that by this method the dissociation constants can be determined to 2% and the heat of dissociation to 0.1%.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

Acid–Base Studies in Gaseous Systems. II. The Anomalous Base Strength of the Methylamines; A New Manifestation of Steric Strain[1,2]

BY HERBERT C. BROWN,[3] HERMAN BARTHOLOMAY, JR., AND MODDIE D. TAYLOR

Organic acids and bases have played a significant role in the development of modern physical theories.[4] The influences which structure and substituents exert on the relative strengths of acids and bases are an important part of the foundations upon which such present-day theories as those of the "inductive effect" and the "resonance effect" are constructed. Although much research has been devoted to this subject, a number of interesting phenomena have not yet received satisfactory explanations.

One such phenomenon is the well-known anomalous behavior of the methylamines. The introduction of a methyl group into the ammonia molecule produces an increase in base strength which is ascribed to the positive inductive effect (+I) of the methyl group. The introduction of a second methyl group causes a further increase which is ascribed to the same effect. Introduction of a third methyl group, however, markedly reduces the strength of the tertiary amine formed[5] (Table I).

TABLE I

BASE DISSOCIATION CONSTANTS FOR AMMONIA AND THE METHYLAMINES AT 25°

Amine	$K_b \times 10^5$
NH_3	1.79
$CH_3 \rightarrow NH_2$	42.5
$(CH_3)_2NH$	59.9
$(CH_3)_3N$	6.31

The behavior of the normal aliphatic acids and amines furnishes other puzzling problems. Acetic acid is considerably weaker than formic acid, a result which might be expected in view of the inductive (+I) effect postulated for the methyl group. Propionic acid is still weaker, a fact which is also in accord with the theory. Butyric acid, however, is stronger than propionic.[6]

(1) This publication is also paper IV in the series, Studies in Stereochemistry; for paper no. III in this series, see THIS JOURNAL, **64**, 2563 (1942).

(2) Presented before the Division of Physical and Inorganic Chemistry at the Detroit Meeting of the American Chemical Society. A preliminary communication was published in *J. Chem. Phys.*, **11**, 43 (1943).

(3) Present address: Department of Chemistry, Wayne University, Detroit, Mich.

(4) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940; Watson, "Modern Theories of Organic Chemistry," 2nd ed., Oxford University Press, Oxford, 1941.

(5) Everett and Wynne-Jones, *Proc. Roy. Soc.* (London), **177A**, 449 (1941). Earlier values for the dissociation constants of the methylamines are summarized in this paper.

(6) Dippy, *Chem. Rev.*, **25**, 151 (1939). Particular attention is called to the graph on page 189 of this review. The increase in the acid strength of butyric acid has been ascribed to hydrogen bond formation between the end methyl group and the carboxyl group. Since we have observed similar phenomena in compounds where such hydrogen bond formation is impossible, this explanation is no longer satisfactory. The subject will be discussed in subsequent papers of this series.

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The normal aliphatic amines exhibit a similar phenomenon. The data, although less precise than those for the carboxylic acids, clearly show that the base strength rises in the series ammonia, methylamine, ethylamine, but drops with propylamine.[7]

Before attempting to explain these facts, it is important to know whether the phenomena are due primarily to the substances themselves or to indirect solution effects. The nature of the hydrogen acids has made their study difficult except by working with solvents of relatively high dielectric constant. Unfortunately, these are just the solvents which are the most complex and the least understood. By adopting the viewpoint advanced by G. N. Lewis[8] that the proton is but one out of many acids, it has become possible to draw conclusions regarding the relative strength of acids and bases from the dissociative characteristics of selected groups of addition compounds. By a suitable choice of the reference compounds, it is possible to make these dissociation studies in non-polar solvents, or even in the gas phase. The complexities of the polar solvents may thus be avoided. Such studies of generalized acids and bases in the comparative simplicity of the gas phase are now under way. The results already obtained not only furnish strong support for the Lewis concept of acids and bases, but they also throw light on the interesting problems previously mentioned. In the present paper, an investigation dealing with the first of these problems—the anomalous behavior of the methylamines—is reported. In this study, trimethylboron serves as the reference acid.

$$R_3N{:}B(CH_3)_3 \rightleftharpoons R_3N{:} + B(CH_3)_3$$
$$R = CH_3 \text{ and/or } H$$

Purification of Compounds

In order to obtain constants of the desired accuracy (heat of dissociation good to 0.1 or 0.2 kcal.; the dissociation constants correct to 1–2%), it was necessary rigorously to purify the substances used in the investigation.[9] Since the experimental technique used is sensitive to impurities of the order of 0.1%, efforts were directed to preparing materials containing this quantity of impurity as the upper limit.

Trimethylboron was prepared by the action of boron trifluoride on methylmagnesium bromide in butyl ether. The crude trimethylboron was distilled (under nitrogen) directly out of the reaction flask; the yields were over 80%. The substance was introduced into the high vacuum apparatus and subjected to a prior distillation, from a U-tube at −112° to a U-tube at −130°. The ammonia addition compound, prepared from the distillate, was purified by distillation from a tube held at 0°. The fraction used was cut when the saturation pressure had become constant and agreed with the known value for the pure compound. This fraction was then distilled into a flask and treated with a deficiency of pure dry hydrogen chloride in order to liberate the trimethylboron.

$$NH_3{:}B(CH_3)_3 + HCl \longrightarrow NH_4Cl + B(CH_3)_3$$

The trimethylboron thus obtained was again distilled from a −112° bath and trapped by a −130° bath. The material exhibited a vapor pressure which was independent of the vapor volume; the pressure observed was 680 mm. at −22.9° (m. p. of carbon tetrachloride). The product combined with pure ammonia exactly in the molecular ratio 1:1 to form an addition compound with the correct saturation pressure. The pure trimethylboron was stored in large flasks as a gas. No change in its properties has been observed over a period of many months of storage.

Ammonia, obtained from a commercial tank of the anhydrous material, was treated with metallic sodium[10] until a permanent blue color was observed. A small middle fraction, sublimed at −80°, was collected in the vacuum apparatus. This ammonia was tensiometrically homogeneous; the vapor pressure was independent of the vapor volume; the value agreed with that of the ammonia vapor tension thermometer used.

Methylamine was generated from hydrochloride purified in the following manner. The hydrochloride (Eastman Kodak Co.) was washed several times with chloroform to remove traces of dimethylamine hydrochloride; then it was twice recrystallized from butanol. Finally, it was freed from possible traces of ammonia and trimethylamine by the process of Sharp and Solomon.[11] The free amine, obtained from the purified hydrochloride, was introduced into the vacuum line and placed over sodium. It was distilled from the sodium at −80°. The vapor pressure of the product was 422 mm. at −18.6° (measured with an ethyl ether vapor tension thermometer); this vapor pressure was independent of the vapor volume.

Dimethylamine was also generated from the hydrochloride (Eastman Kodak Co.) purified in the manner just described. The amine, after being treated with sodium, showed a vapor pressure of 561 mm. at 0°.

Trimethylamine was generated from an aqueous solution (Commercial Solvents Corp.); it was purified by treatment with freshly sublimed phosphorus pentoxide. This simple process, developed by Burg and Ingram,[12] removes ammonia and all primary and secondary amines. The pure trimethylamine thus obtained had a vapor pressure of 680.5 mm. at 0°.

In all of the purifications, the vapor pressure measurements were used only to check the absence of any gross impurity present in an amount greater than 1 mole per cent. The absence of impurities larger than 0.1 mole per cent. was assured by careful measurement of the saturation pressures of the addition compound at 0° and by observations on the constancy of the pressure while the addition compound was distilled.[9]

Results

Ammonia–trimethylboron,[13] $NH_3{:}B(CH_3)_3$.—The addition compound formed by ammona and trimethylboron was described first by Frankland[14] and later by Stock.[15] The melting point reported by these authors,[16] 56°, is much lower than the

(7) "International Critical Tables," Vol. VI, McGraw-Hill Book Co., New York, N. Y., 1929.

(8) Lewis, *J. Franklin Inst.*, **226**, 293 (1938).

(9) It was also necessary to devise improved methods for studying dissociations in the gas phase. These methods are described in the first paper of this series, THIS JOURNAL, **66**, 431 (1944).

(10) The sodium for drying the ammonia and the amines was prepared in the following manner to avoid possible contamination of the amines by hydrocarbon vapors. Molten sodium was kept under high vacuum until gases were no longer evolved. Hydrogen was then introduced and the sodium drawn up into 4-mm. glass tubes, which dipped beneath the surface of the metal. After the sodium had solidified, the tubes were removed. Short lengths of this tubing were cut off as the sodium was needed.

(11) Sharp and Solomon, *J. Chem. Soc.*, 1477 (1931).

(12) Ingram, M. S. Dissertation, University of Chicago, Chicago, 1940.

(13) For a discussion of the nomenclature used for these addition compounds, see Davidson and Brown, THIS JOURNAL, **64**, 316 (1942), footnote 11.

(14) Frankland, *Ann.*, **124**, 129 (1862).

(15) Stock and Zeidler, *Ber.*, **54**, 531 (1921).

(16) It is not entirely clear whether the melting point reported by Stock and Zeidler is their own observation or is merely a republication of Frankland's value.

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value, 73.2–73.7°, observed in the present investigation for the carefully purified product.

The saturation pressure[17] of the compound was studied over the temperature range from 0 to 59.7°. The data are listed in Table II and represented graphically in Fig. 1-A. The saturation pressure exhibits a behavior which appears to be general for addition compounds of the type under discussion. The values at low temperatures show a definite curvature in a log $P - 1/T$ graph; at higher temperatures they fall on a straight line.[18] The straight portion of the curve (20.0° and above) is represented satisfactorily by the equation

$$\text{Log } P = (-3095/T) + 11.229$$

The pressure above the solid would reach 760 mm. at 97.6° if the equation were valid to this temperature. However, since the compound melts at 73°, the "boiling point"[19] must lie somewhat higher than the above calculated value. Frankland[14] reports the boiling point as 110°.

TABLE II

SATURATION PRESSURES OF AMMONIA–TRIMETHYLBORON

Temp., °C.	0.0	4.2	10.5	15.0	20.0	28.0
Press., mm.	.95	1.33	2.12	3.16	4.70	8.81
Temp., °C.	30.0	40.0	46.1	50.0	55.0	59.7
Press., mm.	10.17	21.7	33.9	44.4	62.0	76.1

Stock and Zeidler report the compound to be highly dissociated (above 90%) at room temperature. In the present investigation, the dissociation of the substance over the temperature range from 54.8 to 130° was studied. The results are given in Table III and Fig. 1-B. The variation in the dissociation constants with temperature is represented by the equation

$$\text{Log } K_p = (-3007/T) + 8.723$$

The dissociation constant at 100° is 4.6 and the heat of dissociation is 13.75 ± 0.3 kcal. A comparatively large probable error (0.2% as compared with 0.1% for the derivatives of the other amines) is assumed because of the particularly difficult region (α = 0.90 to 0.99) in which the dissociation of the compound was studied. (The methods used for determining the accuracy of the dissociation data are described in the first paper of this series.)

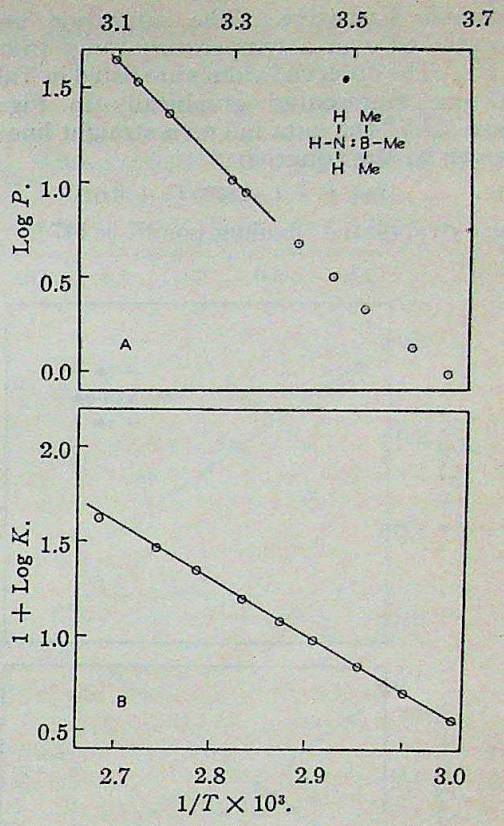

Fig. 1.—Ammonia–trimethylboron: A, saturation pressure data; B, dissociation data.

TABLE III

DISSOCIATION PRESSURES OF AMMONIA–TRIMETHYLBORON

Temp., °C.	Pressure, mm. Observed	Pressure, mm. Calculated[a]	Degree of dissociation, α	Dissociation constant, K (atm.)
54.8	57.62	30.20	0.908	0.356
60.1	59.22	30.68	.930	.501
65.4	60.69	31.17	.947	.695
70.8	62.06	31.67	.960	.951
75.0	63.06	32.06	.967	1.19
77.4	63.64	32.28	.972	1.41
79.9	64.18	32.51	.974	1.57
86.0	65.52	33.07	.981	2.23
91.5	66.67	33.58	.985	2.94
99.6	68.26	34.32	.989	4.18
114.6[b]	71.15	35.70	.993	6.59
130.0[b]	74.10	37.12	.996	12.9

[a] Pressure of ammonia and trimethylboron (calculated to 0°) was 25.15 mm. [b] Values are not included in Fig. 1-B.

Methylamine–trimethylboron, $CH_3NH_2:B(CH_3)_3$.—The preparation and properties of methylamine–trimethylboron have not been previously reported. The addition compound is a white solid which melts at 26.9–27.2°; it is considerably less volatile than the corresponding

TABLE IV

SATURATION PRESSURES OF METHYLAMINE–TRIMETHYLBORON

Temp., °C.	0	15.0	20.0	25.0	34.7	43.4
Press., mm.	.16	0.62	0.87	1.31	2.49	4.34
Temp., °C.	50.1	60.6	71.6	81.4	85.6	93.1
Press., mm.	7.34	13.61	25.31	42.41	54.01	78.8

(17) For reasons which are discussed in the first paper of this series, the precision of the saturation pressure measurements below 20 mm. is considerably lower than the precision of the saturation and dissociation pressures above that value.

(18) The clarification of this unusual behavior does not fall within the limits prescribed for the present series of investigations. It is hoped, however, that the problem will be examined by investigators interested in the physical properties of these addition compounds.

(19) Since the compound is almost completely dissociated at this temperature, this is not a true boiling point.

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ammonia derivative. The saturation pressure was studied over a temperature range from 0 to 93.1°. The observed values are listed in Table IV and are represented graphically in Fig. 2-A. Above 34.7° the data fall on a straight line which is given by the equation

$$\text{Log } P = (-2829/T) + 9.611$$

The extrapolated "boiling point" is 147°.

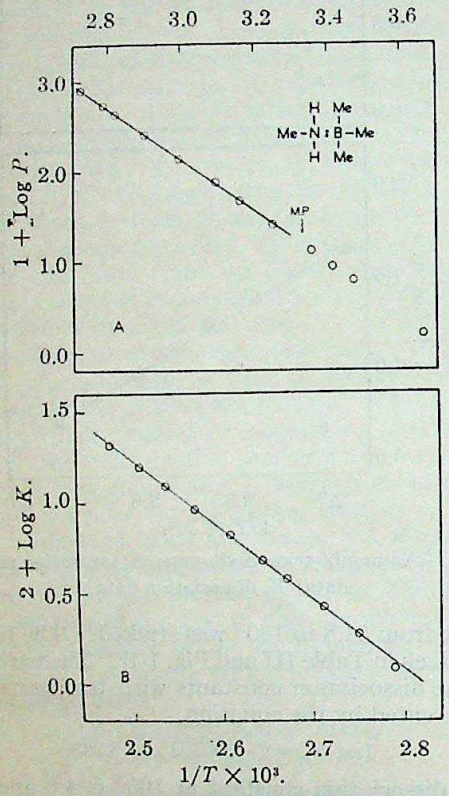

Fig. 2.—Methylamine–trimethylboron: A, saturation pressure data; B, dissociation data.

Under comparable conditions, the compound is considerably less dissociated than the ammonia derivative. The dissociation data observed over the temperature range from 85.4 to 132.9° are listed in Table V and represented graphically in Fig. 2-B. The dissociation constants can be represented by the equation

$$\text{Log } K_p = (-3856/T) + 8.880$$

The value of the dissociation constant at 100° is 0.0350 and the heat of dissociation of the compound is 17.64 ± 0.2 kcal.

Dimethylamine–trimethylboron, $(CH_3)_2NH:B(CH_3)_3$.—The addition compound formed by dimethylamine and trimethylboron also has not previously been described. It is a white solid which melts at 35.0–35.5° and resembles the methylamine derivative in volatility. The saturation pressure data (over the range from 0 to 74.6°) are given in Table VI and represented graphically in Fig. 3-A. The compound behaves like the corresponding methylamine derivative. Above 45.7° the saturation pressures can be represented by the equation

$$\text{Log } P = (-2902/T) + 9.860$$

The extrapolated "boiling point" is 143°.

TABLE VI

SATURATION PRESSURE OF DIMETHYLAMINE–TRIMETHYLBORON

Temp., °C.	0.0	10.0	19.8	31.8	37.8	40.2
Press., mm.	.20	0.40	0.91	2.32	3.63	4.11
Temp., °C.	45.7	50.1	55.2	65.3	70.0	80.0
Press., mm.	5.76	7.75	10.6	19.3	25.1	41.9

The dissociation of the compound was studied over the temperature range from 85.1 to 125.6°. The substance is somewhat less dissociated than the corresponding methylamine derivative under comparable conditions. It is the least dissociated of the four derivatives studied in the present investigation. The dissociation data are given in Table VII and illustrated in Fig. 3-B. The variation of the dissociation constant with temperature can be represented by the equation

$$\text{Log } K_p = (-4211/T) + 9.595$$

The value of the dissociation constant at 100° is

TABLE V

DISSOCIATION PRESSURES OF METHYLAMINE–TRIMETHYLBORON

Temp., °C.	Pressure, mm. Observed	Pressure, mm. Calculated[a]	Degree of dissociation, α	Dissociation constant, K (atm.)
85.4	52.46	37.78	0.3886	0.0123
90.6	55.67	38.33	.4524	.0188
95.6	58.57	38.86	.5072	.0267
101.1	61.68	39.43	.5643	.0379
104.9	63.85	39.83	.6031	.0480
110.1	66.84	40.38	.6553	.0662
115.8	69.96	40.98	.7072	.0921
120.7	72.65	41.50	.7506	.123
125.3	74.93	41.99	.7847	.158
130.6	77.42	42.55	.8195	.208

[a] Pressure of methylamine and trimethylboron (calculated to 0°) was 28.69 mm.

TABLE VII

DISSOCIATION PRESSURES OF DIMETHYLAMINE–TRIMETHYLBORON

Temp., °C.	Pressure, mm. Observed	Pressure, mm. Calculated[a]	Degree of dissociation, α	Dissociation constant K (atm.)
85.1	44.97	34.18	0.316	0.00655
89.3	47.04	34.58	.360	.00924
90.9	47.91	34.73	.379	.0106
94.4	49.66	35.07	.416	.0137
99.8	52.47	35.58	.475	.0201
104.8	55.17	36.06	.530	.0283
110.3	58.18	36.58	.590	.0410
116.1	61.34	37.14	.652	.0595
121.2	64.01	37.62	.701	.0816
125.6	66.25	38.04	.742	.106

[a] Pressure of dimethylamine and trimethylboron (calculated to 0°) was 26.06 mm.

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0.0214 and the heat of dissociation of the complex is 19.26 ± 0.2 kcal.

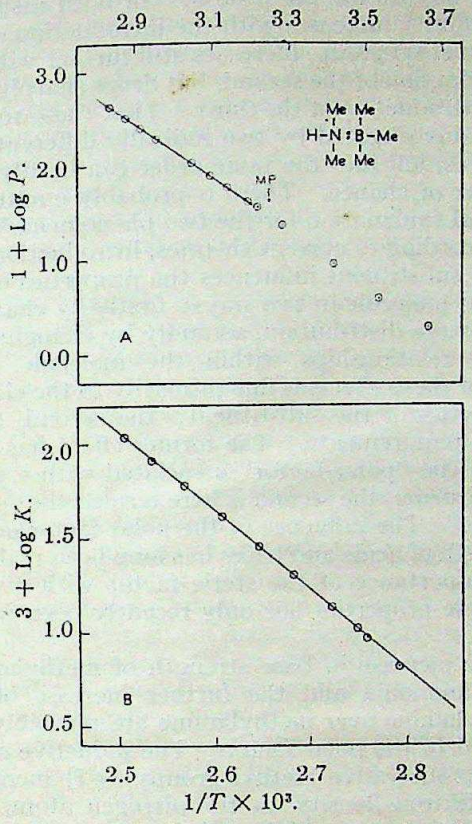

Fig. 3.—Dimethylamine–trimethylboron: A, saturation pressure data; B, dissociation data.

Trimethylamine–trimethylboron, $(CH_3)_3N:B(CH_3)_3$.—The complex, trimethylamine–trimethylboron, has been previously prepared and studied by Schlesinger and co-workers.[20] In view of the high accuracy demanded by the present study, the properties and the dissociation of the compound in the gas phase were reinvestigated. Trimethylamine–trimethylboron is a white crystalline solid which softens at 120° and melts at 128°. It is the second most volatile of the addition compounds under consideration, being exceeded in this respect only by the ammonia derivative.[21] Saturation pressure measurements are listed in Table VIII and illustrated in Fig. 4-A. Above 29.8° the saturation pressure data may be represented by the equation

$$\text{Log } P = -(3467/T) + 11.949$$

Below this temperature the graph shows the curvature to which attention has previously been called. The extrapolated "sublimation point" is 109.6°.

TABLE VIII

SATURATION PRESSURES OF TRIMETHYLAMINE–TRIMETHYLBORON

Temp., °C.	0.0	6.2	10.3	14.9	20.1	24.2	29.8
Press., mm.	0.24	0.42	0.60	0.90	1.41	2.00	3.17
Temp., °C.	34.8	39.1	44.2	50.5	55.8	59.8	65.1
Press., mm.	4.91	7.05	10.47	17.10	25.8	33.9	48.6

(20) Schlesinger, Flodin and Burg, THIS JOURNAL, 61, 1078 (1939).

(21) The volatility appears to be closely connected with the relative degree to which the compounds are dissociated under comparable conditions.

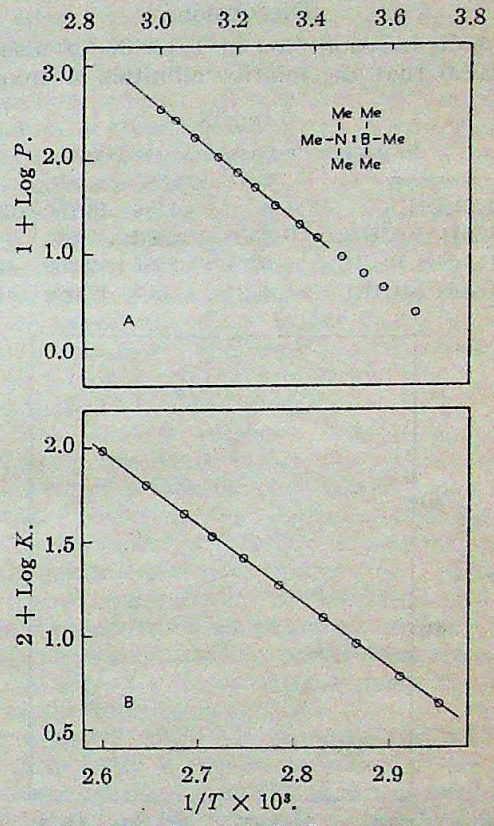

Fig. 4.—Trimethylamine–trimethylboron: A, saturation pressure data; B, dissociation data.

The dissociation of the compound was studied over the temperature range from 65.8 to 111.3°. It is less than that of the ammonia, but more than that of the methylamine, derivative. The dissociation data are listed in Table IX and repre-

TABLE IX

DISSOCIATION PRESSURES OF TRIMETHYLAMINE–TRIMETHYLBORON

Temp., °C.	Pressure, mm. Observed	Pressure, mm. Calculated[a]	Degree of dissociation, α	Dissociation constant K (atm.)
65.8	47.54	29.02	0.638	0.0430
70.4	49.77	29.42	.692	.0601
75.8	52.35	29.88	.752	.0897
80.0	54.35	30.24	.797	.125
85.8	56.70	30.74	.844	.185
90.6	58.48	31.15	.877	.257
95.0	59.90	31.53	.900	.335
99.0	61.18	31.87	.920	.441
104.7	62.79	32.36	.940	.631
111.3	64.47	32.92	.960	.956

[a] Pressure of trimethylamine–trimethylboron (calculated to 0°) was 23.39 mm.

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sented in Fig. 4-B.[22] The dissociation constants can be represented by the equation

$$\text{Log } K_p = -(3852/T) + 9.998$$

The value of the dissociation constant at 100° is 0.472 and the heat of dissociation is 17.62 ± 0.2 kcal.

Discussion

The dissociation data in Table X (*cf.* also Fig. 5) reveal that the relative affinities of ammonia and its methyl derivatives for trimethylboron are almost identical with the relative affinities o these amines for the proton. In both instances the affinity increases with the introduction of the first methyl group, increases still further with the introduction of the second, but drops sharply with the introduction of the third. That these amines, when investigated by two radically different procedures, fall into the same order can hardly be a matter of chance. There is probably one fundamental explanation for the two phenomena.[23]

TABLE X

SUMMARY OF DISSOCIATION DATA

Compound	K_{100}	ΔF_{100}	ΔH	ΔS
NH_3:B$(CH_3)_3$	4.6	−1134	13,750	39.9
CH_3NH_2:B$(CH_3)_3$	0.0350	2472	17,640	40.6
$(CH_3)_2NH$:B$(CH_3)_3$	.0214	2885	19,260	43.6
$(CH_3)_3N$:B$(CH_3)_3$	.472	557	17,620	45.7

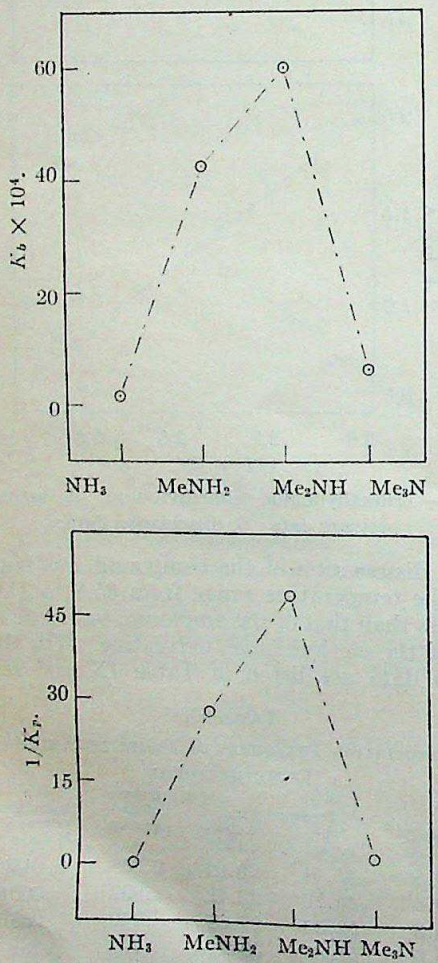

Fig. 5.—Base dissociation constants (K_p) at 25° of ammonia and the methylamines (top); dissociation constants (K_p) at 100° of the addition compounds of ammonia and the methylamines with trimethylboron (bottom).

According to current theories, introduction of a given substituent influences the properties of the parent molecule in two ways: firstly by changing the charge distribution, secondly by changing the steric relationships within the molecule. The first of these effects is due primarily to the electric properties of the substituent; the second, to its space requirements. The former effect has been called the "polar factor" associated with a given substituent; the second is here termed the "steric factor." The influence of the polar factor on the strength of acids and bases has long been realized; the importance of the steric factor with respect to these properties has only recently been recognized.

The increase in base strength of methylamine over ammonia and the further increase of dimethylamine over methylamine are plausibly ascribed to the polar factor. The inductive effect of two successive methyl groups (+I) increases the electron density on the nitrogen atom, and thus augments the ability of that atom to donate an electron pair to an acceptor, such as the proton or the boron atom in trimethylboron. There is, however, no apparent explanation in terms of the polar factor for the marked decrease in the donor properties of the nitrogen atom associated with the introduction of the third methyl group. It is plausible, therefore, to seek the reason for the phenomenon in the steric factor.

Previous investigations have shown that steric strain is important in determining the strength of acids and bases.[24] Thus pyridine is weaker than

(22) Other dissociation measurements of this compound are reported in the first paper of this series, where the dissociation of the complex was used to test the reliability of the experimental technique.

(23) A rough idea of the extent to which the base is weakened by the introduction of the third methyl group may be obtained as follows. The free energy of dissociation (at 100°) of methylamine–trimethylboron is approximately 3600 cal. greater than that of ammonia–trimethylboron. That is, the replacement of a hydrogen atom in ammonia by a methyl group increases by 3600 cal. the work required to separate the trimethylboron from the amine. Replacement of the second and third hydrogen atoms by methyl groups might be expected to increase the free energy of dissociation by approximately the same amounts. The free energy of dissociation (at 100°) of the dimethylamine compound would then be about 6000 cal., and that of the trimethylamine derivative about 9600 cal. The observed values, 2885 and 557 cal. respectively, indicate that some influence lowers the ΔF_{100} of the dimethylamine derivative by about 3500 cal. and that of the trimethylamine derivative by about 9000 cal.

It is interesting that the variation in the base strength of the amines is not due primarily to entropy effects. The interesting behavior of the ΔS term in the dissociation of these and related addition compounds will be discussed in a later paper.

(24) Brown, Schlesinger and Cardon, THIS JOURNAL, 64, 325 (1942).

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trimethylamine when such acids as the proton (hydrogen chloride or hydrogen bromide), boron trifluoride, or borine are used to make the comparison, whereas the reverse is true when trimethylboron is so used. The weakness of trimethylamine when trimethylboron is the reference acid is ascribed to steric interference between the three methyl groups attached to the boron atom and the three methyl groups attached to the nitrogen atom.[25] The interference results in a force which tends to separate the two parts of the addition compound and thereby to increase its dissociation.

Another example of this type of strain is furnished by pyridine and α,α'-lutidine. The latter is a considerably stronger base than pyridine if the proton is used as the comparison acid. (The increase in base strength can readily be accounted for by the inductive effect of the methyl groups.) On the other hand, the comparatively large acid, boron trifluoride, reverses the order of these base strengths. Furthermore, α,α'-lutidine exhibits no basic properties whatsoever when the very bulky trimethylboron is the acid.[25]

These examples furnish clear cut illustrations of the type of steric strain under discussion—a face-to-face interference which markedly increases rissociation. For convenience, this type of steric dasain will be called "F-strain."

F-strain cannot be used as the basis of a satisfactory explanation of the behavior of the methyltmines. It is characteristic of F-strain that its magnitude depends on the steric requirements of both components. Thus, in the previously mentioned illustrations, the relative strengths of the amines differ, depending upon which acid, the proton, boron trifluoride, or trimethylboron, is used for the comparison. In the methylamines, however, the relative base strengths must be largely independent of the acid component since identical orders of base strengths are observed with both the proton and trimethylboron. The close similarity (Fig. 5) in the behavior of the dissociation constants, K_b, and the association constants, $1/K_p$, of the amines,[26] suggests that the correct explanation for this phenomenon must somehow be connected with the transformation of the trivalent nitrogen compound into an ammonium derivative. That is, the steric cause of the phenomenon under investigation must be in some way related to the fourth nitrogen bond; it must be of such a nature as to render relatively unimportant the steric factor of the group adding.

(25) See Fig. 2, p. 327, of reference 24.

(26) The magnitude of the base dissociation constant, K_b, is a measure of the affinity of the free amine for a proton. Actually, K_b/K_w should be compared, since that quantity is the equilibrium constant for the reaction

$$R_3N: + H^+ \rightleftarrows R_3N{:}H^+$$

However, no error is introduced in neglecting the constant factor, $1/K_w$, in making comparisons.

Similarly, the association constant, $1/K_p$, measures the affinity of the free amine for trimethylboron

$$R_3N: + B(CH_3)_3 \rightleftarrows R_3N{:}B(CH_3)_3$$

A simple explanation filling these requirements is available provided a not unreasonable assumption be made regarding the configuration of the free trimethylamine molecule.

There are theoretical reasons for believing that the three bonds of a trivalent nitrogen atom should be directed in space at angles of 90° to each other. In all cases which have been investigated, however, the angles are considerably greater, probably because they must be increased to accommodate the attached groups.[27] An electron diffraction investigation of trimethylamine led Brockway and Jenkins to the conclusion that the C–N–C angle in this molecule is $108 \pm 4°$.[28] In the explanation here proposed, it is assumed that the bond angle in trimethylamine is somewhat greater than the normal tetrahedral angle, probably close to the upper limit set by Brockway and Jenkins. In other words, the three rather bulky methyl groups spread the bonds of the nitrogen atom from their preferred configuration (90°) to a value greater than the tetrahedral angle.

In the trivalent nitrogen derivative, such spreading of the bond angles is relatively easy since the fourth position in the valence shell is not occupied. However, the addition of a fourth group to the vacant position, be it a proton or a trimethylboron molecule, forces the nitrogen atom toward a tetrahedral configuration and results in a reduction of the expanded angles. The methyl groups are, therefore, crowded toward each other, setting up a strain which reduces the stability of the addition compound.

The term "B-strain" is proposed for this effect. (The letter B is used to indicate that the interference which causes the strain is localized at the "back" of the molecule—trimethylamine in the case under discussion—away from the entering group; it is thus contrasted to F-strain which results from interference at the "front" of the molecule, at the interface between the two components of the addition compound.) B-strain should depend greatly upon the size of the groups attached to the nitrogen atom or any other small central atom, but should be relatively independent of the size of the adding group. The absence or relative unimportance of B-strain in ammonia and methylamine is accounted for by the fact that the small hydrogen atoms attached to the nitrogen atom permit the bond angle to approach the tetrahedral value without appreciable B-strain. On the other hand, the two methyl groups in dimethylamine and the three methyl groups in trimethylamine cannot adapt themselves so easily to the space available. The B-strain, in fact, is sufficient to reduce slightly the strength of dimethylamine and to reduce greatly that of trimethylamine.

The suggestion that B-strain is the primary cause of the anomalous behavior of the methyl-

(27) Pauling, "The Nature of the Chemical Bond," Cornell University Press, Ithaca, N. Y., 1939, p. 78.

(28) Brockway and Jenkins, THIS JOURNAL, 58, 2036 (1936).

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amines does not mean that F-strain is absent. Indeed, the results previously reported[24] show that F-strain must be present. However, it probably increases regularly with the introduction of one, two or three methyl groups into the amine. The absolute magnitudes of the amine strengths are thus affected; their relative order, however, is not altered.

The proposed explanation leads to a number of interesting predictions; these are now being tested.

Acknowledgment.—The authors express their appreciation to Professors G. N. Lewis, R. S. Mulliken and Linus Pauling for their kindness in examining the manuscript and for their helpful suggestions.

Summary

1. The trimethylboron addition compounds with ammonia, methylamine, dimethylamine and trimethylamine have been prepared and characterized.

2. The dissociation of these compounds in the vapor phase ($R_3N{:}BMe_3 \rightleftarrows R_3N{:} + BMe_3$) has been studied; ΔH, ΔF and ΔS for the reactions have been measured.

3. The relative affinity of the methylamines for trimethylboron (measured by the dissociation constant of the complex) is identical with their affinity for the proton (measured by the dissociation constant of the base). In both instances, the base strength rises from ammonia to methylamine and to dimethylamine, but drops sharply from dimethylamine to trimethylamine.

4. To account for this observed order the strain resulting from the "steric factor" is divided into two kinds, "B-strain" and "F-strain." The anomalous behavior of the methylamines is ascribed to B-strain.

CHICAGO, ILLINOIS RECEIVED AUGUST 7, 1943

[CONTRIBUTION OF THE DEPARTMENT OF CHEMISTRY, THE OHIO STATE UNIVERSITY]

The Vapor Pressure of Beryllium at 1170–1340°K.

BY ROBERT SCHUMAN AND A. B. GARRETT

The vapor pressure of beryllium was determined by measuring the rate of vaporization in a vacuum. The theory and application of this method are adequately described by other investigators.[1,2,3,4] In the case of beryllium, the accommodation coefficient appears (qualitatively) to be unity within the limits of experimental error. This was true for iron,[2] copper,[2] nickel,[3] nickel oxide,[3] and for liquid and solid mercury.[5,6]

Experimental

The procedure was that of determining the loss of weight due to evaporation of a beryllium ring of known surface area; the ring was held at a constant known temperature by an induction furnace for a known length of time.

The beryllium was a very pure sample supplied by the Brush Beryllium Company with the analysis: 0.03% Fe, 0.008% Al, 0.004% Mg, 0.022% Si. The ring was made from the sample and had an effective area of evaporation of about 8.5 sq. cm.

The water-cooled cell was a modification of the one used by Marshall, Dornte and Norton,[2] but was made of Pyrex glass. The cell was constructed with two small-diameter water-cooled glass tubes sealed just inside the inner tube to prevent the formation of a continuous film of metal on the inside of the tube. The ring was supported by a tungsten tripod. The optical window at the top of the cell was protected from the metal vapors by a glass shutter.

The temperature was measured by a Leeds and Northrup No. 8622-C optical pyrometer with which the readings were easily reproducible to within 5°. The pyrometer was calibrated against the apparent black body temperature of melting silver, the silver being melted in a groove in an iron ring into which small holes had been drilled to serve as black bodies. The pyrometer was checked three times against the melting point of silver, the apparent melting points having a variation of 3°. The temperature of the beryllium ring used for determining the rate of evaporation was taken as the apparent emission temperature, and then corrected to black body temperatures by values of beryllium emissivities determined. The beryllium emissivities were obtained by comparing the apparent temperature readings of a polished beryllium surface and those of 1-mm. diameter, 4-mm. deep holes drilled in the specimen.

A pressure below 10^{-5} mm. of mercury was maintained throughout the run to prevent oxidation. In several runs in which the vacuum was poor, surface oxidation prevented or slowed up evaporation. A period of outgassing at dull red heat was also found valuable to eliminate adsorbed gases.

The weighings were made on a balance accurate to about ±0.05 mg.

Data.—The experimental results are recorded in Table I and Fig. 1 for the rate of vaporization. The temperatures given are the average temperature during the runs, and thus take into account small fluctuations in temperature during the run. The times are the effective times at the temperature indicated. The apparent emission temperatures for $\lambda = 6500$ Å. are given in terms of the black body temperatures by the equation

$$t_e = 0.904t_{bb} + 54.5 \quad (\pm 5°\ 800\text{–}1000°)$$

where t_e is the apparent polished surface temperature in °C. and t_{bb} is the corresponding black body temperature, °C. Runs 9 and 12 were of no value owing to surface oxidation.

Thermodynamic Considerations.—In order to check the validity of the vapor pressure results,

(1) Langmuir, *Phys. Rev.*, **2**, 329 (1913).
(2) Marshall, Dornte and Norton, THIS JOURNAL, **59**, 1161 (1937).
(3) Johnston and Marshall, *ibid.*, **62**, 1382 (1940).
(4) Marshall and Norton, *ibid.*, **55**, 431 (1933).
(5) Knudsen, *Ann. Physik*, **29**, 179 (1909).
(6) Volmer and Estermann, *Z. Physik*, **7**, 1 (1921).

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TABLE I

EXPERIMENTAL RESULTS

Run	T, °K., actual	Time, min.	Loss, g.	Rate of loss, g./sec./sq. cm.	log P
18	1174	217	0.00274	2.52×10^{-8}	−8.189
11	1187	180	.00138	1.52×10^{-8}	−8.405
19	1193	204	.00192	1.88×10^{-8}	−8.313
8	1215	180	.00241	2.63×10^{-8}	−8.162
6	1222	120	.00361	5.91×10^{-8}	−7.809
5	1227	121	.00517	8.38×10^{-8}	−7.655
17	1251	65	.00412	1.267×10^{-7}	−7.473
16	1259	63	.00783	2.48×10^{-7}	−7.179
1_1	1271	120	.0102[a]	1.644×10^{-7}	−7.356
7	1273	65	.00610	1.842×10^{-7}	−7.306
14	1273	50	.00582	2.315×10^{-7}	−7.206
10	1281	61	.00604	1.957×10^{-7}	−7.279
15	1293	40	.00998	4.97×10^{-7}	−6.871
3	1305	36	.0079[a]	4.28×10^{-7}	−6.935
2	1308	38	.0068[a]	3.49×10^{-7}	−7.023
20	1314	21	.00550	5.27×10^{-7}	−6.842
4	1326	28	.0102[a]	7.13×10^{-7}	−6.710
1_2	1330	22	.0100[a]	8.83×10^{-7}	−6.614
13	1336	14.5	.00665	9.10×10^{-7}	−6.601

[a] ±0.2 mg.

the values of ΔH_0^0 were calculated from values of log P and T read off from the graph of log P *vs.* $1/T$ (Fig. 1). The thermodynamic relationship for ΔH_0^0 is

$$\frac{\Delta H_0^0}{T} = -R \ln p - \left(\frac{F^0 - H_0^0}{T}\right)_{\text{gas}} - \left(\frac{F^0 - H_0^0}{T}\right)_{\text{solid}}$$

The free energy function of the gas is dependent both on the vapor pressure results and on the spectroscopic energy levels of beryllium. Any error in it is due solely to the vapor pressure data. The function is

$$\left(\frac{F^0 - H_0^0}{T}\right)_{\text{gas}} = -3/2\ R \ln M - 5/2\ R \ln T + R \ln P - C - R \ln R - R \ln Q$$

For beryllium the ground state is $^1S_0$ and the next higher state is $^3P_0$ with a term value of 21981.4 cm.$^{-1}$. The second state contributes nothing to Q at the temperatures of the experiments, and the *a priori* probability of the ground state is 1, so, for this case, $Q = 1$. If P is measured in atmospheres, the value of $C + R \ln R$ is −7.267 (see ref. 7).

The free energy function of the solid is dependent only on specific heat data. The function is

$$\left(\frac{F^0 - H_0^0}{T}\right)_{\text{solid}} = \frac{1}{T}\int_0^T C_p\, dT - \int_0^T C_p\, d \ln T$$

The specific heats below 298°K. were those given by K. K. Kelley,[8] and the equation used for the higher range is[9]

$$C_p = 4.698 + 1.555 \times 10^{-3}T - 1.210 \times 10^{5}T^{-2} \quad (1\%,\ 273\text{–}1173°\text{K.})$$

(7) For a general discussion of the equation, see K. K. Kelley, *Bureau of Mines Bulletin*, **383**, 1 (1935).
(8) K. K. Kelley, *ibid.*, **434**, 84 (1941).
(9) K. K. Kelley, *ibid.*, **371**, 12 (1934).

In our calculations, this equation was used in a range somewhat above its upper limit of applicability.

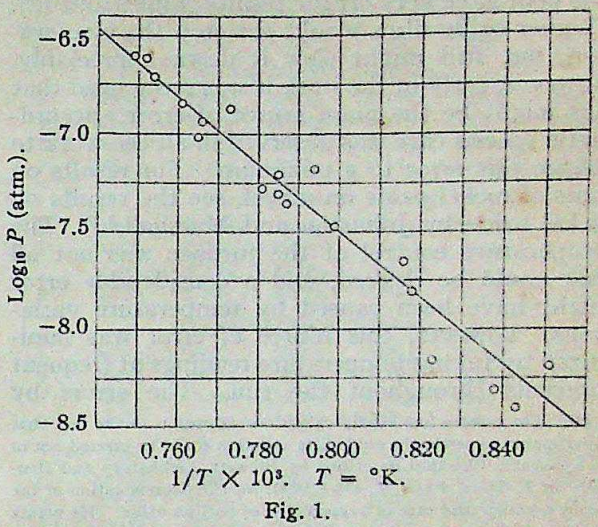

Fig. 1.

The calculated results of ΔH_0^0 are given in Table II. The trend in the ΔH_0^0 values, a variation of 5000 cal./mole over the temperature range studied would indicate that the curve is either (a) somewhat steeper than it should be, or (b), that the trend is due to inaccuracies in C_p, since the temperature is above the range of the C_p equation. We feel, however, that the curve drawn best represents the experimental data.

TABLE II

SUMMARY OF THERMODYNAMIC CALCULATIONS

T, °K.	log P (atm.)	$\frac{F^0 - H^0}{T}$ gas	$\frac{F^0 - H^0}{T}$ solid	ΔH_0^0, cal./mole
1550	−8.670	−73.966	−4.85	125,100
1200	−8.067	−71.421	−5.05	123,900
1250	−7.497	−69.016	−5.23	122,600
1300	−6.970	−66.798	−5.42	121,300
1350	−6.498	−64.826	−5.60	120,100

Other Considerations.—The log vapor pressure *vs.* reciprocal of temperature curve was drawn as a straight line; this plot is given in Fig. 1. The slope of the line in Fig. 1 corresponds to a heat of vaporization for beryllium of 78,800 ± 2000 cal./mole near 1250°K.

The trend in the ΔH_0^0 values might also indicate an accommodation coefficient different from unity; however, it is doubtful that it would differ enough from unity to cause as large a trend as observed. The fact that the beryllium did not deposit behind the small glass tubes in the cell would indicate a value near to unity.

The most likely sources of experimental error in this work are: first, the formation of an oxide film on the beryllium thick enough to greatly hinder the evaporation; second, inaccurately assumed temperatures due to fluctuations of temperature during the run; and also, to a lesser ex-

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tent, errors in the weighings and temperature readings. Of these, the first probably caused the largest errors, since runs in which the vacuum was poor gave very erratic results (runs 9 and 12). Thinner oxide films would not stop the evaporation, but still might slow it down appreciably. However, early in the work it was recognized that this might be the main source of error; accordingly, special care was observed in all the work to reduce this error to a minimum. For results on films of nickel oxide on nickel, see the results on nickel oxide by Johnston and Marshall.[3,10] The temperature control of the furnace was not all that could be desired, and a considerable error might have been caused by temperature variations; however, this source of error was minimized by taking temperature readings at frequent intervals throughout the run. The errors by other causes should be small in relation to these two.

Acknowledgment.—We wish to express our appreciation to the Brush Beryllium Company for the pure beryllium sample, and to Prof. H. G. Heil of the Mendenhall Laboratory of Physics, for the use of the high temperature equipment and for instructions in its use.

Summary

The vapor pressures of metallic beryllium in the range from 1170 to 1340°K. have been determined by the Langmuir method. The results are given in Table I, and a plot of log P *vs*, $1/T$ is given, Fig. 1. Values of ΔH_0^0 have been calculated and found to vary some with temperature, the mean value of ΔH_0^0 being (122,000 ± 2500) cal./mole. The heat of vaporization was also calculated, being 78,800 cal./mole at 1250°K. Possible sources of experimental error are considered, the slowing down of evaporation by thin oxide films probably being the most important. The accommodation coefficient appears to be unity.

COLUMBUS, OHIO RECEIVED NOVEMBER 12, 1943

(10) The referee has kindly called our attention to the fact that experiments to settle the oxide film question could be carried out in an apparatus like that described by Blewett, Liebhafsky and Hennelly in *J. Chem. Phys.*, **7**, 478 (1939), for the determination of the vapor pressure and rate of evaporation of barium oxide. He points out that if the rates of evaporation in such an apparatus are proportional to the area of the opening, then oxide films are not retarding the evaporation, provided that the vapor pressure equilibrium is maintained within.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, AGRICULTURAL AND MECHANICAL COLLEGE OF TEXAS]

Temperature Coefficients of Electrical Conductance of Solutions Containing Sodium Chloride, Potassium Chloride or Magnesium Sulfate or Mixtures Thereof

BY RAYMOND W. BREMNER

Introduction

Very little accurate information on the variation of electrical conductance with temperature is available in the literature. In this paper equations for very accurately calculating equivalent conductance as a function of centigrade temperature have been worked out. Temperature coefficients of equivalent conductance have been calculated with five-place accuracy. Temperature coefficients of specific conductance of certain standard potassium chloride solutions and of conductivity water have also been calculated. The variations of the coefficients due to temperature changes, concentration changes and mixing of electrolytes have been determined.

Calculations

Equivalent Conductance as a Function of Temperature.—Equation I was used for representing the equivalent conductances of twenty different solutions as a function of centigrade temperature.

$$\text{Eq. Cond.} = \Lambda = a + bt + ct^2 + dt^3 \qquad \text{(I)}$$

The preparation of solutions and the experimental data have been described previously.[1,2] The ratio of the number of millimoles of sodium chloride to the number of millimoles of magnesium sulfate in a given quantity of each of the four solutions that contain both of these salts is 16.4315. Similarly the ratio of the number of millimoles of sodium chloride to the number of millimoles of potassium chloride in a given quantity of each of the four solutions that contains both of these salts is 47.2916. The most dilute solution of each type is designated as Solution No. 1, while the most concentrated solution is designated as Solution No. 4. Solutions of intermediate concentrations are numbered 2 and 3, respectively.

The constants a, b, c and d of Equation I were evaluated from the experimental data for each solution by the method of least squares. By use of the resulting equations the equivalent conductance was calculated for each solution at 0, 5, 10, 15, 20 and 25°. The average deviation of the calculated from the experimentally determined value was only 0.006%. In no instance was the deviation greater than 0.02%, which is the approximate maximum error in the original data.

In Table I are listed the values of the constants of equation I for each solution. The constant (d), which is the coefficient of the term of highest degree, is in every instance negative. This indicates a point of inflection at a higher temperature

(1) Raymond W. Bremner, Thomas G. Thompson and Clinton L. Utterback, THIS JOURNAL, **60**, 2616 (1938).

(2) Raymond W. Bremner, Thomas G. Thompson and C. L. Utterback, *ibid.*, **61**, 1219 (1939).

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in each conductance *vs.* temperature curve, which is an essential requirement for an equation that satisfactorily represents electrical conductance as a function of temperature. The second degree equations $\Lambda = a + bt + ct^2$ and $\Lambda = \Lambda_0 (1 + at + bt^2)$ were found to be inadequate for making the calculations. The deviations of the calculated from the experimental values ranged up to 0.1% or more when they were used.

TABLE I

CONSTANTS FOR THE EQUATION $\Lambda = a + bt + ct^2 + dt^3$

Solution	Grams of solute in 1000 g. of water	$a \times 10^4$	$b \times 10^4$	$c \times 10$	$d \times 10^4$
		Sodium Chloride Solutions			
1	NaCl	5.6183_6	57326_9	17669.9	98.08_1	-0.348_1
2	NaCl	11.3002_0	54944_1	16719.7	92.315	− .3292
3	NaCl	19.9443_9	52738_6	15822.3	88.058	− .3191
4	NaCl	27.2615_9	51355_7	15338.6	80.874	− .2277
		Potassium Chloride Solutions			
1	KCl	0.1506_{99}	79601_6	23802.6	125.654	− .7270
2	KCl	0.3014_{42}	78764_0	23472.6	123.695	− .6903
3	KCl	0.5378_{82}	77909_7	23225.7	118.655	− .6413
4	KCl	0.7162_{22}	77443_7	23027.0	119.224	− .6315
		Magnesium Sulfate Solutions			
1	$MgSO_4$	0.7041_{66}	45266_0	14624.2	87.686	− .6457
2	$MgSO_4$	1.41629	40171_7	12922.4	75.583	− .6321
3	$MgSO_4$	2.49969	36145_7	11664.6	60.41_2	− .4536
4	$MgSO_4$	3.41678	34105_3	10905.1	64.458	− .6604
		Mixed Solutions of Sodium Chloride and Potassium Chloride			
1	NaCl	5.61836				
	+ KCl	0.1515_{22}	57582_0	17686.1	97.93_0	− .3787
2	NaCl	11.30020				
	+ KCl	0.3047_{56}	55165_3	16695.6	97.24_0	− .4700
3	NaCl	19.94439				
	+KCl	0.5378_{82}	52913_1	15896.9	85.328	− .2788
4	NaCl	27.26159				
	+ KCl	0.7352_{20}	51573_9	15320.1	85.140	− .3470
		Mixed Solutions of Sodium Chloride and Magnesium Sulfate			
1	NaCl	5.61836				
	+ $MgSO_4$	0.7041_{66}	54853_2	16883.9	97.266	− .3985
2	NaCl	11.30020				
	+ $MgSO_4$	1.41629	52080_2	15835.2	95.810	− .5179
3	NaCl	19.94439				
	+ $MgSO_4$	2.49969	49534_0	14940.6	84.325	− .3418
4	NaCl	27.26159				
	+ $MgSO_4$	3.41678	48002_4	14331.2	83.209	− .3909

For these reasons Equation I is recommended for use in calculating equivalent conductance as a function of centigrade temperature.

Temperature coefficients of equivalent conductance were calculated by use of Equation II and the constants are listed in Table I.

$$\text{Temp. coef. of eq. cond.} = \frac{d\Lambda}{\Lambda dt} = \frac{b + 2ct + 3dt^2}{\Lambda} \qquad \text{(II)}$$

They were calculated with five-place accuracy for each of the 20 different solutions at 0, 5, 10, 15, 20 and 25°, and are listed in Part 1 of Table II.

Specific Conductance as a Function of Temperature.—Equation III has been used previously to calculate the specific conductances of 0.01 demal and 0.1 demal potassium chloride solutions in the temperature range 0 to 25°[3]

$$\text{Sp. cond.} = L = a + bt + ct^2 + dt^3 \qquad \text{(III)}$$

(3) Raymond W. Bremner and Thomas G. Thompson, THIS JOURNAL, 59, 2372 (1937).

TABLE II

PART 1—TEMPERATURE COEFFICIENTS[a] OF EQUIVALENT CONDUCTANCE

Coef. $\times 10^6 = (d\Lambda/\Lambda dt) \times 10^6$

Solution	0°	5°	10°	15°	20°	25°
	Sodium Chloride Solutions					
1	3082_3	28048	25713	23716	21986	20470
2	3043_1	2773_2	25453	23499	2180_2	2031_2
3	3000_1	27403	25195	2329_2	21634	2017_2
4	2986_7	2723_6	2502_6	2314_0	2150_8	2008_0
	Potassium Chloride Solutions					
1	2990_2	2723_6	24953	22973	21235	19696
2	2980_1	2715_6	24895	2293_0	2120_8	1968_3
3	2981_1	2712_8	24845	22876	21154	19634
4	29734	2708_4	2482_5	2287_2	21163	1965_2
	Magnesium Sulfate Solutions					
1	3230_7	2927_2	2666_1	2439_0	22394	20624
2	3216_8	2911_7	26483	24185	2216_0	20359
3	3227_1	29045	2633_3	2401_3	2200_1	20234
4	31975	2896_0	26314	23976	21894	20026
	Mixed Solutions of Sodium Chloride and Potassium Chloride					
1	3071_5	2795_6	2562_8	2363_3	2190_1	2037_9
2	3026_5	2765_9	2541_6	2346_3	21746	2022_1
3	3004_4	2739_3	2516_0	23247	21588	20133
4	2970_5	2716_1	24987	2310_3	21454	19996
	Mixed Solutions of Sodium Chloride and Magnesium Sulfate					
1	3078_0	2805_9	2574_6	2375_3	2201_5	2048_4
2	3040_6	2781_7	2556_8	2359_5	2185_0	2029_5
3	3016_2	2754_4	2531_2	2338_3	2169_7	2020_9
4	2985_5	2733_2	2515_3	2325_1	2157_4	2008_5

PART 2—TEMPERATURE COEFFICIENTS OF SPECIFIC CONDUCTANCE

Coef. $\times 10^6 = (dL/Ldt) \times 10^6$

°C.	0	5	10	15	18	20	25
KCl 0.01D	2979_2	2703_6	2470_4	2270_1	2162_7	2095_7	1942_1
KCl 0.1D	29185	2653_9	2427_2	2230_4	2124_1	2057_5	1904_1
Conductivity water	43_{500}	36_{200}	31_{800}	29_{000}	28_{000}	27_{400}	26_{300}

When applied to the conductivity water used the constants obtained for specific conductance $\times 10^6$ are $a = 0.495$, $b = 0.0218$, $c = -0.000002$ and $d = 0.0000039$. Since the conductance of the water used was only a small correction factor, it was less accurately determined.

By use of Equation IV temperature coefficients of specific conductance were calculated; those of 0.01 demal and 0.1 demal standard potassium chloride solutions with five-place accuracy, and those of the conductivity water with three place accuracy. They are listed in Part 2 of Table II.

$$\text{Temp. coef. of sp. cond.} = \frac{dL}{Ldt} = \frac{b + 2ct + 3dt^2}{L} \qquad \text{(IV)}$$

Discussion of Results

Effects of Concentration.—As illustrated by Part 1 of Table II the temperature coefficients of equivalent conductance decrease with increasing concentration in every instance. This is probably because the coefficients for water are higher, as shown in Part 2 of Table II. The data on standard potassium chloride solutions substantiate this observation.

The effect of temperature on this decrease depends upon the particular salt or mixture of salts

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involved. The decrease is most rapid at 0° and progressively becomes slower up to 25°, for all the solutions containing a high proportion of monovalent ions. Solutions containing only magnesium sulfate and water exhibit the reverse behavior. The decrease is slowest for the most dilute solutions (potassium chloride only) and progressively becomes more rapid to those of higher concentration (sodium chloride). These effects are best observed by plotting coefficients against concentrations.

Effects of Temperature.—The temperature coefficients of equivalent conductance considered decrease by about 1.5 to 2.0% of their values for each degree increase in temperature. The fact that they decrease is consistent with measurements showing coefficients to be negative at much higher temperatures. This decrease is most rapid for water and becomes less rapid the more concentrated the solution, except for solutions containing only magnesium sulfate and water. This difference and also the one mentioned in the preceding paragraph are likely due to the fact that magnesium sulfate is a different type of electrolyte in that it yields divalent ions.

Effects of Adding a Second Salt.—The addition of a salt that forms solutions with temperature coefficients higher or lower than those of sodium chloride solutions to the latter, produces solutions with coefficients of intermediate value. The magnitude of the intermediate value depends upon the concentration, and the temperature, even though the mole ratios are kept constant. The effect of adding a salt is either in opposition to or in addition to the effect of increasing the concentration, depending upon whether the coefficients of solutions of the added salt are higher or lower, respectively, than those of solutions containing only sodium chloride and water. For example, the addition of magnesium sulfate to sodium chloride solutions increases the temperature coefficients of the latter. Thus, two opposing factors are in operation, the effect of adding a salt with a larger temperature coefficient outweighing the effect of increasing the concentration.

When temperature coefficient is considered as a function of concentration, there is a pronounced maximum in the temperature coefficient at concentration no. 3 for magnesium sulfate solutions at 0°. Slight maxima occur also at the same concentration for this salt at 25° and for potassium chloride solutions at 0°. These maxima are reflected in the corresponding sodium chloride solutions to which the salts mentioned have been added. The maxima, particularly for the magnesium sulfate solutions at 0°, are larger than could be attributed to experimental errors, and as yet we can offer no explanation for them. It is a noteworthy fact that they occur mainly at 0°.

Summary

1. An equation is recommended for calculating the equivalent conductances of solutions as a function of centigrade temperature. The maximum deviation of the calculated from the experimental equivalent conductance was 0.02%, and the average deviation was only 0.006%.

2. By use of the differentiated form of the equation the temperature coefficients of equivalent conductance of twenty different solutions have been calculated with five-place accuracy at 0, 5, 10, 15, 20 and 25°. Also temperature coefficients of specific conductance have been calculated at 0, 5, 10, 15, 18, 20 and 25° for the conductivity water used and for 0.01 demal and 0.1 demal standard potassium chloride solutions.

3. Variations of temperature coefficients of electrical conductance of the salt solutions, due to concentration changes, temperature changes and the addition of a second salt have been determined.

COLLEGE STATION, TEXAS RECEIVED AUGUST 31, 1943

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Osmotic Pressures for Mixed Solvents[1]

BY FREDERICK T. WALL

During recent years osmotic pressure measurements have assumed increased importance as a means of determining molecular weights of high polymeric substances.[2a,b] Although the theory of osmotic pressures for simple systems has been well formulated, little attention has been devoted to the theoretical aspects of osmotic pressures for systems with mixed solvents. Since G. Gee[2] has carried out measurements under such conditions, it appears desirable to consider thermodynamically the significance of osmotic pressures for mixed solvents and to find out just what it is that one measures experimentally.

For an ordinary solution consisting of a solvent (A) and a solute (S), the osmotic pressure is a definite thermodynamic property of the solution. It is defined simply as the excess pressure which must be applied to the solution to increase the partial pressure of the solvent up to the vapor pressure of the pure solvent at the same tempera-

(1) Original manuscript received July 12, 1943.

(2) (a) G. V. Schulz, *Z. physik. Chem.*, **176**, 317 (1936); R. M. Fuoss and D. J. Mead, *J. Phys. Chem.*, **47**, 59 (1943); P. J. Flory, THIS JOURNAL, **65**, 372 (1943). See also H. Mark, "Physical Chemistry of High Polymeric Systems," Interscience Publishers, New York, N. Y., 1940, p. 228, for a general discussion. (b) G. Gee, *Trans. Faraday Soc.*, **36**, 1171 (1940).

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ture. If p_A^0 is the vapor pressure of pure A and p_A the partial pressure of A for the solution, then the osmotic pressure is given by[3]

$$P = \frac{RT}{\overline{V}_A} \ln \frac{p_A^0}{p_A} \qquad (1)$$

where $\overline{V}_A$ is the partial molar volume of A in the solution. Although one usually thinks of a semipermeable membrane in connection with osmotic pressure, it will be recognized that such a membrane need not exist to give equation (1) a definite meaning. Of course, if pure A is separated from a solution of S in A by a membrane impermeable to S, then P is just the excess pressure that must be applied to the solution to prevent solvent from passing through the membrane.

Consider now a solution of solute (S) in a mixture of solvents (A and B). One could define an osmotic pressure for each of the solvents by means of equations of type (1). That, however, would in general give two different osmotic pressures, neither of which would correspond to a measured pressure if one used a membrane permeable to both A and B but impermeable to S. Accordingly, it seems desirable to define a new osmotic pressure, bearing in mind the experiment which might be used for the measurement.

Suppose that a solution of S in A and B is separated from a mixture of A and B by a membrane impermeable to S only (Fig. 1). In the following discussion the term "solution" will be applied to the phase containing S and the term "solvent" to the other phase. Let x_i, p_i and $\overline{V}_i$ represent, respectively, the mole fraction, partial pressure and partial molar volume of the i-th component in the solution, and let the same symbols with primes (x_i', p_i', $\overline{V}_i'$) represent the corresponding quantities for the solvent. Also let p_i^0 be the vapor pressure of the pure ith component at the temperature of the experiment. For the sake of simplicity, it will first be supposed that Raoult's law holds. Since for high polymeric substances[4] and for many pairs of solvents, Raoult's law does not hold, the treatment will then be followed by a consideration of the effect of deviations from Raoult's law.

System with Raoult's Law Valid.—If Raoult's law holds, then

$$p_i = x_i p_i^0$$

and

$$p_i' = x_i' p_i^0 \qquad (2)$$

To prevent A from passing through the membrane, it is necessary to apply a pressure P_A on the solution, where

$$P_A = \frac{RT}{\overline{V}_A} \ln \frac{p_A'}{p_A} = \frac{RT}{\overline{V}_A} \ln \frac{x_A'}{x_A} \qquad (3)$$

(3) See, for example, MacDougall, "Physical Chemistry," rev. ed., The Macmillan Co., New York, N. Y., 1943, pp. 255–257.

(4) M. L. Huggins, *J. Phys. Chem.*, **46**, 151 (1942); P. J. Flory, *J. Chem. Phys.*, **10**, 15 (1942).

Likewise to prevent B from passing through the membrane, a pressure P_B must be applied, where

$$P_B = \frac{RT}{\overline{V}_B} \ln \frac{p_B'}{p_B} = \frac{RT}{\overline{V}_B} \ln \frac{x_B'}{x_B} \qquad (4)$$

In general P_A will not equal P_B; to make them equal, it is necessary that

$$\frac{1}{\overline{V}_A} \ln \frac{x_A'}{x_A} = \frac{1}{\overline{V}_B} \ln \frac{x_B'}{x_B} \qquad (5)$$

It is seen from equation (5) that if P_A equals P_B, the mole ratio of A to B on the two sides of the membrane will not be the same unless $\overline{V}_A = \overline{V}_B$.

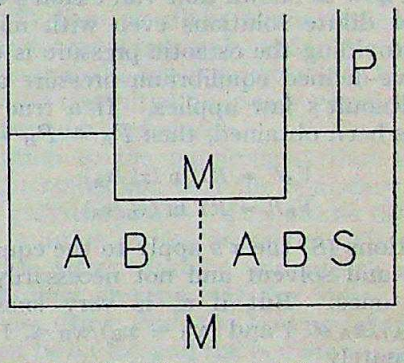

Fig. 1.—Solution (A,B,S,) separated from solvent (A,B) by membrane (M–M) which is impermeable to S.

Let us now investigate what will happen if the experiment illustrated in Fig. 1 is started with the same mole ratio of A to B on each side of the membrane. Then

$$\frac{x_B'}{x_B} = \frac{x_A'}{x_A} \qquad (6)$$

and

$$P_A \overline{V}_A = P_B \overline{V}_B \qquad (7)$$

Suppose $\overline{V}_A > \overline{V}_B$; then $P_A < P_B$. If a pressure P_A is applied to the solution, no A will pass through the membrane, but B will enter the solution, thus increasing the volume of the solution. On the other hand, if a pressure P_B is applied, no B will pass through the membrane, but some A will leave the solution, thereby decreasing its volume. Evidently there will be some intermediate pressure P (where $P_A < P < P_B$) such that the volume of the solution will remain stationary. This will occur when the ratio of the number of moles of A leaving the solution to the number of moles of B entering the solution is in the inverse ratio of their partial molar volumes. When this state is obtained, one might be inclined to call P the "osmotic pressure" of the solution. Actually (if one waits long enough), P will gradually change as diffusion takes place until equation (5) holds, and only then will true equilibrium be established. Accordingly this method of using mixed solvents will make osmotic pressure measurements time consuming, because diffusion must take place and equilibrium cannot be reached by the application of pressure alone. Moreover,

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the final pressure will not be the osmotic pressure of the original solution but will be defined as that of the equilibrated solution.

To get the osmotic pressure of the original solution and to avoid diffusion, it would be necessary in principle to start with solvent and solution already satisfying equation (5). Under such circumstances an osmotic equilibrium can be established simply by the application of pressure. In practice this would be almost impossible to realize (especially if Raoult's law does not hold), since it presupposes more knowledge than is generally available.

It will now be shown that van't Hoff's equation holds for dilute solutions even with mixed solvents, providing the osmotic pressure is taken as the above-defined equilibrium pressure and providing Raoult's law applies. If a true equilibrium has been obtained, then $P_A = P_B = P$, and

$$\overline{V}_A P = RT \ln (x'_A/x_A)$$
$$\overline{V}_B P = RT \ln (x'_B/x_B) \qquad (8)$$

In equations (8) the x's apply to the equilibrated solution and solvent and not necessarily to the original ones. But if x_s is very small, then $(x'_A - x_A)/x_A \ll 1$ and $(x'_B - x_B)/x_B \ll 1$. Then approximately

$$\overline{V}_A P = RT \left(\frac{x'_A - x_A}{x_A}\right)$$

and

$$\overline{V}_B P = RT \left(\frac{x'_B - x_B}{x_B}\right) \qquad (9)$$

But from equations (9) it can be shown that

$$(x_A \overline{V}_A + x_B \overline{V}_B) P = x_S RT \qquad (10)$$

Let N_A, N_B and N_S be the total number of moles of A, B and S in a volume V of solution. Then

$$(N_A \overline{V}_A + N_B \overline{V}_B) P = N_S RT$$

or

$$(V - N_S \overline{V}_S) P = N_S RT \qquad (11)$$

Neglecting $N_S \overline{V}_S$ as compared to V, there is obtained van't Hoff's equation

$$PV = N_S RT \qquad (12)$$

If c equals the concentration of S in grams per unit volume, then

$$P/c = RT/M \qquad (13)$$

where M is the molecular weight of the solute.

System not Subject to Raoult's Law.—If Raoult's law does not apply, then the thermodynamic treatment of osmotic pressures for mixed solvents becomes more involved. The equations become complicated because cognizance must be taken of solvent non-idealities even when the system is infinitely dilute with respect to solute. Because of this persisting non-ideality, it is not obvious that van't Hoff's equation will apply at infinite dilution.

However, if one assumes that Henry's law applies to the solute, it can be shown that van't Hoff's equation should be valid at infinite dilution regardless of the nature of the solvents as long as their vapors obey the perfect gas laws. The proof of this proposition rests upon the use of the three-component counterpart of the Duhem–Margules equation, but the details of the calculation will not be supplied here.

Discussion

The first point to be noted in connection with the use of mixed solvents is that the composition of solvent will not be the same on each side of the membrane after osmotic equilibrium is established. Starting with the same solvent ratio on both sides of the membrane, the apparent osmotic pressure (corresponding to a stationary volume) will not in general be the same as the equilibrium pressure. If the difference is appreciable, then the use of a dynamic method of measurement may lead to erroneous results. However, if the mole fraction of solute is small, the apparent osmotic pressure will be practically the same as the final pressure and the solvent composition will be substantially the same on the two sides of the membrane.

If Raoult's law holds, extrapolation of the osmotic pressure equations to infinite dilution will give van't Hoff's equation. In this event, correct molecular weights for solutes can be obtained by the usual simple means. On the other hand, if Raoult's law does not hold for the mixed solvents, extrapolation to infinite dilution of solute will not yield van't Hoff's equation unless the solute obeys Henry's law, which assumption is reasonable. Accordingly, van't Hoff's equation can always be used in practice for extrapolation purposes.

Although the use of mixed solvents introduces some doubtful points, correct results can be obtained but the measurements may be time consuming because of the necessity for diffusion taking place. Gee[2] reports no complications in connection with the use of mixed solvents; in fact he reports certain advantages. It appears that the magnitudes of the new effects discussed in this paper are small for dilute solutions. What the effect will be on the slope of a curve in which P/c is plotted against c cannot be predicted simply.

The author is indebted to Dr. R. H. Ewart of the United States Rubber Company for helpful discussion and suggestions.

Summary

The problem of osmotic pressures for solutions with mixed solvents is considered thermodynamically. It is shown that in general the measured osmotic pressure has definite significance only if the solvent compositions are different on the two sides of the membrane and subject to certain relationships. However, it is shown that van't Hoff's equation can be expected to hold for in-

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finitely dilute solutions. For concentrated solutions certain complications can be expected in the experimental determination of osmotic pressures using mixed solvents, especially if a dynamic approach is employed.

URBANA, ILLINOIS RECEIVED JANUARY 13, 1944

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

The Concentration Distribution in Two-Salt Moving Boundaries

BY L. G. LONGSWORTH

Introduction.—The development of the schlieren scanning technique[1] for studying the electrophoresis of proteins has, somewhat unexpectedly, provided a tool with which to investigate in detail the moving boundaries that have been used for the measurement of the transference numbers of strong electrolytes. Such boundaries, it will be recalled, are formed between two solutions of binary salts having a common ion, the salt present in the region into which the boundary moves on passage of the electric current being called the "leading" electrolyte whereas that behind the boundary is termed the "indicator" electrolyte. Boundaries of this type will be called "two-salt" boundaries in order to distinguish them from other types of moving boundaries such as protein boundaries[2] and concentration boundaries.[3]

According to the theory developed by Weber[4] the mixing effect of inter-diffusion at a two-salt boundary is balanced by a separating effect due to ion migration[5] if the mobility, u_i, of the indicator ion constituent is less than the mobility, u_1, of the leading ion constituent and if the current is passed in the appropriate direction. Under these conditions the concentration distribution in the boundary for a given current density I is independent of the time and the boundary velocity is given by the relation

$$v = IT_1/FC_1 \qquad (1)$$

in which F is the faraday, T_1 the transference number of the leading ion constituent and C_1 is the concentration, in equivalents per milliliter, in the body of the leading solution. Whereas the concentrations of the salt solutions forming the boundary initially may be selected independently of each other, the concentration, C_i, of the column of indicator electrolyte that is formed by the advancing boundary is not independent of C_1 but is given by the relation

$$C_i = C_1T_i/T_1 \qquad (2)$$

in which T_i is the transference number of the indicator ion at the concentration C_i. If the boundary is formed initially between the leading solution and the indicator solution at a concentration C_i' which is different from that, C_i, required by equation (2), then, as will be demonstrated later in this paper, a concentration boundary between the indicator salt at the two concentrations C_i and C_i' remains near the initial boundary position as the two-salt boundary advances.

In addition to the requirement that $u_i < u_1$ there is the restriction that the boundary system be stable gravitationally. This means that if the indicator solution is less dense than the leading solution the latter must be underneath and the boundary must descend. If the indicator solution is more dense than the leading solution the latter must be on top and the boundary must rise. Moreover, since the densities of most salt solutions increase with increasing concentration, gravitational stability also requires that the initial indicator concentration, C_i', be equal to or greater than that, C_i, of the adjusted indicator solution for a rising boundary whereas for a descending boundary $C_i' \leq C_i$.

Under the conditions prevailing in previous work with two-salt boundaries the transition from one solution to the other occurs within less than a millimeter. Such a sharp boundary can be located accurately with the aid of relatively simple optical arrangements, advantage being taken of the difference of refractive index at the boundary, and this is sufficient for a determination of the boundary displacement and hence the transference number T_1. The optical devices previously employed have not, however, given information concerning the magnitude and distribution of the gradients in the boundary and the manner in which these vary with the current. This information can now be obtained with the aid of the schlieren scanning camera. It is the purpose of this paper to report measurements of the gradients in typical boundaries and to show that they are in agreement with Weber's theory.[4]

Experimental Results.—The patterns of Fig. 1, recorded during the electrolysis at 0.5°, of 0.1 N potassium iodate:0.1 N potassium chloride at a current density of 0.00655 amp./sq. cm., are typical of the results obtained in this research. The time interval between all of the patterns after the second was one hour. In order to avoid overlapping of the concentration boundary peak, each successive pattern has been displaced a fixed distance vertically. The line h_0 in each pattern

(1) Longsworth, THIS JOURNAL, 61, 529 (1939).
(2) Tiselius, *Trans. Faraday Soc.*, 33, 524 (1937).
(3) Longsworth, THIS JOURNAL, 65, 1755 (1943).
(4) H. Weber, "Die partiellen Differential-Gleichungen der mathematischen Physik," Braunschweig, 1910, 5th edition, chapter 24.
(5) MacInnes and Cowperthwaite, *Proc. Natl. Acad. Sci.*, 15, 18 (1929).

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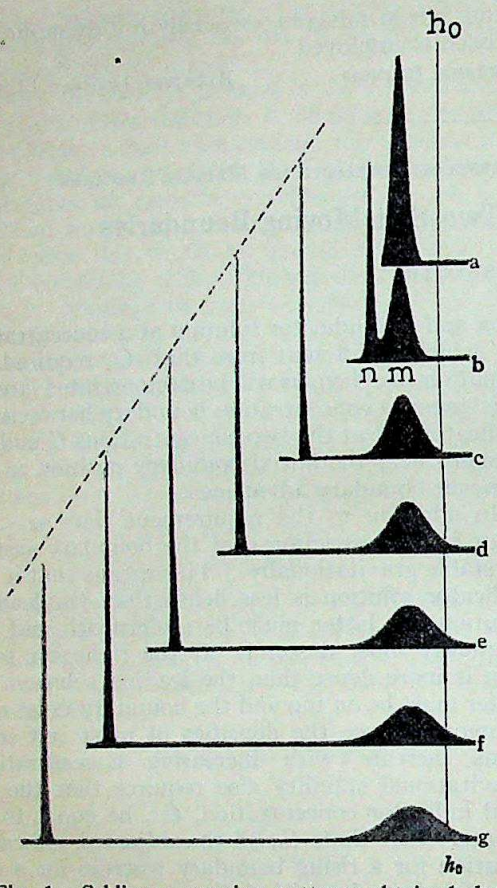

Fig. 1.—Schlieren scanning patterns obtained during the electrolysis of a boundary formed initially between 0.1 N KIO_3 and 0.1 N KCl.

is due to a graduation on the cell that serves as a reference mark from which all boundary displacements are measured. Except for the necessity of automatic regulation of the current[6] in work with two-salt boundaries, the apparatus and experimental procedures employed have been adequately described in recent papers by the author.[3,7]

Several features of the direct moving boundary method, previously inferred but unconfirmed experimentally, are at once apparent in Fig. 1. The first pattern, a, was obtained after the boundary had been formed and shifted from behind the opaque horizontal plates of the cell, but before the electric field was applied. On passage of the current this boundary separated, as shown in Fig. 1b, into the concentration boundary, m, between potassium iodate at the concentrations C_i and 0.1 N and the two-salt boundary, n, between potassium iodate at the concentration C_i and 0.1 N potassium chloride. On continued electrolysis, Figs. 1b–g, the concentration boundary spread progressively due to diffusion whereas the two-salt boundary acquired, by the time the pattern of Fig. 1c was recorded, a salt distribution that remained unchanged.

(6) Longsworth and MacInnes, This Journal, 60, 3070 (1938).

(7) Longsworth, *Chem. Rev.*, 30, 323 (1942).

With the patterns arranged as in Fig. 1, the constancy of the maximum gradient in the two-salt boundary is indicated by the fact that these maxima fall on a straight line. The slight decrease in the height of the peak as the boundary approaches the upper end of the channel, Fig. 1g, is probably due to a small convergence error inherent in the optical system[8] and not to a change in the salt distribution through the boundary. In one experiment in which the boundary displacement was balanced by addition of solution, thereby holding it at the same level and consequently maintaining the convergence error at a constant value, the salt distribution in the boundary did not vary during continuous electrolysis for two weeks.

As recently shown experimentally,[3] the displacement of the concentration boundary, m, of Fig. 1, is proportional to the difference of transference number between the two solutions of potassium iodate forming this boundary. The quantity of electricity passed in this experiment, although sufficient to cause the two-salt boundary, n, to move the length of the channel, was not large enough to permit a reliable determination of the concentration boundary displacement. The area of the peak corresponding to the boundary at m does, however, afford a measure of the concentration adjustment of the indicator electrolyte. Since the refractive index increment[9] for 0.1 N potassium iodate, using the mercury yellow line, is 0.00282 and the area of the concentration boundary corresponds to $\Delta n = 0.00102$, the adjusted concentration C_i is 0.0640 N. The displacement of the two-salt boundary in Fig. 1 gives a value of 0.504 for the anion transference number, T_i, of 0.1 N potassium chloride at 0.5°, in agreement with that, 0.505, obtained by extrapolation of the data of Allgood, Le Roy and Gordon.[10] Substitution of these figures in equation (2) gives 0.323 as the anion transference number, T_i, of 0.064 N potassium iodate. Since the precision of the refraction increments from measurements of pattern areas is about $\pm 1 \times 10^{-5}$, the error in T_i is probably not more than 1%. Although this error is greater than that characteristic of the direct de-

(8) Svensson, *Kolloid-Z.*, 90, 141 (1940).

(9) The refraction increments reported here have been determined at 0.5° with the aid of the schlieren scanning camera and a 60° hollow prism cell. The prism, filled with water, was placed in the thermostat in the focus of the camera, set for minimum deviation, and a scanning photograph was obtained. The prism was then rinsed and filled with a salt solution of known concentration and again photographed. The deflection D due to the salt solution is connected with the refractive index difference Δn and the prism angle α by the relation (R. W. Wood, "Physical Optics," The Macmillan Co., New York, N. Y., 1924) $\Delta n = \sin^{1}/_{2}(\alpha + D)/\sin {}^{1}/_{2}\alpha$. The reproducibility of this differential method, $\Delta n = 5 \times 10^{-6}$, compares favorably with that attainable with the Zeiss-Pulfrich refractometer. I have not been able to find data in the literature for comparison with my values at 0°. I have, therefore, also made measurements at 10°, 18 and 30° for several salts and these are in agreement with the best available data. Contrary to the general impression, the temperature coefficient of the refraction increment is not negligible for many salts at temperatures in the neighborhood of 0°.

(10) Allgood, Le Roy and Gordon, *J. Chem. Phys.*, 8, 418 (1940).

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termination of T_1 for the leading solution from the displacement of the two-salt boundary, the method just outlined will be useful when other methods are not available.

Another feature of the direct moving boundary method is illustrated in Fig. 2. In this figure the patterns of a 0.064 N potassium iodate: 0.1 N potassium chloride boundary, obtained during electrolysis at three different current densities, have been placed at the corresponding positions on the current axis. When mounted in this manner the maximum gradient of each pattern falls on a straight line passing through the origin, *i. e.*, this gradient is directly proportional to the current. With currents heavier than that corresponding to Fig. 2 c the light deflected by the steepest gradients in the boundary fails to enter the camera objective. Some idea of the sharpness of the boundaries used for routine transference number determinations may be obtained from the fact that the current densities employed range from five to ten times the maximum value used in the present research.

With lithium chloride as the indicator electrolyte for the potassium chloride, the boundary descends since the leading solution is heavier and must remain below. Moreover, the initial indicator salt concentration, C_i', should, therefore, be equal to, or less than, the adjusted concentration, C_i. Thus when a 0.05 N lithium chloride: 0.1 N potassium chloride boundary was studied in the same manner as the potassium iodate: potassium chloride boundary a stable concentration boundary was left behind near the initial position as the two-salt boundary descended. Since the refraction increment for 0.05 N lithium chloride is 0.00047_5 and the area of the concentration boundary corresponded to an increment of 0.00008_7, the adjusted concentration, C_i, may be computed to be 0.0592 N and T_i, by equation (1), is 0.294. When a 0.1 N lithium chloride solution was used to form the boundary, this solution, being heavier than the underlying 0.059 N solution produced by the migration of the two-salt boundary, mixed with the latter and the resulting schliere were clearly visible in the focus of the camera. This convective circulation partially penetrated the boundary, distorting it and causing it to move too rapidly. Similar disturbances were also apparent when the lithium chloride concentration was 0.065 N.

The Theory of Two-Salt Boundaries.—As has been shown conclusively in previous experimental work,[11] a two-salt boundary moves with a constant velocity under the influence of a constant current density. The present research demonstrates that under these conditions the concentration distribution through the boundary also does not change with the time. The concentrations are, therefore, functions of the time t and the coordinate h, *i. e.*, the vertical height in the channel, of the form

$$c = f(h - vt) \qquad (3)$$

in which v is the boundary velocity. This relation is the basis of Weber's theory for the concentration distribution in a two-salt boundary. The following is a brief statement of his theory.

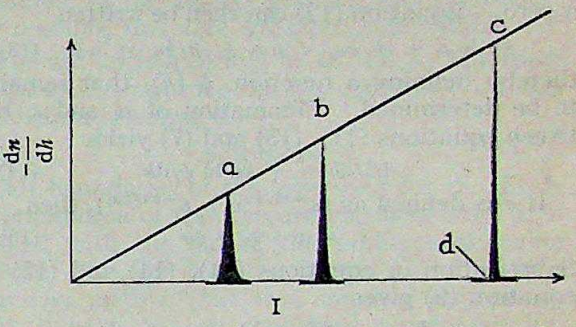

Fig. 2.—Patterns of a 0.064 N KIO_3: 0.1 N KCl boundary at three different current densities.

As has been shown in an earlier paper[11] the equation of continuity for an ion of the j-th kind is

$$\frac{\partial c_j}{\partial t} = \frac{\partial}{\partial h}\left[\frac{c_j u_j}{|z_j|}\left(\frac{\partial \mu_j}{\partial h} + z_j \frac{\partial E}{\partial h}\right)\right] \qquad (4)$$

and the expression for the current density is

$$I = -F\sum_{j=1}^{j=s}\frac{c_j u_j}{z_j}\left(\frac{\partial \mu_j}{\partial h} + z_j \frac{\partial E}{\partial h}\right) \qquad (5)$$

In these equations E and μ are the electrical and chemical potentials, respectively, both expressed in volts. The valence of an ion, account being taken of its sign, is denoted by z whereas $|z|$ indicates the magnitude only.

Since $\partial c/\partial t = -vf'(h - vt) = -v\partial c/\partial h$ from equation (3), equation (4) becomes, after integration

$$vc_j + \frac{c_j u_j}{|z_j|}\left(\frac{d\mu_j}{dh} + z_j \frac{dE}{dh}\right) = A_j \qquad (6)$$

in which A_j is a constant of integration. Since the present treatment will be restricted to a system in which the leading ion, l, and indicator ion, i, are monovalent cations, c denoting the common monovalent anion, equation (6) becomes

$$vc_l + c_l u_l(d\mu_l/dh + dE/dh) = A_l \qquad (7)$$
$$vc_l + c_l u_l(d\mu_l/dh + dE/dh) = A_l \qquad (8)$$
$$vc_c + c_c u_c(d\mu_c/dh - dE/dh) = A_c \qquad (9)$$

At $h = +\infty$, $c_i = 0$ and $A_i = 0$ while at $h = -\infty$, $c_l = 0$ and $A_l = 0$. Moreover, if equation (9) be subtracted from the sum of equations (7) and (8), it will be noted, on comparison with equation (5), that $A_c = I/F$ since electrical neutrality requires that $c_i + c_l - c_c = 0$.

Elimination of dE/dh between equations (7) and (8), followed by integration, assuming the mobilities to be constant, gives

$$\mu_i - \mu_l = (1/u_l - 1/u_i)vh + B' \qquad (10)$$

If, now, the approximation is made that

$$\mu = \mu_0 + k \ln c \qquad (11)$$

in which $k = RT/F$, R being the gas constant in

(11) MacInnes and Longsworth, *Chem. Rev.*, 11, 171 (1932).

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joules per degree and T the absolute temperature, equation (10) may be written

$$\ln(c_i/c_1) = (1/u_1 - 1/u_i)vh/k + B \qquad (12)$$

If the origin is taken at that level in the boundary for which $c_i = c_1$, the constant of integration, B, is zero. Equation (12) can then be written

$$\ln c_i + vh/ku_i = \ln c_1 + vh/ku_1 = \ln \psi \qquad (13)$$

thereby defining a function, ψ (h), that remains to be determined. Elimination of μ_i and c_i between equations (11), (13) and (7) yields

$$dE/dh = -kd \ln \psi/dh \qquad (14)$$

If σ is defined as $(e^{-vh/ku_i} + e^{-vh/ku_1})$, then

$$c_o = c_i + c_1 = \psi\sigma \qquad (15)$$

Substitution of equations (11), (14) and (15) in equation (9) gives

$$d\psi + \left(\frac{v}{2ku_c} + \frac{d \ln \sqrt{\sigma}}{dh}\right)\psi dh = \frac{I}{2kFu_o\sigma}\,dh$$

Since σ is a known function of h, this is an equation of the Bernouilli type[12] whose integrating factor is $\sqrt{\sigma}\, e^{vh/2ku_c}$ and whose solution is, therefore

$$\psi = \frac{I\, e^{-vh/2ku_o}}{2kFu_o\sqrt{\sigma}} \int_{-\infty}^{h} \frac{e^{vh/2ku_o}}{\sqrt{\sigma}}\,dh$$

the lower limit of integration being determined from the condition that ψ must vanish for $h = -\infty$. This is the result obtained by Weber. The same result is also obtained if i and 1 are monovalent anions.

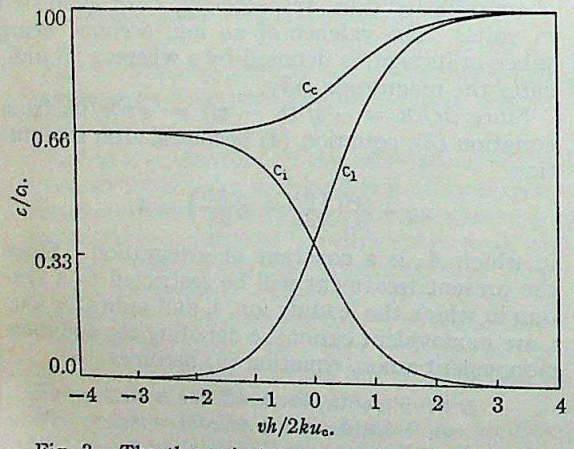

Fig. 3.—The theoretical concentration distributions of the indicator ion, i, the leading ion, 1, and the common ion, c, in a typical two-salt moving boundary.

Computations with the foregoing relations are greatly facilitated if the mobilities u_c and u_1 are simple multiples of u_i, which is very nearly the case for the boundaries studied in this research. Thus, by combining the transference numbers reported earlier in this paper with conductance data, one obtains, at 0° and for 0.1 N solutions, $Fu_K = 35.4 \simeq Fu_{Cl} = 35.9$ whereas $Fu_{Li} = 15.0 \simeq Fu_{IO_3} = 16.2 \simeq {}^1/_2\, Fu_{Cl}$. Consequently a close approximation is made by taking

$$2u_1 = u_1 = u_o = 35.6/F \qquad (16)$$

Equation (13) then becomes, on reference to equation (1)

$$c_1/C_1 = 1 - \sinh^{-1} y/y\sqrt{1 + y^2} \qquad (17)$$

and

$$c_i = c_1/y^2 \qquad (18)$$

in which $vh/2ku_c = \ln y$.

These functions are plotted in Fig. 3 and indicate the distribution of concentrations in a typical two-salt boundary.

Differentiation of equations (17) and (18) yields

$$\frac{2ku_c}{vC_1}\frac{dc_1}{dh} = \frac{1}{1 + y^2}\left(\frac{1 + 2y^2}{y\sqrt{1 + y^2}}\sinh^{-1} y - 1\right) \qquad (19)$$

$$\frac{2ku_o}{vC_1}\frac{dc_1}{dh} = \frac{1}{y^2}\left(\frac{2ku_o}{vC_1}\frac{dc_1}{dh} - 2\frac{c_1}{C_1}\right) \qquad (20)$$

The lower curve of Fig. 4 is a plot, in the reduced coördinates $vh/2ku_c$ and $(2ku_c/vC_1)dc/dh$, of equation (19) after multiplication of the left hand term by 10.8, the equivalent refractive increment for potassium chloride, while the upper curve corresponds to equation (20) after multiplication by 28.2, the increment for potassium iodate. The intermediate curve of Fig. 4 is the sum of the upper and lower curves and represents, therefore, the theoretical gradient curve, dn/dh, of the total refractive index. In so far as the theory is valid, this curve should correspond to those recorded experimentally. The scale of ordinates in Fig. 4 has been inverted to conform to the current practice in the publication of electrophoretic patterns.

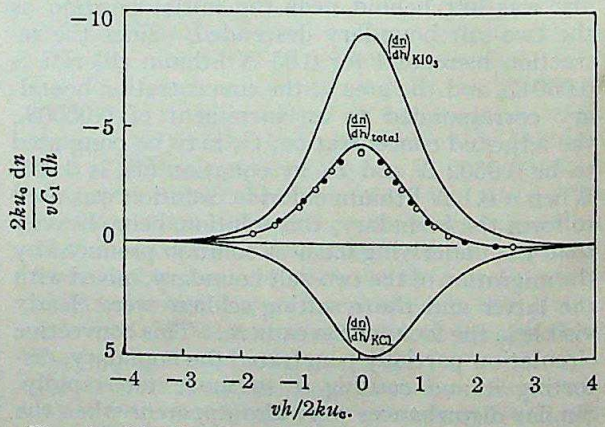

Fig. 4.—Distribution of the gradients dn/dh, of refractive index in a 0.064 N KIO_3:0.1 N KCl boundary.

With the aid of a two-coördinate comparator points were taken from the first two patterns illustrated in Fig. 2 and plotted as the circles and dots, respectively, in Fig. 4.[13] The agreement between

(12) E. B. Wilson, "Advanced Calculus," Ginn and Co., Boston, 1911, p. 210.

(13) Points taken from the pattern of Fig. 2c, corresponding to the highest current density, have not been plotted in Fig. 4 since this sharp boundary appears to be subject to a slight curvature error[3]. A comparison between theory and experiment similar to that of Fig. 4 was also made for the descending lithium chloride: potassium chloride boundary and substantial agreement was found, the somewhat greater deviations being due to divergence of the lithium ion mobility from the relation assumed in equation (16).

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the theory and experiment shown in this figure is surprisingly close, particularly in view of the simplifying assumptions that were found necessary. This agreement would appear to confirm completely the postulated mechanism, *i. e.*, that the boundary is the result of the interaction of diffusion and of ionic migration, and gives us still further confidence in the moving boundary method.

Since the maximum in the total gradient curve does not occur at $h = 0$, it is essential to locate this maximum accurately in order to have a reference point on the abscissa scale from which to plot the experimental data. For this purpose the expression for d^2n/dh^2 was obtained, set equal to zero, and the roots determined from a plot of the function. The position of the maximum depends, of course, on the relative values of the equivalent refraction increments and occurs at $\ln y = 0.419$ for the lithium chloride: potassium chloride boundary and at $\ln y = 0.037$ for the potassium iodate: potassium chloride boundary. In the latter case the theory also predicts a slight minimum in the gradient curve at $\ln y = 2.8$. It is of considerable interest that close inspection of the patterns reveals this minimum (see d of Fig. 2, for example) and that both its position and magnitude are in agreement with the theory. Owing to the relatively great density of potassium iodate solutions the minimum in the refractive index gradient curve is not accompanied by a corresponding minimum in the density gradient and the boundary remains, therefore, gravitationally stable.

The author is indebted to Dr. D. A. MacInnes of these Laboratories for his continued interest and helpful discussion.

Summary

Salt boundaries of the type used for the direct determination of transference numbers have been studied with the aid of the schlieren scanning camera. Several features of the direct moving boundary method that were assumed in previous work have now been confirmed experimentally. Under the influence of a constant current the concentration distribution through a moving boundary does not change with the time and is given accurately by Weber's theory. Moreover, the adjusted concentration of the indicator solution, and hence its transference number, may be determined from the electrophoretic patterns.

NEW YORK, N. Y. RECEIVED NOVEMBER 19, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BOSTON UNIVERSITY]

The System Ammonium Nitrate–Sodium Nitrate

BY EDWARD O. HOLMES, JR., AND DAVID REVINSON

In connection with the volunteer research program conducted by the Committee on Eutectics of the National Research Council, the senior author found that he was unable to confirm the accepted data on the system ammonium nitrate–sodium nitrate that he used to standardize his technique. The discrepancies in the determination of the points on the solubility curves were so large as to suggest that the work of Early and Lowry[1] on this system might be in error.

As a result, this investigation was begun to redetermine all parts of the system and to study the various factors that might lead to error such as (1) the method of purification of materials, (2) the length of drying of the purified materials and (3) the technique of determining points on the curve.

Purification of Materials.—The pure ammonium nitrate was supplied by the Committee on Eutectics.[2] It was of highest purity and the dry material was found by analysis to contain 100.01% ammonium nitrate. It was ground frequently and kept in a desiccator over Anhydrone for the entire period of the research. This material was used in all determinations.

The sodium nitrate (Merck Reagent) was further purified by two methods: (A) thrice recrystallized from water, ground frequently and kept over Anhydrone; (B) precipitated by concentrated nitric acid, washed with water, twice recrystallized, ground and kept over Anhydrone.

Thermometers.—Two thermometers used were of the twenty-four inch 0.1° type. Both were calibrated against the melting points of pure organic compounds and one by the Bureau of Standards, in addition.

The Melting Point Measurements

(a) Standard Microtechnique.—This technique consisted in weighing out a sample of a tenth of a gram into a three-inch test-tube, fusing the mixture and stirring until clear, cooling and removing the solid melt, grinding it to a powder, introducing a portion of the ground material into a 2-mm. capillary tube and then determining the point at which the last crystals disappeared on very slow heating.

It was found that the Thiele–Dennis melting point apparatus did not give satisfactory results, so a melting point apparatus had to be devised that would permit better heat control and give more uniform results. This was accomplished by building a special gas control valve for the conventional apparatus which consists of a beaker full of oil over a microburner, and surrounding the bulb of the thermometer by a glass basket into which the capillary melting point tube was placed. A description of this apparatus can be found in the *Journal of Chemical Education*.[3]

This method worked quite satisfactorily for the left-hand side of the system, the solubility curve of ammonium nitrate, but difficulty was experienced on the right-hand side, the solubility curve of sodium nitrate. The trouble was caused by a rapid settling out of solid sodium nitrate

(1) R. G. Early and T. M. Lowry, *J. Chem. Soc.*, **121**, 963 (1922).

(2) Courtesy of Professor Edward Mack, Jr., Chairman.

(3) Edward O. Holmes, Jr., *J. Chem. Ed.*, **20**, 239–240 (1943).

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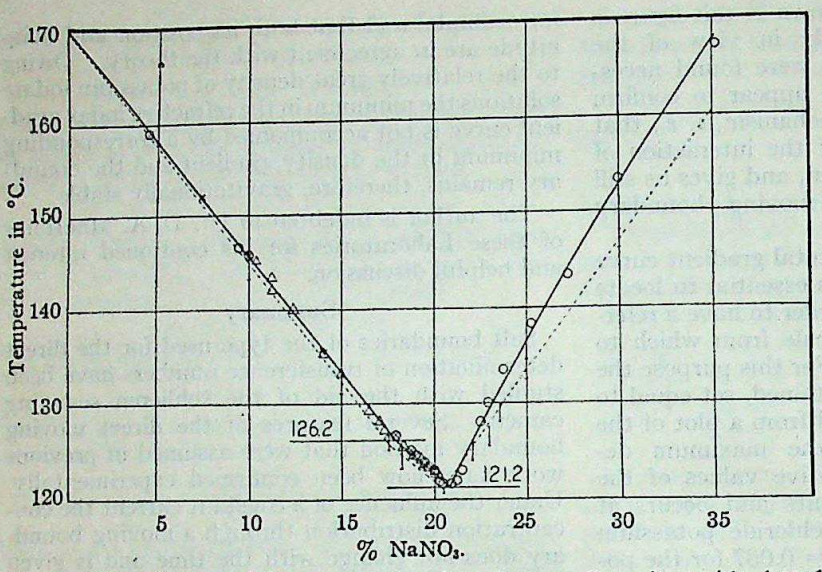

Fig. 1.—Phase diagram of the system ammonium nitrate–sodium nitrate (the dotted lines are Early and Lowry's curves).

crystals on cooling the original melt so that unless the melt was ground and mixed for a long time, a uniform sample could not be obtained. This process was undesirable as ammonium nitrate is very hygroscopic and every effort was made to keep the sample as dry as possible. On account of the steepness of solubility curves, it was absolutely necessary to use samples of accurately known composition, as a 0.1% error in composition makes a 0.3° error in the melting point of the mixture.

No such difficulty was encountered on the ammonium nitrate solubility curves as the crystals were of about the same density as the liquid melt and tended to float or rise slowly, and made a thick mesh long before the eutectic point was reached.

(b) **Improved Microtechnique.**—Our improved microtechnique consisted in eliminating a lack of uniformity of the sample by weighing tenth-gram samples of ammonium nitrate and sodium nitrate directly into a flared 12 mm. tube that had been drawn down into a thin-walled capillary and using the sample as a whole in the melting point determination.

As the rate of heating naturally makes a great difference in the temperature at which the last crystal disappears, observations were usually made at several rates of heating and the melting point at zero rate was obtained by graphical extrapolation.

Vigorous stirring of the oil-bath was necessary regardless of the rate of heating. Once in a while, we succeeded in stopping the oil-bath at the exact temperature at which the last crystal disappeared, which represents a zero-rate of heating. Temperatures so obtained corresponded with those from the zero-rate extrapolation method, as would be expected.

Both samples of sodium nitrate (A) and (B) were used here but no difference was found in the results. Points determined by this technique are considered to be the most reliable and those in which we have the most confidence.

(c) **Macrotechnique.**—The macrotechnique consisted in using a 20-g. sample (to reduce weighing error) in a test-tube, usually six-inch, then heating the sample over a microburner with the same apparatus as in the microdetermination except that the thermometer was placed directly in the melt, and the glass basket omitted. The melt was stirred by a glass stirrer shaped like a ring, which could be moved up and down around the thermometer. With a heating rate of about 0.3–5° per minute, the temperature at which the last crystal disappeared was noted.

The reason for taking such large samples was that Early and Lowry[1] used samples of this size and we wanted to see whether or not the size of the sample had any effect on the temperature at which the last crystal disappeared.

(d) **Cooling Curves.**—In order to compare points obtained by an entirely different method, we ran cooling curves on mixtures weighing 20 g. representing compositions in the various sections of the phase diagram, three on the ammonium nitrate solubility curve, one close to the eutectic and two on the sodium nitrate solubility curve.

The method consisted in weighing the 20-g. samples directly into a test-tube, usually six-inch, fitted with a stirrer. The sample was melted in an oil-bath and then the test-tube with its molten contents was placed in a larger test-tube having glass wool in the bottom and a cork ring to keep the smaller inner tube containing the melt properly centered. The larger tube was placed in an oil-bath over a microburner and the oil stirred with a large ring stirrer during all determinations.

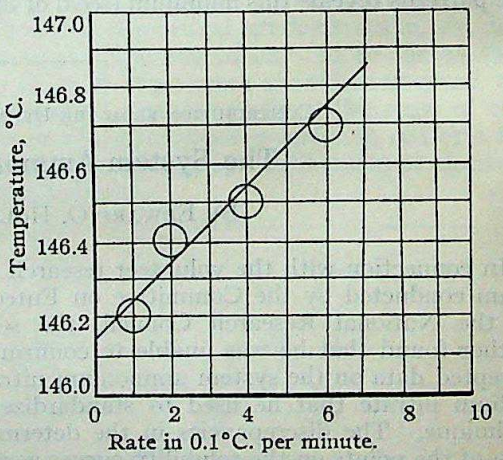

Fig. 2.—Temperatures at which last crystals dissolved, extrapolated to zero rate.

The temperature of the oil-bath was raised until it was several degrees above that at which the crystals were expected to appear on cooling and the melt was perfectly clear. Now the burner valve was set in such a position that the oil-bath would cool slowly to about 115°. The melt and the oil-bath were constantly stirred and the temperature of both read at regular intervals. The temperature at which the first crystals appeared was carefully

TABLE I

% $NaNO_3$ in sample	Temperatures, °C. First crystals appeared at	Break in curve, if any, at	Transition point	Eutectic halt
7.500	151.7	151.7	126.2	117.2
14.000	135.3	135.0	126.2	120.6
19.00	124.0	124.0	...	121.2
20.90	121.6	...	...	121.2
25.00	137.7	134.5	...	121.2
30.00	153.1	...	...	120.9

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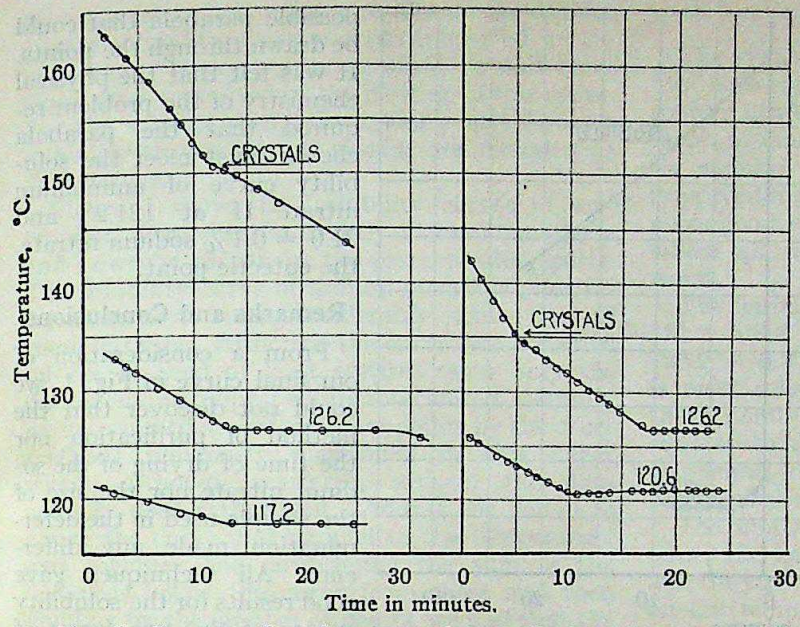

Fig. 3A.—Cooling curve for mixture containing 7.5% $NaNO_3$.

Fig. 3B.—Cooling curve for mixture containing 14.0% $NaNO_3$.

noted in each run. These temperatures appear in Fig. 1 as points marked (X) on the ammonium nitrate solubility curves. Several runs were made on each mixture. In at least one run, each of the mixtures was allowed to cool to the eutectic point. A characteristic cooling curve for each mixture is plotted in Fig. 3 and the results are tabulated in Table I.

When these values, which are averaged values derived from our cooling curves, are considered in relation to the values obtained from our improved microtechnique, it is seen that the temperature of the appearance of crystals and the breaks in the cooling curves correspond closely on the ammonium nitrate side of the diagram. However, on the sodium nitrate side the temperature at which the first crystals appeared on cooling falls above the curve but the break in the cooling curve falls much below in the case of the 25.00% mixture and does not appear at all in the case of the 30.00% mixture. The arrows in Fig. 3 indicate the temperature at which the crystals appeared.

We found the transition temperature for the change of ammonium nitrate I into ammonium nitrate II to be 126.2 ± 0.2° which is a degree higher than the value obtained by Early and Lowry.[1]

We also found that the temperature of the eutectic halt varied with the composition of the melt as Early and Lowry[1] had previously noticed, those values nearer to the eutectic point being constant and in good agreement, while those further away, in either direction, were lower as Table I shows. It seemed reasonable to these authors and also to us to take the average of these constant values near the eutectic point as the true value of the eutectic point, namely, 121.2 ± 0.2°. This value is 0.4° higher than that of Early and Lowry.[1]

Discussion of Results

Both theory and practice indicate that the values of the eutectic temperature from the cooling curve method (Fig. 3) are more reliable than those obtained by any melting point method. It was impossible, no matter how hard we tried nor what technique was used to cause mixtures to melt sharply at or close to the eutectic point: stirring is impossible and heat conduction is the poorest just when the largest amount of heat must be transferred. The melting point methods, whether micro or macro, are at their worst at the eutectic point but improve rapidly at higher temperatures where good stirring is possible and less heat must be transferred through the glass walls of the capillary.

Construction of the Phase Diagram (Fig. 1).—Much careful consideration was given to the construction of the phase diagram. The eutectic temperature and the transition temperature were assumed to be correct, as we obtained repeated check values (±0.2°) for these. We assumed the solubility curve for ammonium nitrate II to be a straight line and its equation was found[4] by the method of least squares, using all points as the consistency of the data is good over

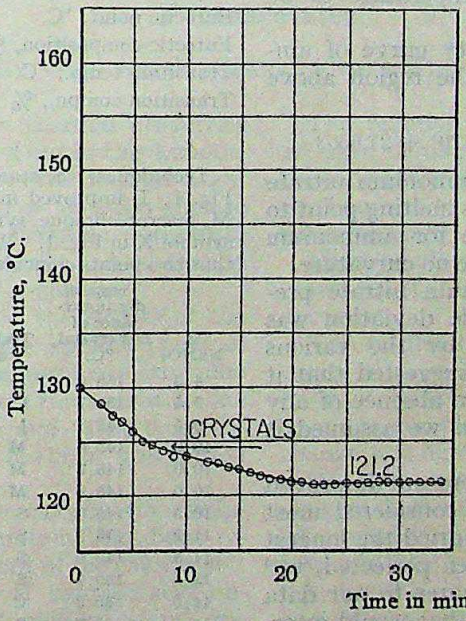

Fig. 3C.—Cooling curve for mixture containing 19.00% sodium nitrate.

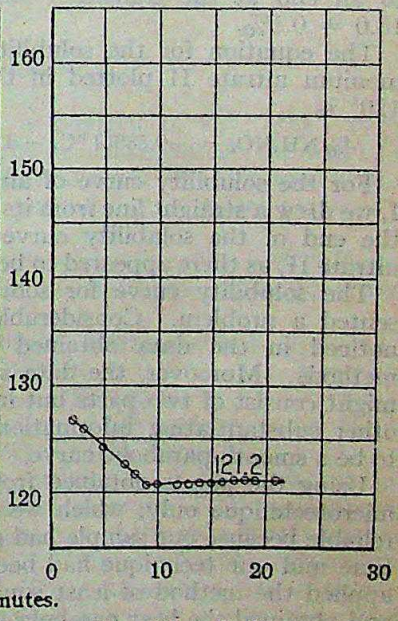

Fig. 3D.—Cooling curve for mixture containing 20.90% sodium nitrate.

(4) The authors wish to acknowledge their indebtedness to Professor Royal M. Frye of the Physics Department for his laborious and painstaking work in applying least square methods to our data.

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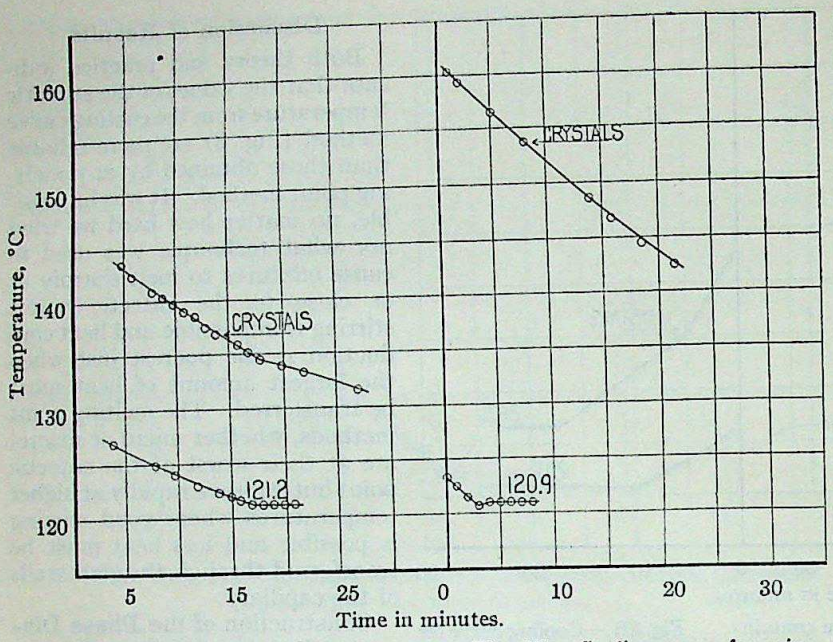

Fig. 3E.—Cooling curve for mixture containing 25.0% $NaNO_3$.

Fig. 3F.—Cooling curve for mixture containing 30.0% $NaNO_3$.

this range. By substituting the eutectic temperature (121.2°) in this equation we found the eutectic composition to be 21.0 ± 0.1%. Similarly, we found the composition at which this line comes to an end at the transition temperature to be 18.0 ± 0.1%.

The equation for the solubility curve of ammonium nitrate II plotted in the region above 120° is

$$\%\ NH_4NO_3 = -0.586(T°C. - 120) + 21.6563$$

For the solubility curve of ammonium nitrate I, we drew a straight line from its melting point to the end of the solubility curve for ammonium nitrate II, as there appeared to be no curvature.

The solubility curve for sodium nitrate presented a problem. Considerable deviation was noticed in the data obtained by the various methods. Moreover, the data suggested that it might consist of two parts but in absence of any other substantiating information we assumed it to be a smooth parabolic curve.

Using the points obtained from our improved microtechnique only, which we considered most reliable because our sample had dried the longest time and our technique had been perfected, we[4] applied the method of least squares to our data and obtained the best parabola that would intersect the solubility curve of ammonium nitrate II at 121.2°. The equation for this parabola plotted in the area above 120° is

$$\%\ NaNO_3 = 20.645 + 0.2556(T°C. - 120) + 0.0009737(T°C. - 120)^2$$

While this is not the best one for the points chosen, the sums of the squares of the deviations are very little greater than those of the best possible parabola that could be drawn through the points. It was felt that the physical chemistry of the problem required that the parabola chosen must meet the solubility curve of ammonium nitrate II at 121.2° and 21.0 ± 0.1% sodium nitrate, the eutectic point.

Remarks and Conclusions

From a consideration of our final curve in Fig. 1, we could not discover that the method of purification nor the time of drying of the sodium nitrate nor the size of the sample used in the determination made any difference. All techniques gave good results for the solubility curves of the two forms of ammonium nitrate. On the other hand the only one that

TABLE II

COMPARISON OF OUR RESULTS WITH THOSE OF EARLY AND LOWRY[1]

	Holmes and Revinson	Early and Lowry
Eutectic point, °C.	121.2	120.8
Eutectic composition, %	21.0 $NaNO_3$	20.5 $NaNO_3$
Transition temp., °C.	126.2	125.2
Transition compn., %	18.0	....

TABLE III

Techniques: S, standard microtechnique, symbol △ in Fig. 1; I, improved microtechnique, symbol ○ in Fig. 1; M, macrotechnique, symbol ⊗ in Fig. 1; C, cooling curve, symbol X in Fig. 1. When two letters are given, it means that two points coincided.

% $NaNO_3$	Temp. of disappearance of last crystal, °C.	Technique used	% $NaNO_3$	Temp. of disappearance of last crystal, °C.	Technique used
4.5	158.6	I	19.2	124.2	S
7.5	151.7	C	19.4	123.9	I
9.5	146.3	I	19.4	123.7	S
10.0	145.6	M	19.6	123.3	S
10.0	145.7	M	19.8	123.4	I
10.0	145.8	M	20.0	122.8	M
10.5	145.0	S	20.0	123.0	M
11.2	143.2	S	20.0	122.7	I
11.3	142.0	S	20.3	122.4	S
12.5	139.9	S	20.5	121.7	I
14.0	135.5	C	20.7	121.8	S. & M.
14.1	135.3	S	20.9	123.0	C
15.0	133.0	S	20.9	121.7	I
16.5	129.4	S	21.2	121.9	I
17.0	128.2	S	21.6	123.1	I
17.2	127.2	S	22.1	125.0	I
17.5	126.1	S	22.6	128.1	I
18.0	126.7	M. & M.	22.9	130.0	I
18.3	125.5	S	23.7	132.3	I
18.8	125.1	M	25.4	138.3	I
18.9	124.6	S	27.2	143.5	I
19.0	124.4	M	30.0	153.2	I
19.0	124.0	M	35.2	167.2	I

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gave consistent and reliable results on the sodium nitrate solubility curve was our improved microtechnique. Hence points obtained by this technique only were used in the plotting of this curve. For the sake of comparison, Early and Lowry's solubility curves for this system are included as dotted lines.

Figure 1 shows the solubility curves of ammonium nitrate to be slightly higher than Early and Lowry's[1] curves for the corresponding parts. The solubility curve of sodium nitrate is most interesting as it runs considerably above that of these authors. Although the curve was obtained by the method of least squares using only the data from our improved microtechnique, actually we determined seventeen other points by the other methods previously mentioned in this paper which, although scattered, support the data actually used rather well. Adding the distances above the curve and parallel to the temperature axis together and subtracting the sum of the distances below the curve from these and then dividing by the number of points, we find that the average deviation per point is 0.05° under the curve.

Summary

The system ammonium nitrate–sodium nitrate has been redetermined over the range 0–35% sodium nitrate. The solubility curves for the two forms of ammonium nitrate are linear while that for sodium nitrate is distinctly parabolic. An improved microtechnique has been developed that gives good results except near the eutectic point where all melting point methods are at their worst.

The eutectic temperature was found to be 121.2 ± 0.2° and the transition temperature to be 126.2 ± 0.2° by the cooling curve method which is most reliable for these temperatures. Using these points and applying the method of least squares to the curves, the eutectic composition was found to be 21.0 ± 0.1% sodium nitrate and the transition composition to be 18.0 ± 0.1%.

The method of purification of the sodium nitrate, the length of time of drying the materials and the size of the sample appear to have no effect on the temperature of disappearance of the last crystal on heating the melt.

BOSTON, MASS. RECEIVED DECEMBER 28, 1943

[CONTRIBUTION NO. 495 FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PITTSBURGH]

The Heat of Acetylation of α- and β-D-Glucose from the Heats of Combustion of the Pentaacetates[1]

BY THEODORE H. CLARKE AND G. STEGEMAN

In the investigation of the thermal properties of sugars which is being carried out in this Laboratory, some interest developed in the determination of the heats of combustion of α- and β-D-glucose pentaacetate, wherein the isomeric structural differences involve a much heavier radical than is present in the case of α- and β-D-glucose.

In this paper are presented the results of the combustion measurements, the specific heats of the compounds at 25°, and an approximate value of the density (used to correct the weight to the vacuum basis). From these and other data the heats of formation and the heats of acetylation were calculated.

A general description of the calorimetric equipment used in these determinations has been reported.[2] The energy equivalent of the calorimeter was determined by the use of benzoic acid obtained from the National Bureau of Standards. Sample No. 39e having a certified heat of combustion of 26428.4 international joules[3] or 6317.60 conventional cal. per gram mass *in vacuo*, was employed under the following conditions which are recommended.

The reaction is referred to 25°; the oxygen pressure should be 30 atmospheres; the weight of the sample should be 3 g. per liter of bomb volume; the bomb is to contain 3 g. of water per liter of bomb volume.

These conditions were adhered to with sufficient exactness so that no additional corrections were necessary.

The results of six determinations produced a value: C_{Sys} = 2772.95 ± 0.2 cal./°C. (precision error, ± 0.009%). The value was redetermined upon the completion of the measurements and no change was detected. The bomb has a volume of 0.516 liter and contained 1.5 ml. of water and oxygen at an initial pressure of 30 atmospheres. The initial temperature of the calorimeter was adjusted to 22.6 to 22.7° and the average temperature rise was 3.15°. The temperature rise in degrees was determined from the resistance *vs.* time readings as outlined by Dickinson.[4] Calculations of the heats of combustion were made following the method outlined by Dickinson which gives the heat of combustion at the final temperature reached in the combustion process. The necessary specific heats were employed to correct the values to 25°.

(1) This investigation was made possible by a grant from the Buhl Foundation, Pittsburgh, Pa.

(2) Clarke and Stegeman, THIS JOURNAL, 61, 1726 (1939).

(3) Jessup, *J. Research Natl. Bur. Standards*, 29, 247 (1942).

(4) Dickinson, *Bur. Standards Bull.*, 11, 189–257 (1915).

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TABLE I

PURIFICATION, DRYING AND COMBUSTION DATA

Sample	Recrystn. abs. alc.	Drying agent	Drying t for final 24 hr. at 0.01 mm.	True mass, g.	Δt cor., °C.	Heat evolved by sample, cal.	Cor. to 25°C., cal./g.	$-\Delta U_B/M$ 25°C., cal./g.	Δ
				α-D-Glucose pentaacetate					
1a	6	$CaCl_2$	40	1.96171	3.1567	8647.91	0.26	4408.09	1.49
1a	6	$CaCl_2$	40	1.97049	3.1676	8680.81	.26	4405.14	−1.46
1b	7	$CaCl_2$	40	1.95958	3.1520	8633.19	.23	4405.40	−1.20
2a	5	$CaCl_2$	60	1.95608	3.1484	8620.61	.21	4406.87	0.27
2a	5	$CaCl_2$	60	1.96266	3.1566	8651.03	.21	4407.59	.99
2b	6	Drierite	60	1.95811	3.1446	8628.93	.23	4406.53	− .07
			Mean = 4406.60 ± 0.97 cal./g. (Precision error = ±0.022%)						
				β-D-Glucose pentaacetate					
1a	4	$CaCl_2$	40	1.95218	3.1424	8622.26	0.24	4416.49	−0.63
1a	4	$CaCl_2$	40	1.95933	3.1628	8658.15	.26	4418.67	1.55
1b	5	$CaCl_2$	40	1.96374	3.1656	8678.26	.27	4418.98	1.86
2a	5	$CaCl_2$	60	1.96270	3.1601	8667.17	.24	4415.70	−1.42
2a	5	$CaCl_2$	60	1.96554	3.1646	8680.17	.24	4415.93	−1.19
2b	6	$CaCl_2$	60	1.96794	3.1731	8696.08	.24	4418.63	1.51
2b	6	Drierite	60	1.96290	3.1610	8667.57	.23	4415.46	−1.66
			Mean = 4417.12 ± 1.19 cal./g. (Precision error = ±0.027%)						

Heat Evolved by the Sample = $(C_{Sys.} + C_{Sample})\Delta t - q_{Fe} - q_{HNO_3} - q_{Igniter}$
(For α-isomer, sample 1a) = 8753.37 + 1.86 − 17.60 − 0.58 − 89.14

The defined calorie = 4.1833 int. j.[5] is the unit of energy employed. Deviations are recorded in terms of the precision error.[6] The optical rotations were determined at 20° using the proper dichromate filter to give D line illumination. A two-decimeter tube was employed. Melting points, obtained by the use of an Anschütz thermometer, were determined in the usual manner.[7]

Treatment of Samples.—Two samples each of α- and β-D-glucose pentaacetate were obtained from Eastman Kodak Co. and were given the following treatment:

The original samples were dissolved in and recrystallized from four to six times from absolute alcohol. It was the purpose of the treatment to produce a material whose heat of combustion would show no change following a recrystallization. For example, product 1a (Table I) was recrystallized six times. The sample was then divided and half of it was given an additional crystallization from absolute alcohol. This product is designated as 1b. The two products were then dried *in vacuo* over calcium chloride and drierite, respectively, at room temperature until a constant weight was obtained. The time interval was about twenty-four hours between weighings. An additional drying for twenty-four hours at 40° and in the case of a second sample at 60° and 0.01 mm. resulted in no further loss in weight.

The values for the optical rotations and melting points were reported by Hudson and Dale.[8] For the α-isomer the value of the optical rotation is listed as 96.7° for a 5.302% solution in benzene and a melting point of 112–113°. For the β-isomer the values listed are 2.2° for a 5.061% solution in benzene and a melting point of 132°. The products prepared in this Laboratory gave rotation values of 96.7° and 2.1°, and melting points of 112.7° and 132.0° for the α and β isomers, respectively.

Data.—The combustion data for the prepared products were obtained in the following manner. The first two determinations indicated as 1a were made on the sample which had received the smaller number of recrystallizations. The third and in one case a fourth determination indicated as 1b were made on the sample which had received an additional crystallization. The combustion data and the number of recrystallizations of each product are listed in Table I.

The derived results and certain other data are presented in Table II. The derived values are $-\Delta U_B$, the isothermal heat of combustion in kcal. per mole under the bomb conditions; $-\Delta U_R$, the heat of combustion in kcal. per mole with the reactants and products at a pressure of one atmosphere; $-\Delta H_R$, the isobaric heat of combustion at one atmosphere; and $-\Delta H^0_{f298.16}$, the heat of formation in kcal. per mole at one atmosphere and constant pressure. It was assumed that the product burned was completely oxidized to carbon dioxide and water. The heats of formation of the pentaacetates were calculated from the heats of combustion employing the values, −68,318.1[9] and −94,029.8[10] cal. per mole

TABLE II

DERIVED RESULTS AND OTHER DATA AT 25°

	α-isomer	β-isomer
Mol. wt.	390.336	390.336
$-\Delta U_B$, kcal./mole	1720.06 ± 0.38	1724.16 ± 0.46
$-\Delta U_R (= -\Delta H_R)$, kcal./mole	1718.62	1722.63
$-\Delta H^0_{f298.16}$, kcal./mole	537.36	533.25
$-d\Delta H/dt$, cal./°C./mole	109	108
C_p, cal./°C./g.	0.301	0.305

(5) Rossini and Deming, *J. Wash. Acad. Sci.*, **29**, No. 10, Oct. 15 (1939).

(6) Rossini, *Chem. Rev.*, **18**, 252 (1936).

(7) Bates, "Polarimetry, Saccharimetry and the Sugars," Circular of the National Bureau of Standards C440, page 547, or U. S. Pharmacopoeia XI, pp. 455–457.

(8) Hudson and Dale, THIS JOURNAL, **37**, 1264 (1915).

(9) Rossini, *J. Research Natl. Bur. Standards*, **22**, 407 (1939).

(10) Magnus and Jessup, *ibid.*, **21**, 1491 (1938).

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for the heats of formation of liquid water and gaseous carbon dioxide.

Discussion of Results

Karrer and Fioroni[11] reported a value for the heat of combustion of glucose pentaacetate. On the basis of the 1942 value for the heat of combustion of benzoic acid and in units of the defined calorie, Karrer and Fioroni's value is 1722.4 kcal. per mole for $-\Delta U_B$. It is not clearly stated that these authors were dealing with α-D-glucose pentaacetate, but this is assumed to be the case. No value has been reported previously for β-D-glucose pentaacetate.

The following equation indicates that the acetylation of glucose with acetic acid is an endothermic reaction for both isomers.

D-glucose (s) + 5 acetic acid (l) = D-glucose pentaacetate (s) + $5H_2O$ (l)

α-isomer, ΔH = 6.32 kcal./mole
β-isomer, ΔH = 8.92 kcal./mole

The use of acetic anhydride, however, produces the acetylation with a considerable evolution of energy.

D-Glucose (s) + 5/2 acetic anhydride (l) = D-glucose pentaacetate (s) + $5/2H_2O$ (l)

α-isomer, ΔH = −30.88 kcal./mole
β-isomer, ΔH = −28.29 kcal./mole

The rather large exothermic value for ΔH in the latter reaction suggests that the use of the acetic anhydride will produce a favorable yield of the pentaacetates since the ΔF value will probably have the same order of magnitude. This is in harmony with experience.

In making the indicated calculations the following thermal values were employed. The values employed have been recalculated by the authors in terms of the defined calorie and based on the 1942 value for the heat of combustion of benzoic acid. This places all values secured by and utilized by the authors on a comparable basis. The heat of combustion of α-D-glucose is given as $-\Delta H_R$ = 669.81 kcal./mole.[12] Employing the values for carbon dioxide and water previously mentioned, the heat of formation was calculated to be −304.28 kcal./mole. The authors used the value obtained by Huffman and Fox for the heat of combustion of β-D-glucose of $-\Delta H_R$ = 671.33 kcal. per mole. Huffman and Fox state that this value is not of the highest precision, but it is probably very near to the true value. While its agreement with a value calculated from solution data is good, Huffman and Fox point out that the same type of irregularities may have complicated both measurements. The calculated heat of formation from the data of Huffman and Fox for β-D-glucose is −302.76 kcal. per mole. The heat of formation of acetic acid was calculated to be −116.20 kcal./mole, from the heat of combustion reported by Schjanberg.[13] The heat of formation of acetic anhydride was calculated to be −149.20 kcal./mole from the heat of combustion by Thomsen.[14]

While the conversion of β- to α-D-glucose is accompanied by a heat evolution of about 1.5 kcal./mole,[12] the conversion of β- to α-D-glucose pentaacetate is accompanied by a heat evolution of about 4.0 kcal./mole. How much of this heat effect is to be attributed to the β- to α-shift about the saccharide carbon cannot be estimated at present on the basis of information now available

Summary

Values for the heats of combustion at 25° and 1 atm. pressure are given for α- and β-D-glucose pentaacetate. The value for the specific heat at 25° is also reported. From these and other data, the heats of formation and heats of acetylation were computed.

(11) Karrer and Fioroni, *Helv. Chim. Acta*, **6**, 396 (1923).

(12) Huffman and Fox, THIS JOURNAL, **60**, 1403 (1938).

(13) Schjanberg, *Svensk. Kem. Tids*, **44**, 227–231 (1932).

(14) Thomsen, *Z. physik. Chem.*, **52**, 343 (1905).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Mode of Action of Sulfonamides

BY IRVING M. KLOTZ

Since the discovery that *p*-aminobenzoic acid inhibits the action of sulfonamides,[1] attempts have been made to correlate the activity of these drugs with their structure. Some investigators[2] soon observed that the sulfonamide potency seemed to be directly related to the amount of the ionic form of the drug. The work of Cowles[3] indicated that sulfonamide activity increased as the acid *pK* of the drug decreased toward 7, but that further increase in acid strength resulted in diminished activity. A more comprehensive study by Bell and Roblin[4] has shown that bacteriostatic activity is a parabolic type of function of acid strength of the sulfonamide, with maximum potency being obtained, in a solution of *p*H 7, with drugs whose *pK*'s are approximately 6.7.

Inasmuch as current opinion attributes sulfonamide activity to the blocking of an enzyme system,[1] it was considered advisable to examine

(1) Woods, *Brit. J. Exptl. Path.*, **21**, 74 (1940).

(2) Fox and Rose, *Proc. Soc. Expll. Biol. Med.*, **50**, 142 (1942); Schmelkes, Wyss, Marks, Ludwig and Strandskov, *ibid.*, **50**, 145 (1942).

(3) Cowles, *Yale J. Biol. Med.*, **14**, 599 (1942).

(4) Bell and Roblin, THIS JOURNAL, **64**, 2905 (1942).

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the available data from the point of view of the general concepts of acidity and the law of mass action. A brief qualitative description of the approach has been given previously.[5] A detailed account of the treatment and results is presented in this paper.

Bacteriostatic Effect of Sulfonamides

Consider a buffer solution with a fixed hydrogen ion concentration, (H^+), a fixed total concentration, T, of the enzyme or protein, P, and a given total concentration, S, of the sulfonamide, HD. Since the buffer equilibrium and the ionization product of water are fixed and known we need consider only the following equilibria in the solution.

$$H^+ + D^- = HD \quad (1)$$
$$H^+ + P = PH^+ \quad (2)$$
$$P + OH^- = POH^- \quad (3)$$
$$P + D^- = PD^- \quad (4)$$

(For basic sulfonamides HD would be replaced by HD^+, D^- by D and PD^- by PD.) For each of these equilibria we may set up the corresponding mass law expression.

$$(H^+)(D^-)/(HD) = K_{HD} \quad (5)$$
$$(P)(H^+)/(PH^+) = K_{PH^+} \quad (6)$$
$$(P)(OH^-)/(POH^-) = K_{POH^-} \quad (7)$$
$$(P)(D^-)/(PD^-) = K_{PD^-} \quad (8)$$

Since the total concentration of sulfonamide must equal the sum of the concentrations of the various forms in which the drug is present in solution, we can write the equation

$$S = (D^-) + (HD) + (PD^-) \quad (9)$$

Similarly for the protein

$$T = (P) + (PH^+) + (POH^-) + (PD^-) \quad (10)$$

It is now possible to derive an expression for S in terms of variables having experimental significance. For convenience in algebraic manipulation, the following definitions have been made.

$$\frac{(D^-)}{(HD)} = \frac{K_{HD}}{(H^+)} = \lambda \quad (11)$$

$$1 + \frac{(H^+)}{K_{PH^+}} + \frac{(OH^-)}{K_{POH^-}} = \sigma \quad (12)$$

Using (6) and (7) to eliminate (PH^+) and (POH^-) from (10) and re-grouping terms one obtains the expression

$$T = \sigma(P) + (PD^-) \quad (13)$$

Similarly, making use of (11) and (8) one can eliminate (D^-) and (HD) in (9) and then use (13) to replace (P) in the resultant expression and obtain

$$S = \left[\left(1 + \frac{1}{\lambda}\right)\frac{\sigma K_{PD^-}}{T - (PD^-)} + 1\right](PD^-) \quad (14)$$

It seems reasonable to assume that bacteriostasis occurs when a given amount of the sulfonamide–enzyme complex, PD^-, has been formed. If S is the quantity of sulfonamide just sufficient to produce bacteriostasis, (PD^-) in (14) must be a constant. To find the drug of maximum potency at a given pH one must minimize S with respect to K_{HD} while (PD^-) and the pH are held constant.

$$\frac{\partial S}{\partial K_{HD}} = \frac{1}{(H^+)}\frac{\partial S}{\partial \lambda} = \frac{(PD^-)\,\sigma K_{PD^-}}{(H^+)[T - (PD^-)]}\left\{\left(1 + \frac{1}{\lambda}\right)\left(\frac{1}{K_{PD^-}}\right)\left(\frac{\partial K_{PD^-}}{\partial \lambda}\right) - \frac{1}{\lambda^2}\right\} = 0 \quad (15)$$

Inspection shows quickly that the factor within the brackets must be the vanishing one. Rearrangement of terms within the brackets and use of (11) to replace λ, leads to the following form of the minimizing condition

$$\frac{d \ln K_{PD^-}}{d \ln K_{HD}} = \frac{(H^+)}{K^0_{HD} + (H^+)} \quad (16)$$

where K^0_{HD} is the acid ionization constant of the drug which is active at a minimum S. Using the symbol f to represent the left-hand side of (16) and then converting the latter equation into its logarithmic form, one obtains

$$pK^0_{HD} = p\mathrm{H} - \log\left(\frac{1 - f}{f}\right) \quad (17)$$

Were f known for the bacterium–sulfonamide complex, one could calculate K^0_{HD}, and for *E. coli*, for example, the value so obtained could be compared with that observed by Bell and Roblin.[4] In the absence of the pertinent data, one can still test (17) by using the known value of pK^0_{HD}, calculating f for the *E. coli*-sulfonamide complex, and comparing the value so obtained with that which may be derived from the work of Davis and Wood[6] for the plasma protein–sulfonamide complex.

Bell and Roblin[4] found that a plot of bacteriostatic effectiveness versus pK for about a hundred sulfonamides in a solution at pH 7 showed a maximum at a pK of about 6.7. Substituting the appropriate values into (17) we find $f = 0.3$.

Davis and Wood,[6] using a dialysis technique, have determined the amounts of sulfonamide bound to plasma protein for a series of seven drugs. They have expressed their results "as the percentage of the value of the unbound drug which is bound per gram of protein."[6] If we designate this percentage by 100α, and in view of the approximate nature of the following calculation consider P directly proportional to T (see equation (13)), then

$$(\text{Bound drug}) = \alpha\sigma(P)\,(\text{Unbound drug}) \quad (18)$$

where the parentheses represent concentrations. Since the unbound drug may consist of HD and D^-, (18) becomes

$$(PD^-) = \alpha\sigma(P)[(HD) + (D^-)] \quad (19)$$

Making use of (5) one obtains

$$(PD^-) = \alpha\sigma(P)\left[(D^-)\frac{(H^+)}{K_{HD}} + (D^-)\right] \quad (20)$$

Since the pH of the solutions used by Davis and Wood was 7.4, one may insert the numerical value of (H^+) and transform (20) into

(5) Klotz, *Science*, **98**, 62 (1943).

(6) Davis and Wood, *Proc. Soc. Exptl. Biol. Med.*, **51**, 283 (1942).

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$$\frac{(PD^-)}{(P)(D^-)} = \alpha\sigma\left[\frac{4.0 \times 10^{-8}}{K_{HD}} + 1\right] \qquad (21)$$

The left-hand side of (21) is the inverse of K_{PD^-}, the dissociation constant of the serum protein–sulfonamide complex (P being expressed in grams, the other concentrations in moles). Hence, one may write

$$\sigma K_{PD^-} = \frac{1}{\alpha\left[\frac{4.0 \times 10^{-8}}{K_{HD}} + 1\right]} \qquad (22)$$

Using values of α given by Davis and Wood[6] and those of K_{HD} in the tables of Bell and Roblin[4] we have calculated σK_{PD^-} for six of the seven drugs for which data are available. (The results for sulfaguanidine have been omitted, because of the conflicting data in the literature on its acid ionization constant. If the acidity is actually too small to be measured in water then the ionization constant of the acid form of sulfaguanidine, HD^+, should be used in the following graph.) Figure 1 shows that a straight line is a sufficiently good approximation to the relationship between log (σK_{PD^-}) and log K_{HD}, for the available data are not very precise. The slope of the line is f and is equal to 0.5. Thus if there is any similarity in behavior of the proteins in *E. coli* to those in blood plasma, the value of 0.3 obtained for the former case is apparently a very reasonable one.

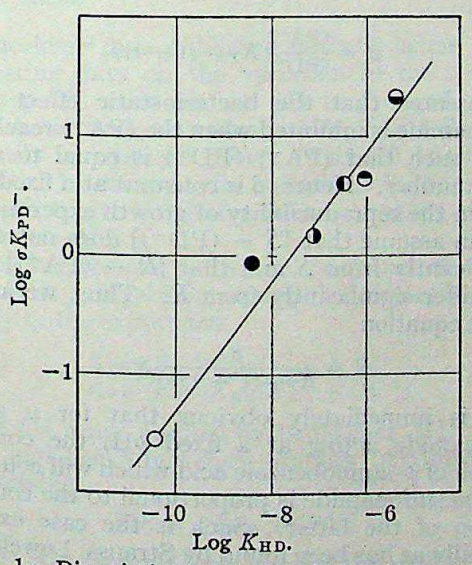

Fig. 1.—Dissociation constants of the plasma protein–sulfonamide complexes: ◒, sulfacetamide; ◓, sulfapyrazine; ◐, sulfadiazine; ◑, sulfathiazole; ●, sulfapyridine; ○, sulfanilamide.

Equation (17) also predicts that as the pH of the medium is increased, the pK of the sulfonamide of maximum potency should also increase. This is in agreement with the results reported by Cowles[3] for *E. coli*. His data, summarized in Fig. 2, show a definite displacement of the potency curves toward higher pK's as the pH is increased. Similar results have been obtained by Brueckner[7] for *Staph. aureus*, *B. subtilis* and *Ps. pyocyanea*.

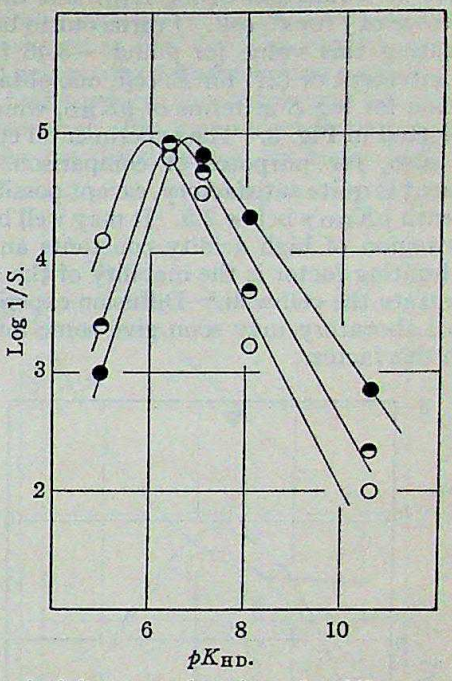

Fig. 2.—Activity as a function of acidity at various pH's for *E. coli*: ○, pH 6.0; ◓, pH 6.8; ●, pH 7.6.

These results indicate that a reasonable first approximation to the relationship between K_{PD^-} and K_{HD} would be

$$K_{PD^-} = kK_{HD}{}^{f} \qquad (23)$$

the integrated form of

$$\frac{d \ln K_{PD^-}}{d \ln K_{HD}} = f \qquad (24)$$

f and k being constants. This equation may be substituted into (14) to give an explicit expression for S, which in turn may be converted into logarithmic form

$$\log [S - (PD^-)] = \log k' + \log\left(1 + \frac{H^+}{K_{HD}}\right) + f \log K_{HD} \qquad (25)$$

k' is a constant for a fixed pH and is given by the equation

$$k' = \frac{\sigma k(PD^-)}{T - (PD^-)} \qquad (26)$$

In general, the amount of bound drug, (PD^-), will be small compared to the total amount of sulfonamide. Hence, we may use log S instead of log $[S - (PD^-)]$ in equation (25), and obtain the following expression after a simple rearrangement

$$\log S - \log\left(1 + \frac{H^+}{K_{HD}}\right) = \log k' + f \log K_{HD} \qquad (27)$$

This relationship affords an alternative and more reliable method of evaluating f from the entire range of data, as well as an opportunity for evaluating k'.

[7] C. Brueckner, *Yale J. Biol. Med.*, **15**, 813 (1943).

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Using the data of Bell and Roblin,[4] one can plot the sum of the terms on the left-hand side of equation (27) as a function of log K_{HD} and thus obtain a value of f for *E. coli*. f turns out to be 0.37. Substituting this value for f and -3.46 for log k', the intercept of (27) for *E. coli*, one obtains an expression for log S in terms of pK_{HD}, which has been plotted in Fig. 3. The experimental curve is shown also, for purposes of comparison. The agreement is quite satisfactory, except possibly for drugs with pK_{HD}'s below 3.5. It may well be that in this region of high acidity constants an additional limiting factor is the inability of the anions to penetrate the cell wall.[3] Diffusion experiments in this Laboratory may soon give some information on this factor.

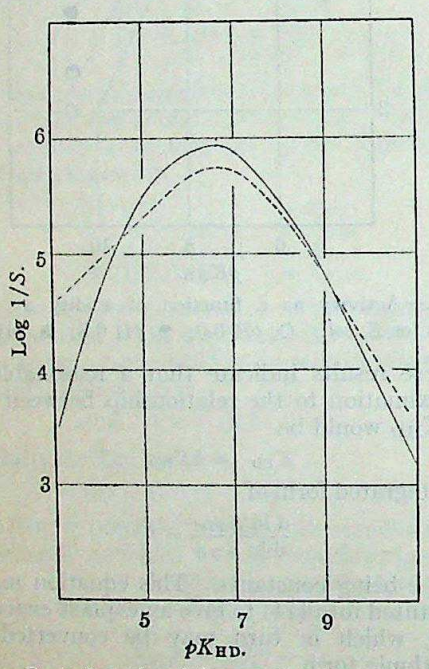

Fig. 3.—Bacteriostatic acivity as a function of acidity, for *E. coli*: - - -, calculated; ——, experimental.

Inhibition of Bacteriostasis by *p*-Aminobenzoic Acid

The inhibitory action of *p*-aminobenzoic acid on sulfonamide activity is also amenable to the mass law treatment. Consider a buffer solution containing a total concentration, T, of enzyme and a concentration, R, of *p*-aminobenzoic acid, HA. To this solution the sulfonamide is added until one reaches a concentration, S, beyond which bacteriostasis will set in. For the solution described one must consider two more equilibria in addition to those of equations (1) to (4).

$$H^+ + A^- = HA \quad (28)$$
$$P + A^- = PA^- \quad (29)$$

In addition to equations (5), (6), (7), (8) and (9) which the system must satisfy we can set up the following mass law expressions

$$(H^+)(A^-)/(HA) = K_{HA} \quad (30)$$
$$(P)(A^-)/(PA^-) = K_{PA^-} \quad (31)$$

and the following stoichiometric relationships

$$R = (A^-) + (HA) + (PA^-) \quad (32)$$
$$T = (P) + (PH^+) + (POH^-) + (PD^-) + (PA^-) \quad (33)$$

With these new equations one can derive a suitable expression for R. Rearrangement of (9) gives the equation

$$(D^-) = \frac{S - (PD^-)}{1 + 1/\lambda} \quad (34)$$

A similar expression, obviously, can be written for (A^-)

$$(A^-) = \frac{R - (PA^-)}{1 + 1/\rho} \quad (35)$$

where

$$\rho = \frac{K_{HA}}{(H^+)} = \frac{(A^-)}{(HA)} \quad (36)$$

The quotient of (34) by (35) becomes

$$\frac{(D^-)}{(A^-)} = \frac{S - (PD^-)}{R - (PA^-)} \frac{1 + 1/\rho}{1 + 1/\lambda} \quad (37)$$

Making use of (8) and (31) to obtain another expression for the ratio $(D^-)/(A^-)$

$$\frac{(D^-)}{(A^-)} = \frac{(PD^-)K_{PD^-}}{(PA^-)K_{PA^-}} \quad (38)$$

we can obtain the following equation

$$[R - (PA^-)] = \frac{\beta}{K_{PD^-}(1 + 1/\lambda)} [S - (PD^-)] \quad (39)$$

where

$$\beta = \frac{(PA^-)}{(PD^-)} K_{PA^-}(1 + 1/\rho) \quad (40)$$

We assume that the bacteriostatic effect of a sulfonamide is inhibited when the (PA^-) reaches a value such that $(PA^-)/(PD^-)$ is equal to some fixed number. Hence, β is constant at a fixed pH. Within the reproducibility of growth experiments, we can assume that $[S - (PD^-)]$ does not differ significantly from S and that $[R - (PA^-)]$ does not differ significantly from R. Thus, we arrive at the equation

$$R = \frac{\beta}{K_{PD^-}(1 + 1/\lambda)} S \quad (41)$$

It is immediately obvious that for a given sulfonamide acting at a fixed pH, the concentration of *p*-aminobenzoic acid which will counteract the sulfonamide is proportional to the concentration of the latter. Such is the case experimentally as has been found by Strauss, Lowell and Finland,[8] by Wood,[9] and by Brueckner.[7]

Furthermore, the following equation can be derived readily from (41) and (23)

$$\log \frac{R}{S} = \log \frac{\beta}{k} - 0.37 \log K_{HD} - \log \left(1 + \frac{H^+}{K_{HD}}\right) \quad (42)$$

The data of Rose and Fox[10] have been used to test this relationship. Only one constant, log β/k, has been evaluated from their data, and the calcu-

(8) Strauss, Lowell and Finland, *J. Clin. Invest.*, **20**, 189 (1941).
(9) Wood, *J. Exp. Med.*, **75**, 369 (1942).
(10) Rose and Fox, *Science*, **95**, 112 (1942).

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lated values of log R/S have been compared, in Fig. 4, with the logarithm of the observed ratios. The experimental points do not deviate from the theoretical line to a degree greater than the reproducibility of the results.

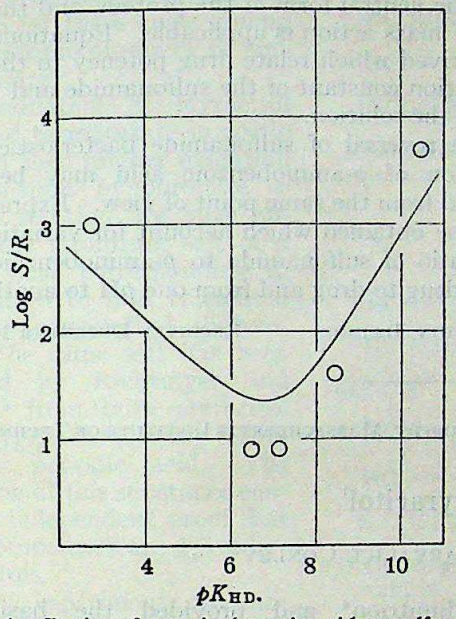

Fig. 4.—Ratios of *p*-aminobenzoic acid to sulfonamide. The solid line is the calculated curve, the circles the experimental points.

Brueckner[7] has published recently some very interesting data on the variation in the sulfonamide–p.a.b. ratio as the *p*H is changed. His work shows that for sulfanilamide, S/R falls continuously as the *p*H range from 6.5 to 8.9 is covered. In contrast, for sulfathiazole, S/R falls from *p*H 6.0 to 7.0 but remains constant thereafter until *p*H 8.9.

Such behavior is a direct consequence of equation (41). Algebraic manipulation leads one readily to the expression

$$\frac{S}{R} = \frac{K_{PD^-}(PD^-)K_{HA}[K_{HD} + (H^+)]}{K_{PA^-}(PA^-)K_{HD}[K_{HA} + (H^+)]} \qquad (43)$$

In the *p*H range studied by Brueckner, $(H^+) << K_{HA}$, and hence one may simplify (43) into the relationship

$$S/R = \epsilon[K_{HD} + (H^+)] \qquad (44)$$

where ϵ is a constant for a given sulfonamide. The reason for the very different behavior of sulfanilamide and sulfathiazole now becomes obvious. In the former case ($pK = 10.43$), $K_{HD} << (H^+)$ over the entire *p*H range, and hence S/R should be directly proportional to the (H^+) concentration. For sulfathiazole ($pK = 7.12$), however, (H^+) is larger than K_{HD} only for *p*H's quite a distance below 7, and at *p*H's appreciably above 7, (H^+) becomes negligible with respect to K_{HD}. Hence, S/R falls uniformly down to a *p*H of about 7, but beyond that becomes constant, because the right-hand side of (44) becomes essentially constant.

That the experimental data agree satisfactorily with the quantitative predictions of equation (44) is shown in Fig. 5. The results have been plotted in logarithmic fashion to expand the region of low hydrogen-ion concentration, but it should be noted that this form of representation also magnifies the discrepancies for small S/R ratios.

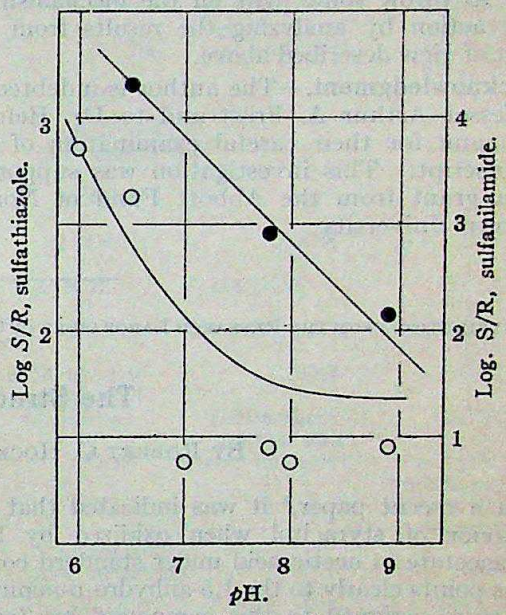

Fig. 5.—Ratios of *p*-aminobenzoic acid to sulfonamide as a function of *p*H for *Staph. aureus:* ●, sulfanilamide; ○, sulfathiazole; ——, calculated values.

Conclusion

These calculations show that on the basis of the simple assumption that sulfonamide inhibition of bacterial growth is due to a reversible combination between the basic molecule or anion and an enzyme one can account quantitatively for the various aspects of bacteriostasis and for the resumption of growth by the addition of *p*-aminobenzoic acid. Other more detailed hypotheses[3,4] are unnecessary, and do not give as comprehensive a picture as that derived from the law of mass action.

It should be pointed out, however, that the equations which have been derived may express only a necessary condition for activity but not a sufficient one. It is quite likely that some compounds combine with the enzyme and, nevertheless, are not chemotherapeutically active. Thus, Davis and Wood[6] have found that metanilamide and various inactive substituted sulfonamides, as well as active sulfonamides, combine with blood plasma proteins. Perhaps some structural factor is included in the conditions for activity, but the nature of this additional factor will probably be uncertain until the enzyme system or systems involved are identified clearly.

The equations derived here are based on very

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general fundamental principles which may be applicable to many other chemotherapeutic or biological actions. Anionic antiseptics in general, if their action is reversible, may fit equations analogous to those derived above. The equations describing the action of cationic reagents can also be derived very readily. When comprehensive quantitative data on drug activities in these various cases are available, it may be possible to throw some light on the mechanism of their action by analyzing the results from the point of view described above.

Acknowledgment.—The author is indebted to Professor Arthur A. Frost and to Dr. Helmut Gutmann for their careful examination of the manuscript. This investigation was supported by a grant from the Abbott Fund of Northwestern University.

Summary

The inhibition of bacterial growth by sulfonamides may be accounted for quantitatively by assuming that the action is due to a reversible combination between the basic form of the drug and the neutral form of the protein, and that the law of mass action is applicable. Equations may be derived which relate drug potency to the acid ionization constant of the sulfonamide and to the *p*H of the solution.

The reversal of sulfonamide bacteriostasis by addition of *p*-aminobenzoic acid may be considered from the same point of view. Expressions may be obtained which account for variations in the ratio of sulfonamide to *p*-aminobenzoic acid from drug to drug and from one *p*H to another.

EVANSTON, ILLINOIS RECEIVED DECEMBER 10, 1943

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 292]

The Structure of Styracitol[1]

BY ROBERT C. HOCKETT AND MARYALICE CONLEY[2]

In a recent paper,[3] it was indicated that the behavior of styracitol when oxidized by lead tetraacetate in acetic acid under standard conditions points clearly to the 1,5-anhydro-D-mannitol structure assigned to this compound by Zervas and Papadimitriou.[4] It was stated further that because the configuration of styracitol has been the subject of so much controversy[5] and because this oxidation method is relatively new, we would seek other evidence concerning the configuration of this substance. The rate-of-oxidation measurement would appear to offer an extremely simple and rapid method of solving such structural problems as this, provided that it can be depended upon invariably to give the right answer. Hence the establishment of the styracitol structure beyond question was essential to any extension of the oxidation procedure to other problems.

In 1931, Asahina and Takimoto[5] reported the complete methylation of this anhydro-alcohol and claimed the isolation of *d*-dimethoxysuccinic acid from the products of oxidation of tetramethyl styracitol by nitric acid. The formation of this acid is entirely incompatible with the 1,5-anhydromannitol structure assigned by Zervas and Papadimitriou[4] and provided the basis for Asahina's claim that styracitol is 1,5-anhydro-D-sorbitol. Zervas' synthesis of the compound[5] appears to establish the position of the ring and to limit the structural possibilities to the two alternatives mentioned.

We have undertaken to repeat the work of Asahina and Takimoto in order to discover the cause of this disagreement. Styracitol has been prepared synthetically by the method of Zervas.[5] Methylation by the procedure of West and Holden[6] yielded a tetramethyl ether of the expected composition and whose properties agreed well with those reported by the Japanese workers and by Freudenberg and Sheehan.[5] On oxidation of this ether with nitric acid, we obtained two substances that were definitely identified by means of well-known derivatives. These were oxalic acid and *l*-(−)-dimethoxysuccinic acid. None of the *d*-(+)-dimethoxysuccinic acid was found and the mother liquor left after separation of the two acids described above was somewhat levorotatory. Therefore, the experimental observations of Asahina and Takimoto were erroneous.

It should be noted that while the formation of the *d*-dimethoxysuccinic acid would be definitive, the levo isomer could be produced from either structure proposed for styracitol. Hence, the present work must be regarded as only removing a puzzling discrepancy and not in itself a structure proof. The isolation of *meso*-dimethoxysuccinic acid, D-arabotrimethoxyglutaric acid or of D-xylotrimethoxyglutaric acid would be necessary to complete the proof. Since, however, Richtmyer

(1) This paper is taken from a thesis submitted by Maryalice Conley to the graduate School of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy in January, 1943.

(2) Ellen H. Richards Memorial Fellow from 1939–1942. Now Mrs. James F. Moore, Pigments Department, E. I. du Pont de Nemours and Company, Newport, Delaware.

(3) Hockett, Dienes and Ramsden, THIS JOURNAL, **65**, 1474 (1943).

(4) Zervas and Papadimitriou, *Ber.*, **73**, 174 (1940).

(5) Asahina and Takimoto, *ibid.*, **64**, 2032 (1931); Freudenberg and Rogers, THIS JOURNAL, **59**, 1602 (1937); Freudenberg and Sheehan, *ibid.*, **62**, 559 (1940); *cf.* Zervas, *Ber.*, **63**, 1689 (1930).

(6) West and Holden, THIS JOURNAL, **56**, 930 (1934).

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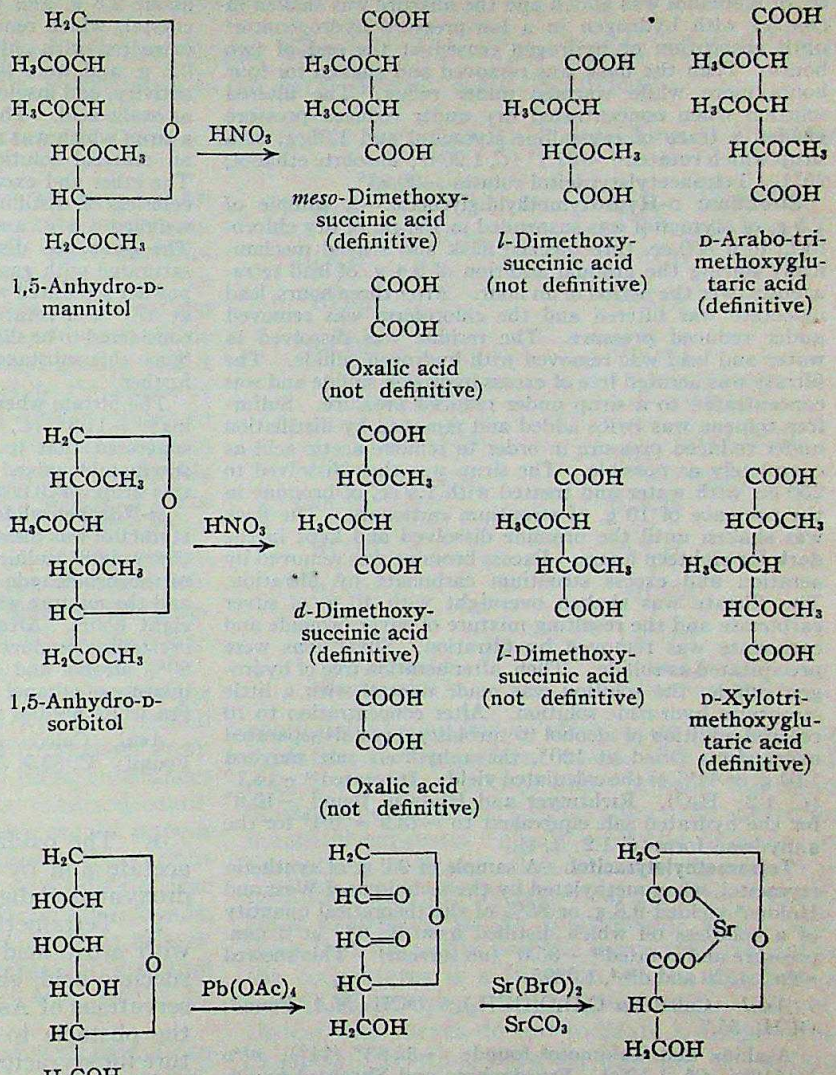
and Hudson have further confirmed the conclusions of Zervas and Papadimitriou first by demonstrating that polygalitol and styracitol are epimers and then by synthesis of polygalitol,[7] a search for these acids among the oxidation products is now unnecessary.

By oxidation of styracitol with lead tetraacetate in acetic acid and then further oxidation by strontium hypobromite in aqueous solution, we have obtained the strontium salt of a dibasic acid corresponding in composition to that calculated for D-hydroxymethyl diglycolate. The same salt has been obtained by Richtmyer and Hudson[8] from both styracitol and polygalitol following oxidation by periodic acid. The formation of this substance constitutes independent proof that these compounds are 1,5-anhydrohexitols.

In one experiment, we substituted Adams platinum oxide catalyst[9] in an alcoholic medium for palladium in acetic acid for the hydrogenation of tetraacetylhydroxyglucal to tetraacetyl-1,5-anhydrohexitol. The hydrogen absorption occurred normally but the main product was not tetraacetylstyracitol. Instead, a sirup of opposite sign of rotation[10] +37.1 (*C*, 1.2037; alcohol; 25°) was obtained. Richtmyer and Hudson[8] have reported a rotation of +38.9° (in $CHCl_3$) for tetraacetylpolygalitol. This experiment not only supports the claim that these two anhydro alcohols are epimers[11] but suggests the possibility of controlling the course of hydrogenation. This possibility will be explored further.

We report also the properties of a mono-*m*-nitrobenzylidenestyracitol prepared by Dr. Mortimer H. Nickerson, formerly of this Laboratory.[12]

POSSIBLE OXIDATION PRODUCTS OF TETRAMETHYLSTYRACITOL



Experimental

Tetraacetylstyracitol.—Tetraacetylhydroxyglucal was prepared by the method of Maurer and Mahn[13] and palladium black by the method of Willstätter and Waldschmidt-Leitz.[14] A sample of 13.2 g. (0.08 mole) of the former and 2.0 g. of the latter was placed with 100 cc. of pure acetic acid in a modified Adams hydrogenation apparatus[9] and shaken in contact with hydrogen at 23 lb. pressure. The pressure fell about 4.5 lb. (900 cc. of hydrogen absorbed) within a few hours (calcd. 895 cc.). After eight hours at room temperature, the catalyst was filtered and the solution was diluted with an equal volume of water. Three extractions with 75-cc. portions of chloroform were made and the combined extracts were washed free of acetic acid with 3% aqueous sodium bicarbonate, dried with sodium sulfate and concentrated under reduced pressure to a sirup.

Styracitol.—The sirupy tetraacetylstyracitol was dissolved in 40 cc. of dried methanol in which a tiny piece of sodium had been dissolved and the mixture was heated under reflux at 70° bath temperature for one hour. On cooling, 3.2 g. of styracitol separated, and 0.5 g. more was recovered after concentrating; yield, 57%. The product melted 154–155° and rotated[10] −50.9° (*C*, 0.4900; H_2O). Asahina gives m. p. 155° and rotation −49.9° (H_2O; 17°) as the constants for styracitol from *Styrax obassia*.

Hydrogenation of Tetraacetylhydroxyglucal with Platinum Catalyst.—Adams platinum oxide[9] (0.3 g.) was reduced with hydrogen in the presence of 10 cc. of dry

(7) Richtmyer and Hudson, THIS JOURNAL, **65**, 64 (1943); Richtmyer, Carr and Hudson, *ibid.*, **65**, 1477 (1943).
(8) Richtmyer and Hudson, *ibid.*, **65**, 64 (1943).
(9) Adams, "Organic Syntheses," Coll. Vol. I, New York, N. Y., 1941, p. 463; see also p. 61.
(10) All rotations cited in this paper are specific rotations of the D line of sodium at 20° unless exception is noted.
(11) Shinoda, Sato and Sato, *Ber.*, **65**, 1219 (1932).
(12) *Cf.* Bleyer, Diemair and Lix, *Z. Untersuch. Lebensm.*, **65**, 37–41 (1933).
(13) Maurer and Mahn, *Ber.*, **60**, 1316 (1927); Maurer, *ibid.*, **62**, 332 (1929).
(14) Willstätter and Waldschmidt-Leitz, *ibid.*, **54**, 130 (1921).

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methanol. Then 2 g. of acetylated hydroxyglucal in 40 cc. of methanol was added and the mixture was shaken in contact with hydrogen in a low-pressure hydrogenator[9] until absorption of hydrogen ceased at the end of two hours. Then the flask was removed and shaken for four hours more while warmed under reflux. The filtered solution when concentrated dry under reduced pressure yielded a trace of crystalline styracitol and 1.05 g. of a sirup which rotated[10] +37.1° (*C*, 1.2037; absolute ethanol; 25°). Tetraacetylstyracitol rotates −20.86°.

Strontium D-Hydroxymethyldiglycolate.—A sample of 1.5 g. of styracitol was suspended in 150 cc. of dry chloroform in a 500-cc. three-necked flask and stirred mechanically during the gradual addition of 9.4 g. of lead tetraacetate over the period of an hour. After three hours, lead diacetate was filtered and the chloroform was removed under reduced pressure. The residue was dissolved in water and lead was removed with hydrogen sulfide. The filtrate was aerated free of excess hydrogen sulfide and was concentrated to a sirup under reduced pressure. Sulfur-free toluene was twice added and removed by distillation under reduced pressure in order to remove acetic acid as completely as possible. The sirup was then dissolved to 250 cc. with water and treated with 1.5 cc. of bromine in the presence of 10 g. of strontium carbonate. The flask was shaken until the bromine dissolved and kept in the dark for eighteen hours. Excess bromine was removed by aeration and excess strontium carbonate by filtration. The filtrate was shaken overnight with 10 g. of silver carbonate and the resulting mixture of silver bromide and carbonate was removed by filtration. Silver ions were precipitated as sulfide. Then, after aeration free of hydrogen sulfide, the solution was made neutral with a little strontium hydroxide solution. After concentration to 10 cc. and addition of alcohol to turbidity, crystals separated overnight. Dried at 120°, the anhydrous salt weighed 1.04 g. or 44% of the calculated yield. It rotated[10] −14.1° (*C*, 1.2; H_2O). Richtmyer and Hudson[7] found −10.8° for the hydrated salt equivalent to −13.9 ± 0.4° for the anhydrous form (*C*, 1.2; 1, 4).

Tetramethylstyracitol.—A sample of 9.0 g. of synthetic styracitol, when methylated by the technique of West and Holden[6] yielded 9.8 g. or 85% of the theoretical quantity of a colorless oil which distilled from 88–93° at 2 mm. pressure and rotated[10] −35.0° (no solvent). This showed $n^{23}D$ 1.4520 and $d^{26.5}_4$ 1.0895.

Anal. Calcd. for $C_6H_8O(OCH_3)_4$: OCH_3, 56.4. Found: OCH_3, 55.7.

Asahina and Takimoto[5] found: −35.63° (14°); $n^{14}D$ 1.45162; d^{18}_4 1.1092. Freudenberg and Sheehan[5] found: −36.5°(23°); n^{25} 1.4520; d 1.0849.

Oxidation of Tetramethylstyracitol by Nitric Acid.—A mixture of 5 g. of tetramethylstyracitol and 33 cc. of concentrated nitric acid (d. 1.42) was digested on the steam-bath for five hours. Then the mixture was diluted with water and concentrated under reduced pressure to a sirup. Water was added and reëvaporated six times to remove most of the nitric acid. The residue weighed about 2.5 g. and was a mixture of sirup and large flat crystals which remained undissolved when the sirup was extracted with chloroform. The crystals weighed about 0.5 g. and were identified by melting point, optical inactivity, and insolubility of the calcium salt in acetic acid, as oxalic acid. The chloroform extract was evaporated to a sirup which was redissolved in dry ether and mixed with an ethereal solution of diazomethane[15] in large excess. The ether and excess reagent were evaporated to leave a colorless oil distilling from 70–85° at 0.5 mm. The liquid weighed 1.6 g. and rotated[10] −8.4° (*C*, 2.3; CH_3OH). The ester was dissolved in dry methanol (10 cc.) and saturated with gaseous ammonia. Almost at once a fine powder separated which was filtered and dried. It melted at 270° and rotated −78.2° (*C*, 0.0192; H_2O). It was considered to be slightly impure *l*-dimethoxysuccinamide.[16] Since this substance is not definitive, it was not purified further.

The filtrate when evaporated dry yielded a sirup rotating[10] −11.3° (*C*, 1.7288; CH_3OH). The low rotation suggested that it contained a little more *l*-dimethoxysuccinamide mixed with inactive material. The weight of this sirup was 0.6634 g.

***m*-Nitrobenzylidenestyracitol.**—A sample of 0.4 g. of styracitol was dissolved in 1 cc. of water and 1 cc. of 50% (by weight) sulfuric acid was added. Then 1 g. of *m*-nitrobenzaldehyde in 3.5 cc. of butyl acetate was added and the mixture was shaken mechanically for about forty-eight hours. After two more days in a refrigerator, a crystalline product was filtered, washed with 50% alcohol, 80% alcohol and dry ether. Recrystallized from a 1:3 mixture of ethanol and ethyl acetate, the substance formed fine white needles melting 175–175.5°.

Anal. Calcd. for $C_{13}H_{16}O_7N$: C, 52.6; H, 5.05. Found: C, 52.9, 52.5; H, 5.60, 5.72.

Summary

1. The oxidation of styracitol by lead tetraacetate and by strontium hypobromite to D-hydroxymethyl diglycolate is described.

2. Tetramethylstyracitol has been oxidized with nitric acid to oxalic acid and *l*-dimethoxysuccinic acid, showing that the experimental observations of Asahina are incorrect and removing the obstacle to acceptance of the Zervas structure for styracitol.

3. A *m*-nitrobenzylidene derivative of styracitol is described.

CAMBRIDGE, MASSACHUSETTS RECEIVED SEPTEMBER 29, 1943

(15) Arndt, "Organic Syntheses," **15**, 3 (1935).

(16) Purdie and Irvine, *J. Chem. Soc.*, 957 (1901).

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 293]

Lead Tetraacetate Oxidations in the Sugar Group. V.[1] The Rates of Oxidation of Open-Chain Polyalcohols in Dry Acetic Acid Solution[2]

BY ROBERT C. HOCKETT, MARGARET T. DIENES, HEWITT G. FLETCHER, JR.,[3] AND HUGH E. RAMSDEN

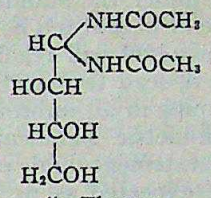
In a series of recent papers,[1,4] we have shown the behavior toward lead tetraacetate, of a number of vicinal triols in which the three carbinol groups form part of a six-membered ring. In such structures, the configurations of the carbon atoms are responsible for definite and predictable space relations among the hydroxyl groups and it has been found possible to correlate the shape of the oxidation curves obtained under standard conditions, with these space relations and certain other structural features. It appears possible from these correlations, to predict which of three types of oxidation curve will be found for a given glycopyranoside or, conversely, to deduce certain structural features from the type of curve observed. Moreover, the same considerations apply to anhydrides of polyalcohols[4] as to glycopyranosides of like ring type.

It now becomes of interest to determine the types of oxidation curve which will be obtained from open-chain polyalcohols with various numbers of hydroxyl groups, when these substances are oxidized under the same standardized conditions.[5] In such compounds there would appear to be no fixed space relations among the various hydroxyl groups because of the possibility of free rotation around the carbon-to-carbon single bonds. A definite relation between the amount of oxidant consumed and the number of carbinol groups present in an unbroken row, might be expected.

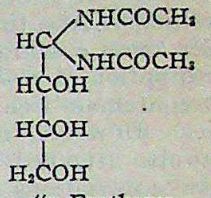
In the present paper, we report such oxidations of glycol, glycerol, erythritol, arabitol, mannitol, sorbitol and dulcitol. Another group of open-chain compounds is provided by the diacetamide derivatives of the sugars which are obtained in the course of the Wohl degradation.[6] Four of these were on hand from previous studies: "D-threose diacetamide,"[7] "D-erythrose diacetamide,"[8] "D-arabinose diacetamide"[9] and "D-lyxose diacetamide."[9]

The results are shown in two figures. First, it may be noted that the configuration of an open-chain polyalcohol has no effect upon the course of oxidation in the present cases. Mannitol, dulcitol and sorbitol do not differ beyond the limits of experimental error, so that the curve shown for mannitol expresses equally well the behavior of the other hexitols. Second, the curves when examined in a purely empirical manner, seem to show a striking family relationship which indicates that the position of the curve with respect to the coördinates is a function of the number of free COH groups in an *unbroken* series. Nevertheless, the curves do not indicate a simple stoichiometric relation between amount of oxidant used and the number of such alcohol groups. We have many evidences that the reactions are complex and do not accept for the oxidation of polyalcohols by lead tetraacetate in dry acetic acid, the simple mechanism proposed by Malaprade[10] for the oxidation of such polyols by periodic acid in water. One of the several disturbing elements is the oxidation of by-product formic acid by lead tetraacetate. The rate of this reaction, measured under comparable conditions, is recorded for comparison. Only glycol which produces no formic acid ceases to consume oxidant at the "theoretical" level of one mole.

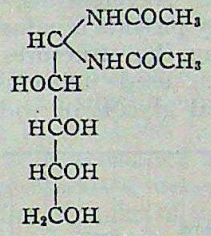
Nevertheless, if standard conditions are used, it is probable that open-chain polyalcohols containing the same number of C–OH groups in a series, will give similar curves so long as substituents of extreme difference in polarity are absent. A case in point is the striking similarity between the oxidation curves of glycerol and the two "tetrose diacetamides" on the one hand and



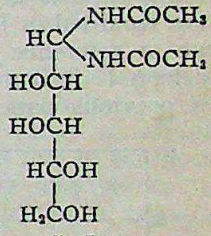
"D-Threose diacetamide"



"D-Erythrose diacetamide"



"D-Arabinose diacetamide"



"D-Lyxose diacetamide"

(1) Number IV of this series, THIS JOURNAL, 65, 1474 (1943).

(2) The material in this paper is taken in part from theses submitted by Margaret T. Dienes in May, 1940, by Hewitt G. Fletcher, Jr., in September, 1942, and by Hugh E. Ramsden in February, 1943, in partial fulfillment of the requirements for the degrees, respectively, of Bachelor of Science, Doctor of Philosophy and Bachelor of Science.

(3) Moore Fellow in Chemistry, 1941–1942.

(4) Hockett and Conley, THIS JOURNAL, 66, 464 (1944).

(5) *Cf.* Criegee, *Sits. Ges. Beförder. ges. Naturw. Marburg*, 69, 25 (1934).

(6) Wohl, *Ber.*, 32, 3666 (1899).

(7) Hockett, THIS JOURNAL, 57, 2265 (1935).

(8) Hockett and Maynard, *ibid.*, 61, 2111 (1939).

(9) Hockett, Deulofeu, Sedoff and Mendive, *ibid.*, 60, 278 (1938).

(10) Malaprade, *Compt. rend.*, 186, 382 (1928).

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those of erythritol and the two "pentose diacetamides" on the other.

Standard conditions, of course, must be chosen arbitrarily and such a choice has been recorded in the fourth paper of this series.[1] It may also be helpful to attempt an expression in words of the position where the curve of any polyol should be found if it is determined under the standard conditions: At a time between five and ten hours under these conditions, each polyol will reach a consumption of $n - 1$ moles of lead tetraacetate if it contains n free COH groups in an unbroken series. However, no stoichiometric significance is to be attached to this statement and progressive deviations are to be expected as we ascend the series since the excess of oxidant cannot be made infinite in practice. Nevertheless, the curves recorded in Fig. 1 may provide a valuable frame of reference in solving the structures of polyalcohol derivatives when used judiciously. In a previous paper[11] several glycols of widely differing structures were shown to be similar enough in behavior so that no difficulty would be experienced in identifying them as compounds containing one adjacent pair of C–OH groups.

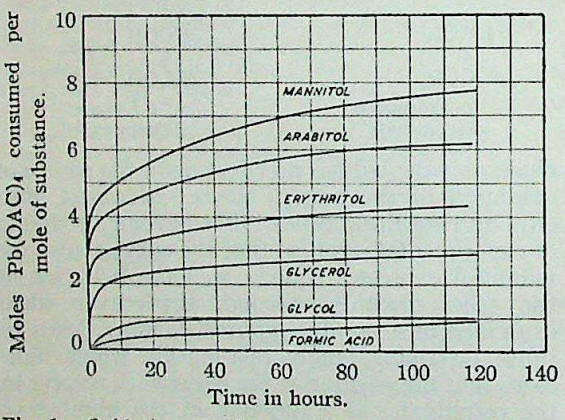

Fig. 1.—Oxidations in dry acetic acid: samples 0.0025 molar; ratio of oxidant, 15.2/1.

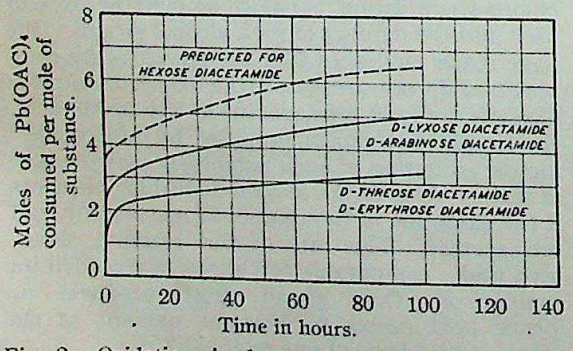

Fig. 2.—Oxidations in dry acetic acid: samples 0.0025 molar; ratio of oxidant, 15.2/1.

(11) Hockett and McClenahan, THIS JOURNAL, 61, 1670 (1939).

We are indebted to the Atlas Powder Company for samples of pure mannitol and sorbitol.

Experimental

Procedure.—These experiments were carried out under the exact conditions described by Hockett, Dienes and Ramsden.[1]

Materials

Mannitol and Sorbitol.—Highly pure samples were supplied by the Atlas Powder Company of Wilmington, Delaware.

Dulcitol.—Eastman Kodak Company material was used.

Arabitol.—This substance was prepared by deacetylation of the pure pentaacetate.[12]

Erythritol.—A sample from the Eastman Kodak Company was found to be highly pure.

Glycerol.—A sample of C. P. grade was fractionated in an efficient column under reduced pressure. Because of the hygroscopic nature of this substance, an analysis was made for water. A few drops were placed in a 25.0-cc. volumetric flask which was immediately stoppered and weighed. The glycerol was then dissolved and made up to the mark with dry acetic acid which had been analyzed for water by the method of Almy, Griffin and Wilcox.[13] An aliquot of the acetic acid solution was analyzed for water and the dry weight of the glycerol calculated. The water content of the glycerol was found to be only 1.32%. Then a volume sufficient to give the desired sample weight of glycerol (0.0230 g.) was measured from a dry buret into a 100.0-cc. volumetric flask. The oxidation was carried out as usual.

Glycol.—Eastman C. P. ethylene glycol was fractionated under reduced pressure.

Formic Acid.—Mallinckrodt Analytical Reagent grade of specific gravity 1.20, containing about 13% water, was allowed to stand in contact with anhydrous oxalic acid for several days and was then decanted and distilled under reduced pressure. The distillate was kept for several days in contact with boric anhydride and then distilled from boric anhydride.[14]

Summary

1. The oxidation of open-chain polyalcohols by lead tetraacetate in dry acetic acid under standard conditions, has been measured.

2. An empirical relation between the position of the oxidation curve and the number of carbinol groups present in a continuous chain is stated.

3. The lack of effect of configuration on the oxidation behavior of open-chain polyalcohols is noted.

4. The action of lead tetraacetate upon dry formic acid under the standard conditions is described.

CAMBRIDGE, MASS. RECEIVED SEPTEMBER 29, 1943

(12) Hockett and Hudson, *ibid.*, 57, 1753 (1935).

(13) Almy, Griffin and Wilcox. *Ind. Eng. Chem., Anal. Ed.*, 12, 392 (1940).

(14) Schlesinger, THIS JOURNAL, 36, 1589 (1914).

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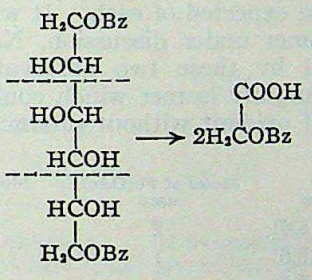
[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, NO. 294]

Lead Tetraacetate Oxidations in the Sugar Group. VI.[1] The Structures of Certain Di- and Tribenzoates of D-Sorbitol and D-Mannitol

BY ROBERT C. HOCKETT AND HEWITT G. FLETCHER, JR.[2]

In 1898, Einhorn and Hollandt[3] described a dibenzoyl mannitol prepared by the action of a limited amount of benzoyl chloride upon mannitol in pyridine solution. Some years later, Ohle and collaborators[4] assigned these benzoyl groups to the four and five positions since oxidation with neutral potassium permanganate yielded a product which they identified as dibenzoyl mesotartaric acid. Brigl and Grüner[5] showed that this identification was erroneous and that the oxidation product is benzoylglycolic acid. Not only was the product compared directly with synthetic benzoylglycolic acid and dibenzoyl mesotartaric acid, but crystalline glycolic acid was isolated after debenzoylation. Since, moreover, the dibenzoylmannitol sample appeared to be a pure chemical individual and since the yield of benzoylglycolic acid was more than 50% of the theoretical, the benzoyl groups were assigned to the one *and* six positions.



This structure implies that the primary hydroxyl groups are acylated much more rapidly than the more numerous secondary ones, an observation which is entirely in accord with many others to the same effect which have been made in recent years.[6]

In 1932, Alexander Müller[7] isolated a dibenzoyl-D-sorbitol by acylating D-sorbitol under similar conditions. It has been assumed without direct proof that this is also a 1,6-dibenzoate, because of the now general view that the primary alcohol groups will react first. A confirmation of this assumption is to be desired.

In a previous publication,[1] we have shown the behavior of open-chain polyalchohols when they are oxidized by lead tetraacetate under certain standard conditions. Similar oxidation of partially esterified polyalcohols should provide information concerning their structures very rapidly, easily and with samples on a micro scale. The observation of whether or not formaldehyde is produced and the number of moles of this aldehyde, is also carried out very easily and with very small samples.[8]

Fifteen isomeric D-sorbitol diesters are possible if the two substituent groups are identical. The table below shows how many moles of oxidant should be consumed by each in five to ten hours under standard conditions. It also shows the number of moles of formaldehyde to be expected from each.

No.	Isomer	Moles of $Pb(OAc)_4$ used	Moles of HCHO produced
1	1,2	3	1
2	1,3	2	1
3	1,4	2	1
4	1,5	2	0
5	1,6	3	0
6	2,3	2	1
7	2,4	1	1
8	2,5	1	0
9	2,6	2	0
10	3,4	2	2
11	3,5	1	1
12	3,6	2	1
13	4,5	2	1
14	4,6	2	1
15	5,6	3	1

These two experimental observations alone, will positively identify isomers no. 5, 8 and 10 since they give unique combinations of oxidant consumption and formaldehyde production. Three other combinations occur twice each so that in these six cases, the two experiments will limit the possible structures to two (4 and 9, 7 and 11, 1 and 15). Choice between the two alternatives will require further observations upon the oxidation products and this may not always be possible on a micro scale. Finally, the remaining combination occurs six times so that distinction of the corresponding isomers (2, 3, 6, 12, 13, 14) will be relatively difficult.

We succeeded in preparing a dibenzoyl-D-sorbitol with the properties reported by Müller. On oxidation it gave no trace of formaldehyde. Under standard conditions, it consumed just

(1) Number V of this series, THIS JOURNAL, 66, 467 (1944).

(2) The material in this paper is taken from a thesis submitted by Hewitt G. Fletcher, Jr., to the Graduate School of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy in September, 1942. Mr. Fletcher was Moore Fellow in Chemistry during 1941–1942.

(3) Einhorn and Hollandt, *Ann.*, 301, 95 (1898); *cf.* Fischer, *Ber.*, 48, 266 (1915).

(4) Ohle, *et al.*, *Ber.*, 62, 2982 (1929).

(5) Brigl and Grüner, *ibid.*, 65, 641 (1932).

(6) Compton, THIS JOURNAL, 60, 395 (1938); Cramer and Purves, *ibid.*, 61, 3458 (1939); Hockett and Downing, *ibid.*, 64, 2463 (1942).

(7) Müller, *Ber.*, 65, 1058 (1932).

(8) *Cf.* Criegee, *ibid.*, 64, 260 (1931); *Ann.*, 495, 211 (1932).

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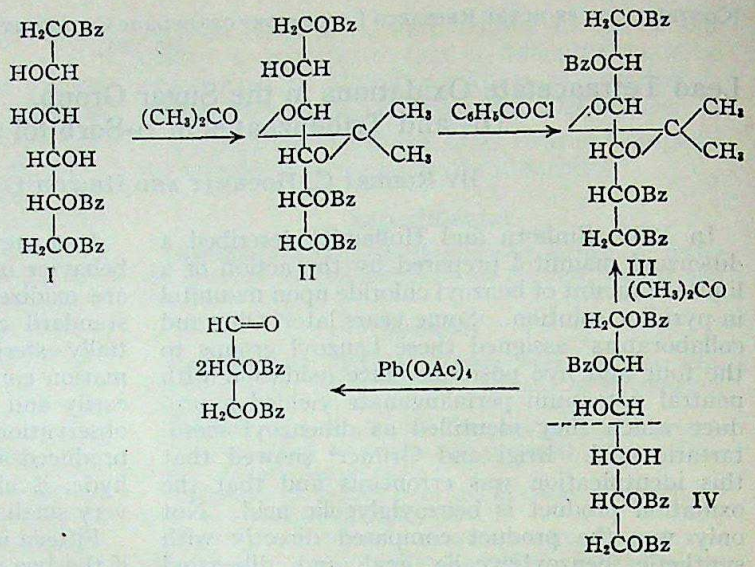
under three moles of oxidant in the critical time (Fig. 1). Therefore, $n - 1 = 3$ and $n = 4$ carbinol groups in an unbroken series. This behavior is very much like that of erythritol whose oxidation curve is plotted in Fig. 1 for comparison. Thus the 1,6 structure is confirmed.

As a by-product in the preparation of 1,6-dibenzoyl mannitol, Ohle and collaborators[4] obtained a tribenzoyl mannitol which melted at 162° and rotated[9] −18.0° in acetone (*C*, 1.721) or −44.0° in pyridine (*C*, 1.862). This compound was considered by Brigl and Gruner to be 1,2,6-tribenzoylmannitol[10] (which is identical with the 1,5,6 isomer). Their evidence is as follows: This tribenzoyl mannitol (I) combines with acetone to give a sirupy monoacetone derivative (II) whose one remaining hydroxyl group may be benzoylated to give the known 1,2;5,6-tetrabenzoyl-3,4-isopropylidene-D-mannitol (III). The structure of the last has been proved by the observation that it can be made by combining acetone with 1,2;5,6-tetrabenzoyl-D-mannitol (IV) whose structure in turn was proved by its nearly quantitative oxidation by lead tetraacetate to dibenzoyl-D-glyceric aldehyde.[11] These deductions are valid only if there is no shift of benzoyl groups.



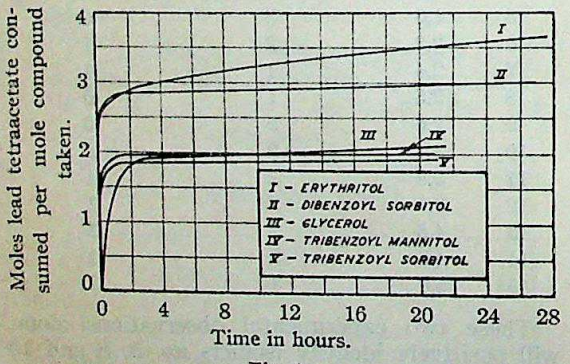


Fig. 1.

It should be noted that this evidence is not quite sufficient to *prove* the structure of the tribenzoyl-mannitol since a 2,5,6-tribenzoate could give the same reactions. The 1,2,6 structure is the more probable of the two possibilities since it is reasonable to suppose that the tribenzoate is formed by further acylation of the predominating 1,6-dibenzoyl-mannitol. However, an oxidation by lead tetraacetate under standard conditions can settle this point definitely since a 1,5,6 ester should behave like glycerol while a 2,5,6 ester would behave more like ethylene glycol. The oxidation curve plotted on Fig. 1 shows unequivocally that the 1,5,6 (1,2,6) formulation is correct.

The following table, showing all the possible trisubstituted mannitols in which the three substituting groups are alike, indicates the lead tetraacetate consumption and the formaldehyde production to be expected of each. It will be noted that the isomer under discussion, No. 4, could be identified by these two observations alone since it is the only isomer which could consume two moles of oxidant without producing formaldehyde.

No.	Isomer	Moles of $Pb(OAc)_4$ used	Moles of HCHO produced
1	1,2,3 (4,5,6)	2	1
2	1,2,4 (3,5,6)	1	1
3	1,2,5 (2,5,6)	1	0
+4	1,2,6 (1,5,6)	2	0
5	1,3,4 (3,4,6)	1	1
6	1,3,5 (2,4,6)	0	0
7	1,3,6 (1,4,6)	1	0
8	1,4,5 (2,3,6)	1	0
9	2,4,5 (2,3,5)	0	0
10	2,3,4 (3,4,5)	1	1

In the course of our repreparation of 1,6 dibenzoyl-D-sorbitol we obtained as a by-product, a small quantity of a tribenzoyl-D-sorbitol which apparently has not been described before. The possible number of trisubstituted D-sorbitols is twice as great as for trisubstituted mannitols since the sorbitol molecule is less symmetrical. These isomers are listed with their expected behavior.

No.	Isomer	Moles of $Pb(OAc)_4$ used	Moles of HCHO produced
1	1,2,3	2	1
2	1,2,4	1	1
3	1,2,5	1	0
+4	1,2,6	2	0
5	1,3,4	1	1

(9) All rotations cited in this paper refer to specific rotations of the D line of sodium at 20° unless otherwise stated.

(10) Brigl and Grüner, *Ber.*, **66**, 931 (1933).

(11) Fischer, see ref. 3; Criegee, *Ber.*, **64**, 260 (1931); *Ann.*, **481**, 268 (1930).

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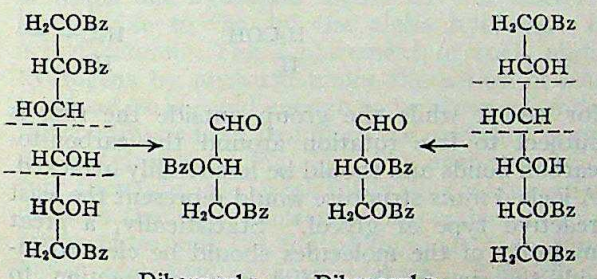
No.	Isomer	Moles of $Pb(OAc)_4$ used	Moles of HCHO produced
6	1,3,5	0	0
7	1,3,6	1	0
8	1,4,5	1	0
9	1,4,6	1	0
10	1,5,6	2	0
11	2,3,4	1	1
12	2,3,5	0	0
13	2,3,6	1	0
14	2,4,5	0	0
15	2,4,6	0	0
16	2,5,6	1	0
17	3,4,5	1	1
18	3,4,6	1	1
19	3,5,6	1	1
20	4,5,6	2	1

No formaldehyde was obtained when tribenzoyl-D-sorbitol was oxidized and the consumption of oxidant was two moles at the critical time (Fig. 1). The structure therefore is limited to 4 or 10.

To distinguish between these two possibilities it is only necessary to determine whether this tribenzoate yields dibenzoyl-D-glyceric aldehyde or dibenzoyl-L-glyceric aldehyde on oxidation with lead tetraacetate.



1,2,6-Ester | Dibenzoyl-L-glyceraldehyde | Dibenzoyl-D-glyceraldehyde | 1,5,6-Ester

The D-form of this reference compound is well-known from the work of Brigl and Grüner[10] and has a rotation[9] of $-35.6°$ in benzene. It follows that the L-form would rotate $+35.6°$. Since an oxidation by lead tetraacetate would be expected to destroy all other asymmetric centers and to yield the triose derivative almost quantitatively, it should suffice to oxidize a weighed sample of tribenzoyl hexitol with lead tetraacetate in a definite volume of benzene solution and to observe the final rotation attained. This plan was first tried out upon 1,2,6-tribenzoylmannitol which should yield dibenzoyl-D-glyceraldehyde mole for mole. The reading obtained was $-0.21°$ in a 2-dm. tube as compared with $-0.22°$ calculated. A similar oxidation was then performed upon an equal weight of tribenzoylsorbitol and a final rotation of $+0.22°$ was recorded. This must be due to the L-form of dibenzoylglyceraldehyde and establishes the structure of the original compound as 1,2,6-tribenzoyl-D-sorbitol.

We wish to express our indebtedness to the Atlas Powder Company of Wilmington, Delaware, for samples of pure mannitol and sorbitol.

Experimental

1,6-Dibenzoyl-D-mannitol.—Prepared as described by Brigl and Grüner,[5] our product was obtained in 29.1% yield and melted 182.3–183.3° (cor.).

1,2,6-Tribenzoyl-D-mannitol.—The alcoholic mother liquors from preparation of the 1,6-dibenzoate deposited crystals on standing in the refrigerator. Recrystallized from alcohol, these formed large needles melting sharply at 166.5–167.0° (cor.) and rotating[6] $-43.7°$ (*C*, 1.0096; pyridine). A melting point of 163° and rotation of $-44°$ have been recorded.[4]

1,6-Dibenzoyl-D-sorbitol.—Thirty grams of pure sorbitol was dissolved in 600 cc. of pyridine at 80° and, after cooling to 10°, the rapidly stirred solution was treated with 36 cc. of benzoyl chloride added dropwise over the period of one and one-half hours. After two hours of standing at 20°, about two-thirds of the pyridine was removed under reduced pressure at 50° and the remaining solution was poured in a thin stream into 500 cc. of water with rapid stirring. Overnight in an ice-chest, the precipitated sirup became largely crystalline. Concentration of wash waters *in vacuo* yielded a few grams more material. The combined precipitates were dissolved in 120 cc. of boiling 95% alcohol which, on cooling, deposited 18.6 g. of crude 1,6-dibenzoylsorbitol. Recrystallization from 70 cc. of boiling alcohol gave 16.8 g. of white crystals melting at 142.2–143.2° (cor.); yield, 26.2%. They rotated $+1.11°$ (*C*, 0.9006; pyridine). Müller[7] reported a melting point of 141° and a rotation in pyridine of $+1.85°$.

1,2,6-Tribenzoyl-D-sorbitol.—The combined mother liquors from the dibenzoate were treated with water to the turbid point. On standing first at room temperature and then in the ice-chest, there separated 8.8 g. of microcrystalline material which was much more soluble in alcohol than the dibenzoate. This product consisted of two or more difficultly-separable compounds (possibly the 1,5,6 isomer was present). By fractionation from hot toluene and then from chloroform, 2.8 g. of 1,6-dibenzoate was removed. The residue was recrystallized from alcohol several times by addition of water and attained a maximum melting point at 147.7–148.3° (cor.). The final yield was 0.125 g. The compound rotated $-11.1°$ (*C*, 1.080; $CHCl_3$; 24.8°).

Anal. Calcd. for $C_{27}H_{26}O_9$: C, 65.58; H, 5.30. Found: C, 65.3, 65.5; H, 5.87, 5.67.

Rates of Oxidation of 1,6-Dibenzoylsorbitol, 1,2,6-Tribenzoylsorbitol and 1,2,6-Tribenzoylmannitol.—Exactly the conditions described by Hockett, Dienes and Ramsden[12] were used except that the molar concentration of samples was exactly twice the now-established standard of 0.0025 *M*. This difference in concentration has only a very small effect upon the oxidation rates of polyalcohols.

Oxidation of 1,2,6-Tribenzoyl-mannitol to Dibenzoyl-D-glyceric-aldehyde.—A sample of 0.0261 g. was suspended in 4.3415 g. of sulfur-free benzene saturated with water. With shaking 0.0521 g. (a 2.23 molar ratio) of crystalline lead tetraacetate was added. The mixture was shaken a minute and then left for twenty-four hours at room temperature. At 20°, the clear supernatant liquid then rotated $-0.21°$ in a 2-dm. tube. A rotation of $-0.22°$ would be expected if conversion to the glyceraldehyde ester was quantitative.

Oxidation of 1,2,6-Tribenzoyl-sorbitol to Dibenzoyl-L-glyceric-aldehyde.—A similar experiment was made using 0.0250 g. of tribenzoylsorbitol, 4.3434 g. of damp benzene and 0.0510 g. (2.28 molar ratio) of lead tetraacetate. At the end of thirty-six hours the supernatant liquid rotated $+0.22°$ in a 2-dm. tube. Calculation, assuming quantitative oxidation to dibenzoyl-L-glyceraldehyde of specific rotation $+35.6°$, predicts $+0.22°$.

Summary

1. The compounds previously described as

(12) Hockett, Dienes and Ramsden, THIS JOURNAL, 65, 1474 (1943).

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1,6 - dibenzoyl - D - sorbitol, 1,6 - dibenzoyl - D - mannitol and 1,2,6-tribenzoyl-D-mannitol by other workers have been reprepared.

2. The assigned structures have been tested by oxidation of the compounds with lead tetraacetate under standard conditions and found correct.

3. A new tribenzoate of D-sorbitol has been described and its structure shown to be 1,2,6 by oxidation with lead tetraacetate.

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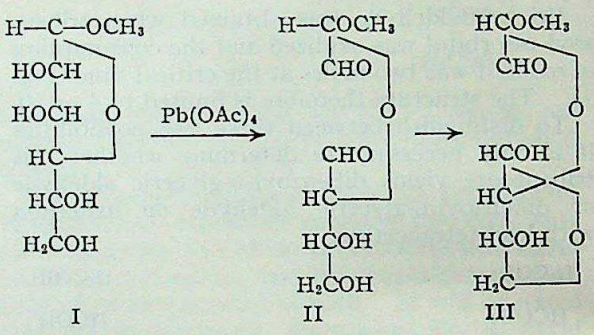
Lead Tetraacetate Oxidations in the Sugar Group. VII.[1] The Oxidation Rates of Ethyl β-D-Galactofuranoside, Methyl α-D-Mannofuranoside and 3,6-Anhydro-D-sorbitol[2]

BY ROBERT C. HOCKETT, MORTIMER H. NICKERSON AND WILLIAM H. REEDER, III

In previous publications,[1] we have described the behavior of two types of compounds toward lead tetraacetate in dry acetic acid under standard conditions: (1) polyalcohols with a six-membered glycoside or ether ring and (2) open-chain polyalcohols. We have also demonstrated the use of lead tetraacetate oxidations in establishing the structures of new compounds of these classes.[3] Interest now centers upon the behavior of glycofuranosides and anhydroalcohols with a five-membered ether ring.

Criegee[4] has already reported some work upon oxidation of furanosides and of aldonic acid gamma lactones by this agent. In particular, he has pointed out the impossibility of obtaining formaldehyde by the cleavage of hexo-pyranosides whereas certain furanosides will produce this easily identified aldehyde. He has also performed certain kinetic experiments and has assigned second-order rate constants to some of the reactions. However, since many lead tetraacetate oxidations have two or more distinct successive stages, we have found it instructive to record the oxidation rates in graphical form and have preferred to use a large excess of the oxidizing agent in order to render some of the reactions pseudo-unimolecular.

Hence, we have repeated the oxidation of methyl α-D-mannofuranoside under the conditions that have been established as standard in this Laboratory.[5] An inspection of the structural formula (I) permits prediction of the type of curve to be expected, on the basis of generalizations previously stated.[5] Thus, of the two glycol structures which can be attacked, the one inside the ring is held rigidly in a *cis* position favorable



I II III

for attack while the group outside the ring is subject to free rotation around the carbon-to-carbon bonds and should be less readily attacked. A locked *trans* structure would represent the least reactive type of glycol.[6] Statistically, a great majority of the molecules should be cleaved inside the ring in the initial stage of reaction, to give the dialdehyde marked II. The latter, being a *gamma* hydroxy-aldehyde, would be expected to rearrange to a cyclic hemiacetal, establishing an equilibrium in which the proportion of open-chain isomer would be exceedingly small but finite.[4,7] The cyclic hemiacetal itself should be unoxidized but the small proportion of free aldehyde present would account for a slow further oxidation.

The over-all prediction, therefore, is (1) the consumption of one molar equivalent of lead tetraacetate very rapidly, followed by a sharp break in the curve and a very much slower subsequent oxidation; (2) formation of only a trace of formaldehyde.[4] The figure shows that the first prediction is very strikingly realized.

The predicted behavior of ethyl β-D-galactofuranoside is quite different. Examination of the structure shows two positions initially available for attack. Since the one inside the ring is locked in the unfavorable *trans* position, it appears that, statistically, most of the molecules would first be attacked outside the ring. This con-

(1) Number VI of this series, THIS JOURNAL, 66, 469 (1944).

(2) This paper includes material from a thesis presented by Mortimer H. Nickerson to the Graduate School of the Massachusetts Institute of Technology in May, 1940, in partial fulfillment of the requirements for the degree of Doctor of Philosophy. It was read before the Division of Organic Chemistry at the Detroit Meeting of the American Chemical Society, September, 1940.

(3) Hockett and Conley, THIS JOURNAL, 66, 464 (1944).

(4) Criegee, *Ann.*, 495, 211 (1932).

(5) Hockett, Dienes and Ramsden, THIS JOURNAL, 65, 1474 (1943).

(6) *Cf.* Criegee, *Ann.*, 507, 159 (1933).

(7) *Cf.* Hockett and McClenahan, THIS JOURNAL, 60, 2061 (1938).

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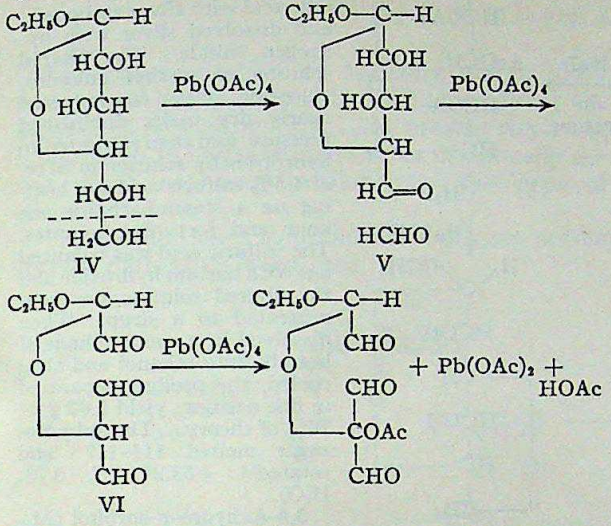
ception leads to prediction of a nearly equi-molar production of formaldehyde along with an aldehyde V. The latter, having an unbroken ring, is



sterically impeded in forming a cyclic hemiacetal. Therefore, further oxidation may proceed at the 2,3 position to give a hypothetical trialdehyde VI in which one hydrogen should have an activity comparable to that of the alpha hydrogens in acetylacetone. The replacement of such alpha hydrogens by acetoxyl under the action of lead tetraacetate is rapid enough to be observed under the conditions used (compare the oxidation curve for acetyl acetone Fig. 1). The over-all prediction, therefore, is (1) a relatively slow consumption of more than two molecular proportions of lead tetraacetate and (2) the production of an equimolar quantity of formaldehyde. The figure shows confirmation of the first prediction and formaldehyde was found qualitatively.

A consideration of the possible aldohexofuranosides suggests that they may all fall into one or the other of two groups with respect to their oxidation behavior. All those with a *cis* structure inside the ring may be expected to act like methyl α-D-mannofuranoside while all containing a *trans* structure may very well give curves of the type observed for the ethyl β-D-galactofuranoside. Further experimentation will be required to substantiate this hypothesis. Criegee's observation that methyl β-D-glucofuranoside produces formaldehyde is in accord with it.

The case of a ketohexofuranoside or of an aldopentofuranoside differs in that there is no glycol pair outside the ring. Therefore, formaldehyde should never be found and the two types (*cis* and *trans*) will both consume only one molar proportion of oxidant, differing markedly in rate. The fructose furanosides show this behavior.[7]

In 1912, Fischer and Zach[8] described a crystalline 3,6-anhydro-D-sorbitol. This substance differs from a furanoside only in that the alkoxyl

(8) Fischer and Zach, *Ber.*, **45**, 456, 2068 (1912); *cf.*, Ohle, von Vargha and Erlbach, *ibid.*, **61**, 1211 (1928).

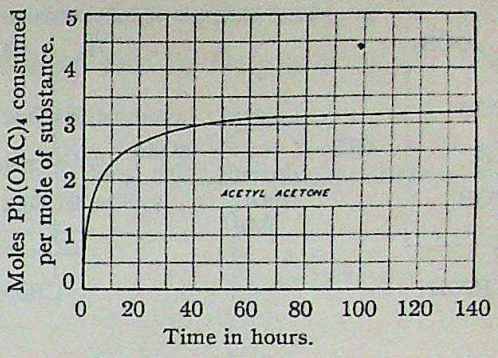


Fig. 1.

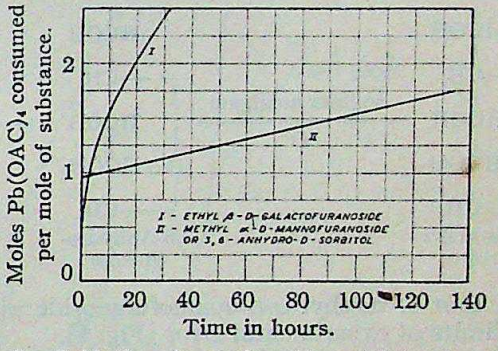


Fig. 2.—Oxidations in acetic acid containing less than 0.05% water: concentration of sample, 0.0025 molar; molar ratio of oxidant, 15.2/1.

group has been replaced by hydrogen. It might be expected to show an oxidation curve of the first type and to resemble the mannofuranoside closely. A close resemblance between the behavior of these two compounds would encourage us to apply the oxidation procedure in solving some of the many structural problems remaining in the little-known group of the anhydrides of polyalcohols.

Fischer and Zach introduced the anhydro ring by treating methyl 6-desoxy-6-bromo-2,3,4-triacetyl-α-D-glucopyranoside with barium hydroxide. We preferred to use the corresponding iodo compound prepared as described by Compton,[9] following Fischer's procedure in hydrolyzing the anhydroglucoside to the anhydro-glucose and in reducing the last with sodium amalgam to the anhydro-sorbitol.

The method of preparation eliminates any possibility of a Walden inversion at carbon atom number three during ether formation. Since there is no oxygen attached to the sixth carbon, the ether ring oxygen must be provided from the group upon carbon number three. Hence no bond of the third carbon atom has been broken and no inversion can have occurred. The structure of 3,6-anhydro-D-sorbitol, for the reasons enumerated, can be considered as established without question.

Oxidation of this sorbitan by lead tetraacetate under standard conditions, gave a curve identical

(9) Compton, THIS JOURNAL, **60**, 398 (1938).

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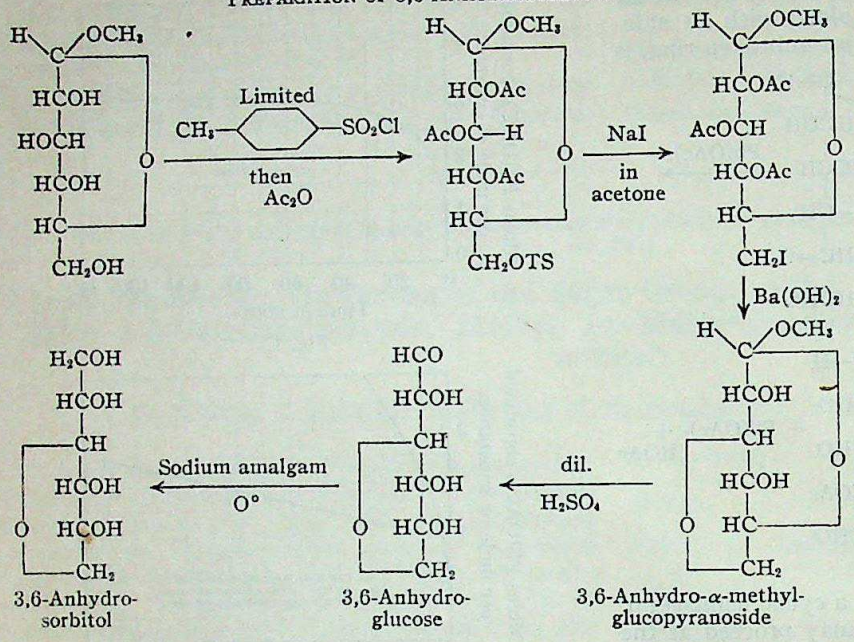
PREPARATION OF 3,6-ANHYDROSORBITOL



with that of methyl α-D-mannofuranoside within the limits of experimental error (Fig. 1).

We are very greatly indebted to Professor Eugene Pacsu of Princeton University for samples of the two furanosides, to Dr. Morris Zief of this Laboratory for repeating rate-of-oxidation measurements under more strictly anhydrous conditions and to Mr. Edward B. Weinberger, formerly of this Laboratory, for measuring the rate of oxidation of acetylacetone.

Experimental

Ethyl β-D-Galactofuranoside.[10]—This sample melted at 85–86° and rotated[11] −102° (*C*, 0.500; H_2O).

Methyl α-D-Mannofuranoside.[12]—This sample melted at 118–119° and rotated[11] +108°.

Methyl 2,3,4-Triacetyl-6-*p*-toluenesulfonyl-α-D-glucopyranoside (M.H.N.).—The sirupy compound was prepared exactly as described by Compton[9] from a 10-g. sample of methyl α-D-glucopyranoside.

Methyl 2,3,4-Triacetyl-6-desoxy-6-iodo-α-D-glucopyranoside (M.H.N.).—The entire sample of sirupy tosyl ester was treated with sodium iodide as described by Compton.[9] Our product weighed 9 g., representing 40.5% of the theoretical yield from the methyl glucoside used. It melted 143–145° and rotated[11] +113.3° (*C*, 0.94; $CHCl_3$).

3,6-Anhydro-D-glucose (M.H.N.).—The purification of methyl 3,6-anhydro-α-D-glucopyranoside was omitted in the present work.[8] A sample of 20 g. of nearly pure methyl 6-desoxy-6-iodo-triacetyl-α-D-glucopyranoside was dissolved at the boiling point in 300 cc. of 50% (by vol.) ethanol. One hundred grams of barium hydroxide octahydrate, finely ground, was added and the mixture was heated under reflux for two hours. After cooling, filtration through carbon and evaporation to a sirup, the latter was extracted repeatedly with a 50:50 mixture of ethanol and ethyl acetate. The combined extracts were evaporated and the remaining sirup was dissolved in water. Barium ions were balanced out accurately with dilute sulfuric acid, hydriodic acid with silver carbonate, and dissolved silver with hydrogen sulfide. The filtered solution of methyl anhydroglucoside was concentrated nearly dry under diminished pressure, and then subjected to hydrolysis by solution in 50 cc. of 4.5% sulfuric acid and heating on a steam-bath for one hour and forty-five minutes. The sulfuric acid was balanced out with barium hydroxide and the filtered solution was concentrated to a sirup. When dissolved in a small volume of hot absolute ethanol and then cooled, the product separated in fine needles; yield 5.67 g. or 76% of theory. The anhydrosugar melted 114–117° and rotated[11] +53.2° (*C*, 0.73; H_2O).

3,6-Anhydro-D-sorbitol (M.H.N.).—Five grams of anhydro glucose dissolved in 50 cc. of water was subjected to a rapid stream of carbon dioxide gas while 140 g. of sodium amalgam was added in successive 10-g. portions. The gas both served to keep the solution stirred and maintained the medium at the very slight alkalinity of a sodium bicarbonate solution. No cooling was used. By the time the last portion of amalgam was exhausted, only a faint reducing power toward Fehling solution remained. Mercury was separated and sodium bicarbonate was converted to sulfate by titration with dilute sulfuric acid (methyl orange). After filtration through carbon the solution was evaporated nearly dry under reduced pressure. The salts were extracted repeatedly with hot absolute ethanol and the combined, filtered extracts were concentrated to a sirup. This was redissolved in a minimum volume (30 cc.) of hot ethanol and ethyl acetate was added to incipient turbidity. Tabular crystals soon separated; yield, 3.85 g. Recrystallized from hot ethyl acetate, these melted at 108–109°.

Rate of Oxidation Measurements.—The samples were oxidized in solutions of the concentration adopted as standard by Hockett, Dienes and Ramsden,[5] that is, 0.0025 molar with respect to sample and with a 15.2/1 molar ratio of oxidant to substance.

Detection of Formaldehyde.—The sample is dissolved in a small volume of water in a distilling flask and an excess of lead tetraacetate in acetic acid is added. After a few minutes, the water and acetic acid are distilled under reduced pressure into a receiver cooled in an ice and salt mixture. The distillate is then tested for formaldehyde by adding a saturated solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid. If formaldehyde is present there occurs an almost instantaneous precipitation of the hydrazone, melting at 166°. This method is adaptable for either qualitative or quantitative determination.

Summary

1. The rates of oxidation of methyl α-D-mannofuranoside, ethyl β-D-galactofuranoside and 3,6-anhydro-D-sorbitol have been measured.

2. Correlations between structure and oxidation behavior have been pointed out.

(10) Pacsu and Green, THIS JOURNAL, 59, 1204 (1937).

(11) All rotations cited in this paper are specific rotations of the D line of sodium at 20°. Concentrations are expressed as grams per one hundred cc. of solution.

(12) Scattergood and Pacsu, THIS JOURNAL, 62, 903 (1940).

CAMBRIDGE, MASS. RECEIVED NOVEMBER 1, 1943

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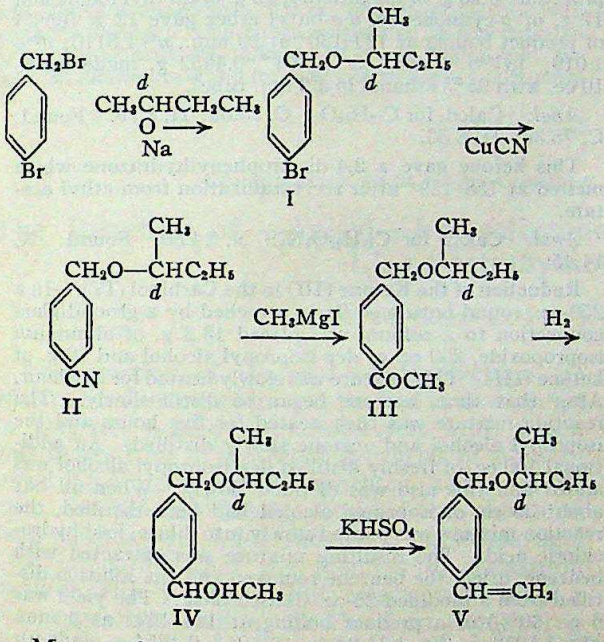
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

An Optically Active Styrene Derivative and its Polymer[1]

BY C. S. MARVEL AND C. G. OVERBERGER

The polymerization of optically active vinyl monomers[2] has been found useful in studying the kinetics of polymerization. The present work was undertaken to increase the number of optically active vinyl monomers available for this type of research.

The method used to obtain the optically active styrene derivative is outlined



Many of these reactions were first carried through with the methyl benzyl ether series so that there would be the least possible waste of the optically active *s*-butyl alcohol in the final synthesis. Since some of these derivatives are new, they are recorded in the experimental part of this paper.

The optically active styrene derivative (V) obtained in this synthesis had a specific rotation of +12.07° when prepared from *d*-*s*-butyl alcohol with a rotation of +11.5°. The change in specific rotation during polymerization was not great; the polymer had a specific rotation of +10.15° based on the monomer unit. In kinetic work this means an observed rotation change of 0.92° to 0.77° over a period of twenty-seven hours. The readings made at two to three hours intervals varied only by 0.03 to 0.04°. Since the polarimeter cannot be read with greater accuracy than ±0.01°, due to convection currents, the progress of this polymerization cannot be very accurately followed by polarimetric methods. However, taken as a whole the experiment plotted in the curve indicates that the polymerization follows first order kinetics.

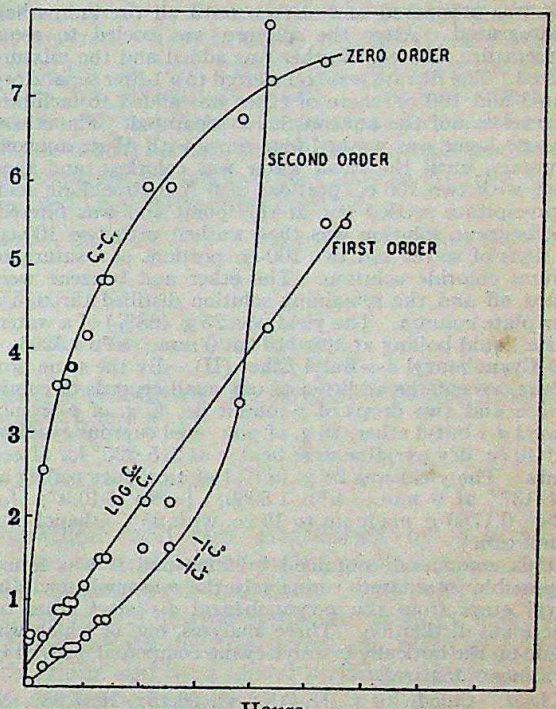


Fig. 1.

Experimental Part

p-Bromobenzyl *d*-*s*-Butyl Ether (I).—The method of Sah and Lei[3] for making benzyl ethers was modified for this reaction.

In a 500-cc., three-necked, round-bottomed flask equipped with condenser, stirrer and dropping funnel were placed 35 g. of *d*-*s*-butyl alcohol ($[\alpha]^{25}D$ +11.5°), 200 cc. of dry benzene and 10.9 g. of sodium (small shavings). The reaction mixture was allowed to reflux on the steam-bath with stirring for fifteen hours until all the sodium had dissolved. To this was added with stirring 118 g. of *p*-bromobenzyl bromide dissolved in 200 cc. of dry benzene. The addition took about fifteen minutes. The reaction mixture was then stirred for five hours while refluxing on a steam cone. The sodium bromide which precipitated was filtered and washed with two 75-cc. portions of benzene. The benzene layer was extracted with two 100-cc. portions of water to remove sodium bromide, the layers were separated and the benzene solution was dried over sodium sulfate. The solvent was removed and the resulting solution distilled through a column. The ether boiled at 109–110° at 8 mm. The yield was 70 g. (49.1%) $n^{20}D$ 1.5331; d^{24}_{24} 1.255; $[\alpha]^{25}D$ +10.2° (α, 0.39°, 0.1921 g. made up to 10 cc. with 95% ethanol in a 2-dm. tube).

Anal. Calcd. for $C_{11}H_{15}OBr$: C, 54.33; H, 6.22. Found: C, 53.80; H, 5.90.

p-Cyanobenzyl Methyl Ether.—This ether has been prepared by von Braun and Zobel[4] by a different and more involved set of reactions.

(1) This is the eighteenth communication on vinyl polymers. For the seventeenth see THIS JOURNAL, 65, 2054 (1943).

(2) Marvel, Dec and Cooke, *ibid.*, 62, 3499 (1940); Marvel and Frank, *ibid.*, 64, 1675 (1942).

(3) Sah and Lei, *Science Reports, National Tsing Hua Univ.*, Ser. AI, 193–195 (1932); see *C. A.*, 26, 5927 (1932).

(4) Von Braun and Zobel, *Ber.*, 56, 691 (1923).

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In a dry, 200-cc., round-bottomed flask fitted with a ground-glass condenser and protected from moisture with a calcium chloride tube was placed 50 g. of *p*-bromobenzyl methyl ether, 22.3 g. of dry powdered cuprous cyanide and 35 cc. of pyridine dried over potassium hydroxide. This mixture was heated in a Wood's metal bath at 215–225° for fifteen hours. The reaction mixture was poured while still hot (100°) into 150 cc. of aqueous ammonia (sp. gr. 0.90) and 150 cc. of water. One hundred and forty cubic centimeters of benzene was added and the flask was stoppered and shaken until all the lumps had disintegrated. After the mixture was cooled to room temperature, 100 cc. of ether was added and the mixture filtered. The filtrate was transferred to a 1-liter separatory funnel and 100 cc. more of ether was added to facilitate separation and the aqueous layer separated. The ether–benzene layer was washed four times with dilute aqueous ammonia, until the wash water was colorless, and then twice with two 100 cc. portions of 6 *N* hydrochloric acid. A precipitate settled out at this point and was filtered. The benzene solution was then washed with two 100-cc. portions of water and two 100-cc. portions of a saturated sodium chloride solution. The ether and benzene were boiled off and the remaining solution distilled through a four plate column. The yield was 25 g. (68%) of a water-white liquid boiling at 108–110° at 9 mm.; $n^{20}D$ 1.5265.

p-Cyanobenzyl *d-s*-Butyl Ether (II).—By the same procedure, except the addition of ten small crystals of cupric sulfate and two drops of *p*-tolunitrile, 40 g. of *p*-bromobenzyl *d-s*-butyl ether, 16 g. of powdered cuprous cyanide, and 40 cc. dry pyridine were heated at 215–225° for fifteen hours. The yield was 28 g. (90%) of a product boiling at 134–137° at 9 mm.; $n^{20}D$ 1.5080; $[\alpha]^{23}D$ +10.9°; (α, 0.39°, 0.1780 g. made up to 10 cc. with 95% ethanol in a 2-dm. tube).

This compound contained bromine and it was found impossible to separate completely the *p*-bromobenzyl *d-s*-butyl ether from the *p*-cyanobenzyl *d-s*-butyl ether by fractional distillation. Three analyses, one of which was made on the optically inactive cyano compound, proved to be almost identical.

Anal. Calcd. for $C_{12}H_{15}ON$: C, 76.15; H, 7.98; N, 7.40. Found: Sample 1, C, 74.63; H, 7.94; Sample 2, C, 74.32; H, 7.49; Sample 3, C, 74.33; H, 7.93; N, 6.85.

Sample (3) was made with *dl-s*-butyl alcohol. By calculation, the amount of *p*-bromobenzyl *d-s*-butyl ether in the mixture is 8.3%. No further attempt to separate the compound was made as this intermediate is relatively unimportant and the next compounds in the series proved to have the correct analyses.

Hydrolysis of *p*-Cyanobenzyl *dl-s*-Butyl Ether.—In order to have evidence of the quality of the cyano compound, it was converted to the acid by hydrolysis. In a 200-cc. round-bottomed flask equipped with condenser was placed 15 g. of potassium hydroxide dissolved in 50 cc. of 95% ethyl alcohol. To this was added 5 g. of *p*-cyanobenzyl *d-s*-butyl ether. This was then refluxed by means of an oil-bath for thirty hours. The solution was filtered and the sodium salt dissolved in 20 cc. of water. The solution was then acidified with dilute hydrochloric acid and the precipitate filtered. Upon purification by treatment with Norite and recrystallization from a water–95% alcohol mixture a small amount of a white solid was obtained melting at 77–78°.

Anal. Calcd. for $C_{12}H_{16}O_3$: C, 69.20; H, 7.74. Found: C, 69.09; H, 7.69.

p-Acetobenzyl Methyl Ether.—In a 200-cc., three-necked, round-bottomed flask equipped with a stirrer, condenser, and dropping funnel was placed 8.56 g. of magnesium covered with 30 cc. of dry ether. To this with stirring was added over a period of one-half hour, 50 g. of methyl iodide dissolved in 120 cc. of ether (to give 3 moles excess of methylmagnesium iodide). The mixture was allowed to stir for fifteen minutes after all the iodide had been added. To this Grignard reagent was added with stirring 26 g. of *p*-cyanobenzyl methyl ether in 100 cc. of ether. This addition took ten minutes. The mixture was then heated under a reflux condenser for two hours. The complex was decomposed in iced, dilute hydrochloric acid. Benzene was added (about 200 cc.) and the organic layer separated. Fifty cubic centimeters of a 2% hydrochloric acid solution was added to the benzene layer and the solution refluxed for one hour. The water layer was then separated, the benzene layer dried, benzene removed and the resulting solution distilled through a four-plate column. The yield was 15 g. (52%) of a water-white liquid boiling at 104–105° at 9 mm., $n^{20}D$ 1.5280.

The ketone was converted to the 2,4-dinitrophenylhydrazone by the standard method[5] and this derivative was recrystallized from ethyl acetate, m. p. 170–171°.

Anal. Calcd. for $C_{16}H_{16}O_5N_4$: C, 55.80; H, 4.68. Found: C, 55.56; H, 4.67.

p-Acetobenzyl *d-s*-Butyl Ether (III).—Using the same procedure 9.26 g. of magnesium, 52 g. of methyl iodide and 17 g. of *p*-cyanobenzyl *d-s*-butyl ether gave 12 g. (65%) of product boiling at 129–130° at 10 mm., n^{20} 1.5110; d^{24}_{24} 1.019; $[\alpha]^{20}D$ +10.8° (α +0.91°, 0.4952 g. made up to 10 cc. with 95% ethanol in a 2 dm. tube).

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.69; H, 8.79. Found: C, 75.36; H, 8.56.

This ketone gave a 2,4-dinitrophenylhydrazone which melted at 158–159° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_{19}H_{22}O_5N_4$: N, 14.50. Found: N, 14.45.

Reduction of the Ketone (III) to the Carbinol (IV).—In a 250-cc., round-bottomed flask, attached by a ground-glass connection to a column was placed 13.2 g. of aluminum isopropoxide, 200 cc. of dry isopropyl alcohol and 10 g. of ketone (III). This mixture was slowly heated for one hour. After that time, acetone began to distill slowly. The reaction mixture was then heated for five hours and the isopropyl alcohol and acetone slowly distilled. An additional 100 cc. of freshly distilled dry isopropyl alcohol was added and this also was distilled slowly. When all but about 30 cc. of isopropyl alcohol had been distilled, the reaction mixture was poured slowly into dilute, iced hydrochloric acid. The resulting mixture was extracted with benzene, dried, the benzene removed and the solution distilled from a modified 25-cc. Claisen flask. The yield was 6 g. (60%) of a product boiling at 144–149° at 9 mm. $n^{20}D$ 1.5056, $[\alpha]^{23}D$ +11.2° (α, +0.91°, 0.4054 g. made up to 10 cc. with 95% ethanol in a 2-dm. tube).

Anal. Calcd. for $C_{13}H_{20}O_2$: C, 74.95; H, 9.67. Found: C, 75.76; H, 9.62.

p-Vinylbenzyl *d-s*-Butyl Ether (V).—A mixture of 1.2 g. of fused, finely powdered potassium hydrogen sulfate and 0.2 g. of hydroquinone was fused in a 50-cc. modified Claisen flask fitted with a receiver and heated with a metal bath (200–220°). A stream of nitrogen, purified to remove oxygen and water, was introduced beneath the surface by means of a capillary tube through the same rubber stopper that contained a dropping funnel. The flask was evacuated to a pressure of 60–100 mm. Seven grams of the alcohol was dropped slowly (fifteen minutes) onto the molten potassium hydrogen sulfate at the temperature and pressure specified. About 4 g. of impure product was carried over into the receiver. The distillate was dissolved in 40 cc. of ordinary ether, washed with 20 cc. of a 5% sodium hydroxide solution, then with 20 cc. of a saturated calcium chloride solution and dried over calcium chloride. The solvent was removed and residue distilled in a 10-cc. modified Claisen flask. The yield was 3 g. (47%) of a product boiling at 111–113° at 8 mm., $n^{20}D$ 1.5179; $[\alpha]^{25}D$ 12.8; (α, +0.57, 0.4459 g. made up to 10 cc. with dry dioxane).

Anal. Calcd. for $C_{13}H_{18}O$: C, 82.05; H, 9.53. Found: C, 82.10; H, 9.25.

(5) Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 143.

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Polymerization of *p*-Vinylbenzyl *d*-*s*-Butyl Ether.—A mixture of 0.7600 g. of the styrene derivative and 0.1748 g. of benzoyl peroxide was made up to 10 cc. in dry dioxane and placed in a 1-dm. water-jacketed polarimeter tube and held at 55°. The rotation of this solution when first measured was +0.917°. After heating at 55° for twenty-four hours the rotation had dropped to +0.722°. Readings were made at various intervals during this time and the results of the experiment are plotted in Curve I. It will be noted that the best curve is obtained when first order kinetics are assumed. The errors in reading any one rotation are probably about 10%. The polymer which precipitated from the solution at the end of the run by adding methyl alcohol was a soft mass which could not be obtained in a satisfactory state for further study. Evaporation of the solvent gave a brittle mass. In order to obtain a sample for analysis, a dioxane solution of this polymer was slowly dropped into 100 cc. of methyl alcohol with vigorous stirring. One cubic centimeter of concentrated hydrochloric acid was added, 10 cc. of water and the solution allowed to stand for over twelve hours. A gummy powder or a gum settled which hardened on standing. This was finely ground and dried for two weeks in a vacuum desiccator.

Anal. Calcd. for $(C_{12}H_{16}O)_n$: C, 82.05; H, 9.53. Calcd. for $C_6H_5CO_2[(C_{12}H_{16}O)_8(O)_{11}]_n$: C, 73.27; H, 8.25. Found: C, 73.47; H, 8.44.

Summary

p-Vinylbenzyl *d*-*s*-butyl ether, an optically active styrene derivative, has been prepared and polymerized. The rotation change during polymerization is not great and accurate kinetic studies are difficult to make. The indication is that the polymerization follows first order kinetics.

Some methyl ethers related to the intermediates were synthesized by new methods or for the first time and they were characterized.

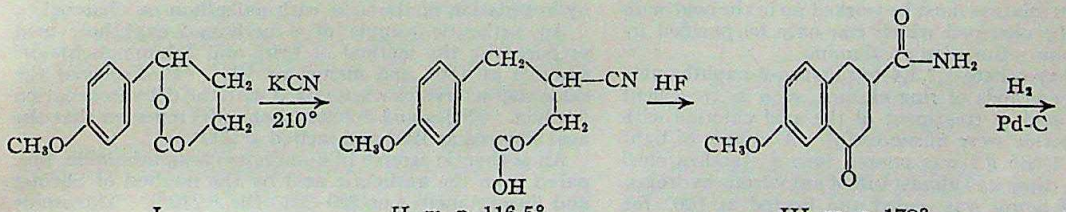
URBANA, ILLINOIS RECEIVED DECEMBER 24, 1943

[CONTRIBUTION FROM NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

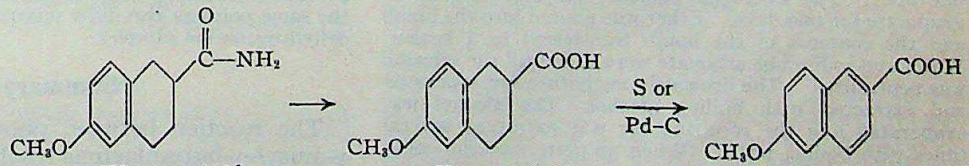
The Reaction of γ-Anisyl-γ-butyrolactone with Potassium Cyanide: 6-Methoxy-1,2,3,4-tetrahydro-2-naphthoic Acid

BY CHARLES C. PRICE AND WILLIAM KAPLAN

The reaction of γ-anisyl-γ-butyrolactone (I) with potassium cyanide[1] was studied in an attempt to prepare γ-anisyl-γ-cyanobutyric acid, which was desired for a projected synthesis of 6-methoxy-1,2,3,4-tetrahydro-1-naphthoic acid. However, the product finally obtained was shown to be 6-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid (V), indicating that the reaction of potassium cyanide with γ-anisyl-γ-butyrolactone involves a rearrangement leading to the formation of γ-anisyl-β-cyanobutyric acid (II).



I II, m. p. 116.5° III, m. p. 178°



IV, m. p. 141° V, m. p. 151° VI, m. p. 196°

A similar rearrangement was observed by Blaise,[2] who found that the reaction of potassium cyanide with γ-methyl-γ-valerolactone yielded γ-methyl-β-cyanovaleric acid instead of the expected γ-cyano acid.

The structure of 6-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid was established by dehydrogenation with sulfur or palladium on charcoal to yield 6-methoxy-2-naphthoic acid (VI). The identity of the dehydrogenation product was established by its melting point, the melting point of its amide and by a mixed melting point of each with authentic samples.[3]

Experimental

β-Anisoylpropionic Acid.—Following the directions of Fieser and Hershberg,[4] a 95% yield of β-anisoylpropionic acid, m. p. 144°, was obtained from the reaction between anisole (302 g.) and succinic anhydride (294 g.) in the presence of aluminum chloride (777 g.) when the precaution was taken of finely powdering the succinic anhydride crystals.

γ-Anisyl-γ-butyrolactone.—The keto-acid (140 g.) was added to 1 liter of absolute ethyl alcohol and the solution refluxed for several days, water being removed by calcium

(1) Wislicenus, *Ann.*, **233**, 101 (1886).
(2) Blaise, *Compt. rend.*, **124**, 89 (1897).
(3) Fries and Schimmelschmidt, *Ber.*, **58**, 2840 (1925).
(4) Fieser and Hershberg, THIS JOURNAL, **58**, 2314 (1936).

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carbide in a Soxhlet extractor. Upon completion of esterification the excess alcohol was removed by distillation and 500 cc. of isopropyl alcohol and 85 g. of vacuum-distilled aluminum isopropylate were added. Distillate boiling at 60° was very slowly removed through a fractionating column until ten drops failed to give a precipitate with a dilute hydrochloric acid solution of 2,4-dinitrophenylhydrazine. The isopropyl alcohol was then removed by distillation and excess 20% sulfuric acid added. The organic layer and the ether washings of the aqueous layer were combined and extracted with sodium hydroxide solution. The material remaining in the ether was refluxed for several hours with sodium hydroxide solution after removal of the ether by distillation. This sodium hydroxide solution was then washed with ether and added to the previous sodium hydroxide solution. The combined solutions were acidified and kept on the steam cone for an hour. The organic layer was taken up in ether and washed with dilute sodium bicarbonate solution. The ether solution was concentrated and placed in the icebox for several days. The lactone crystallized; filtration yielded 96 g. (79%) of γ-anisyl-γ-butyrolactone.

γ-Anisyl-β-cyanobutyric Acid (II).—The lactone (101 g.) and dried potassium cyanide (100 g.) in small crystals were put in a flask which had been dried in a Bunsen flame. A mechanical stirrer was attached. Dry nitrogen was passed slowly into the flask, which was kept at 210° for three and a half hours. The cold mass was dissolved in water and washed with ether. The water solution was acidified under the hood, cooled and extracted with ether. The ether was extracted with sodium bicarbonate solution and the dissolved ether was removed from the bicarbonate solution at room temperature by bubbling air through the solution. When the bicarbonate solution was acidified, a brown oil separated which solidified in a few hours. The solid mass was washed several times with cold benzene until the washings were colorless. A yield of 35 g. of tan solid was obtained which was used directly in the next step. Pure crystals for analysis and neutral equivalent were obtained by extraction of the light tan solid with a mixture of 50% benzene and 50% heptane in which the compound was moderately soluble at elevated temperatures. The pure γ-anisyl-β-cyanobutyric acid (II) melted at 116.5° (cor.).

Anal. Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; N, 6.38; neut. eq., 219. Found: C, 65.90; H, 5.98; N, 6.23; neut. eq., 221.

The reaction mixture must be worked up in the cold or an oily tar will be obtained which can only be purified by chromatographic adsorption on alumina.

6-Methoxy-4-keto-1,2,3,4-tetrahydro-2-naphthamide (III).—Usual methods of ring closure, such as treatment with sulfuric acid or treatment of the acid chloride with aluminum chloride were unsuccessful. A sample of light tan cyano-acid (35 g.) was poured into a stainless steel bomb (250-cc. capacity) almost full of anhydrous hydrogen fluoride. The bomb was sealed and heated at 100° for one hour. The hydrogen fluoride was then allowed to evaporate for two days. Ether was poured into the bomb and the contents of the bomb transferred to a beaker. Water and sodium bicarbonate were added till the solution was neutralized. The brownish precipitate was separated and extracted with boiling alcohol. The alcohol was evaporated and the resulting tar was extracted several times with boiling water. When no more material could be extracted from the tar, concentrated sulfuric acid was added to it. After a week the acid was diluted with water and the tar was boiled with 20% sodium hydroxide. The small white residue thus obtained was added to the material previously extracted from the tar and the whole was washed with dilute sodium hydroxide and recrystallized from water. A yield of 10 g. of **6-methoxy-4-keto-1,2,3,4-tetrahydro-2-naphthamide (III), m. p. 178° (cor.),** was obtained.

Anal. Calcd. for $C_{12}H_{13}O_2N$: C, 65.74; H, 5.98; N, 6.38. Found: C, 65.59; H, 5.97; N, 6.59.

The oxime was prepared following the directions of Shriner and Fuson,[5] m. p. 217–219° (cor.).

Anal. Calcd. for $C_{12}H_{14}O_4N_2$: C, 61.95; H, 6.02; N, 11.92. Found: C, 62.16; H, 6.25; N, 12.06.

6-Methoxy-1,2,3,4-tetrahydro-2-naphthamide (IV).—The amide (400 mg.) and 0.4 g. of 10% palladium on charcoal were put in a citrate bottle and 40 cc. of absolute alcohol added. The bottle was put in a shaker under 41 lb. pressure of hydrogen for two hours. The catalyst was then removed by filtration and the alcohol evaporated. The residue was washed with ether and recrystallized from boiling water. A yield of 250 mg. (68%) of **6-methoxy-1,2,3,4-tetrahydro-2-naphthamide, m. p. 141°** (cor.), was obtained.

Anal. Calcd. for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.37; N, 6.83. Found: C, 70.40; H, 7.57; N, 6.66.

6-Methoxy-1,2,3,4-tetrahydro-2-naphthoic Acid (V).—A sample of 0.866 g. of the amide in 12 cc. of hydrochloric acid, 12 cc. of water and 8 cc. of glacial acetic acid was refluxed for three hours. The precipitate was removed by filtration and dissolved in sodium bicarbonate solution. The solution was acidified after treatment with Norite. The original mother liquor was evaporated to a small volume and the precipitate worked up with the main fraction. A yield of 0.730 g. (85%) of **6-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid, m. p. 151°** (cor.), was obtained.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 69.88; H, 6.84. Found: C, 69.65; H, 6.87.

Attempts at demethylation with alcoholic potassium hydroxide and with glacial acetic acid–constant boiling hydrobromic acid mixtures were unsuccessful.

Dehydrogenation to 6-Methoxy-2-naphthoic Acid.—The amide (0.389 g.) and sulfur (0.140 g.) were heated at 210–245° for twenty minutes. The reaction mixture was sublimed at 5 mm. and sulfur removed from the sublimate with concentrated sodium sulfide solution. The residue was digested with alcohol and recrystallized from benzene. The product melted at 225° and gave a positive test for sulfur upon elementary analysis. This substance was probably the thio-amide. The amide was hydrolyzed with an alcoholic potassium hydroxide solution and an acid was obtained which melted at 194–196°. Dehydrogenation of the 6-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid with sulfur also gave a product melting at 194–196°. The same compound was also obtained by catalytic dehydrogenation of the acid with palladium on charcoal.

An authentic sample of 6-methoxy-2-naphthoic acid prepared by the method of Fries and Schimmelschmidt[3] sintered at 186° and melted at 196°. It displayed the same characteristics when mixed with the dehydrogenation product. (Fries and Schimmelschmidt[3] reported that the acid sintered at 190° and melted at 209°.)

An authentic sample of 6-methoxy-2-naphthamide, prepared from the authentic acid by the method of Shriner and Fuson,[5] melted at 220–221° (lit.,[3] 219°). The amide prepared from the dehydrogenation product melted at the same point as also did a mixture of the authentic and dehydrogenation samples.

Summary

The reaction between potassium cyanide and γ-anisyl-γ-butyrolactone resulted in the formation of γ-anisyl-β-cyanobutyric acid. The successful conversion of this cyano acid to 6-methoxy-4-keto-1,2,3,4-tetrahydro-2-naphthamide and 6-methoxy-1,2,3,4-tetrahydro-2-naphthoic acid has been described.

URBANA, ILLINOIS RECEIVED NOVEMBER 17, 1943

(5) Shriner and Fuson, "Identification of Organic Compounds," 2nd edition, John Wiley and Sons, Inc., New York, N. Y., 1940.

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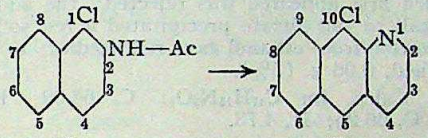
[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Derivatives of 10-Chlorobenzo(g)quinoline

BY FRANCIS H. GERHARDT[1] AND CLIFF S. HAMILTON

Several series of benzoquinolines have been prepared in this Laboratory and studied as intermediates for possible antimalarials.[2] In this particular investigation some nitro and amino derivatives of 10-chlorobenzo(g)quinoline were synthesized.

1-Chloro-2-acetamidonaphthalene (I) was subjected to the Skraup reaction to give 10-chlorobenzo(g)quinoline (V).[3] By the same Skraup



I V

procedure, the 5-nitro- (II), 6-nitro- (III), and 8-nitro- (IV) derivatives of (I) yielded, respectively, the 6-nitro- (VI), 7-nitro- (VII) and 9-nitro- (VIII) derivatives of (V). The action of fuming nitric acid on (V) gave chiefly (VI), together with a smaller amount of (VIII).

(II), (III) and (IV) were prepared by chlorination of the corresponding nitroacetamidonaphthalenes by the same procedure[4] used to prepare (I). They were also formed by the nitration of (I); thus the position of the chlorine atom was established.

Morpholine and piperidine condensed with (V) in sealed tubes in poor yields; no reaction occurred with diethylamine. The lability of the chlorine atom of (V) was not markedly increased by the introduction of a nitro group into the benzo ring. Morpholine condensed with (VI) and with (VII) under reflux in poor yields; no reaction occurred with diethylamine in sealed tubes. (VI) was reduced to 6-amino-10-chlorobenzo(g)-quinoline with iron and dilute acetic acid.

Treatment of (V) in chloroform with chlorine gave the dichlorobenzo(g)quinoline reported by Koeberle and Ploetz.[3] This compound was proved to be 5,10-dichlorobenzo(g)quinoline by its oxidation to the known benzo(g)quinoline-5,10-dione.[5]

Experimental

Preparation of Naphthalene Intermediates.—(I), (II), (III) and (IV) were prepared by the direct chlorination of the corresponding acetamidonaphthalene derivative in acetic acid according to the procedure of Franzen and Stäuble,[4] the resulting compounds being recrystallized from ethanol, forming white needles.

1-CHLORO-X-NITRO-2-ACETAMIDONAPHTHALENE, $C_{12}H_9ClN_2O_3$

X	M. p., °C.	Yield, %	Percentage composition: Carbon Calcd.	Carbon Found		Hydrogen Calcd.	Hydrogen Found	
5	183–185	80	54.45	54.28	54.66	3.43	3.48	3.46
6[a]	221–223	76	54.45	54.55	54.48	3.43	3.40	3.47
8	188–190	65	54.45	54.59	54.63	3.43	3.57	3.66

[a] Pale yellow.

Treatment of (I) with fuming nitric acid (d. 1.49) at −10° gave a mixture of (II) and (IV) which was separated by fractional crystallization from ethanol. No depression in melting point resulted when samples of (II) obtained by nitration and by chlorination were mixed; mixtures of samples of (IV) from the two sources also exhibited no melting point depression.

The action of fuming nitric acid (d. 1.49) on a solution of (I) in glacial acetic acid at room temperature resulted in some (III). Samples of (III) prepared by nitration and by chlorination exhibited no depression in melting point when mixed.

10-Chlorobenzo(g)quinoline (V).—Sulfuric acid, glycerol, arsenic acid and (I) were heated according to the procedure of Koeberle and Ploetz.[3] The crude product was extracted with acetone, the extract treated with charcoal and added dropwise to water with rapid stirring. (V) was obtained as cream-colored crystals; m. p. 138–140°; yield, 34%.

6-Nitro-10-chlorobenzo(g)quinoline (VI).—To 10 ml. (0.23 mole) of fuming nitric acid (d. 1.49) cooled to −18° in a snow–hydrochloric acid bath was added 2 g. (0.01 mole) of (V) in small portions. After fifteen minutes the solution was poured into 200 ml. of water. The precipitate which separated was filtered, washed with sodium bicarbonate solution to remove oxides of nitrogen, and extracted with 100 ml. of boiling ethanol. The extract was set aside (see preparation of (VIII) below) and the residue recrystallized from ethanol to give (VI) as fluffy yellow needles; m. p. 211–212°; yield, 1 g. (45%).

Anal. Calcd. for $C_{13}H_7ClN_2O_2$: C, 60.36; H, 2.72. Found: C, 60.29, 60.31; H, 2.44, 2.73.

(VI) was also prepared by subjecting (II) to the same Skraup procedure used to prepare (V). The two samples of (VI) exhibited no depression in melting point when mixed.

7-Nitro-10-chlorobenzo(g)quinoline (VII).—A mixture of 32 g. (0.12 mole) of (III), 50 ml. (0.66 mole) of glycerol and 100 ml. of 70% sulfuric acid (1.6 mole) was heated to gentle reflux by means of an oil-bath. A solution of 30 g. (0.13 mole) of arsenic acid in 75 ml. of 70% sulfuric acid (1.2 mole) was added in the course of thirty minutes. Heating was continued for another thirty minutes and the cooled mixture poured into 800 ml. of water and allowed to stand a few hours. The solution was filtered through a cellite pad and the filtrate neutralized with dilute sodium hydroxide. The crude product was extracted with acetone, the extract treated with charcoal and slowly poured into water. The resulting yellow solid was recrystallized three times from ethanol; yellow needles; m. p. 243–245°; yield, 1.2 g. (4%).

Anal. Calcd. for $C_{13}H_7ClN_2O_2$: C, 60.36; H, 2.72. Found: C, 60.60, 60.36; H, 2.90, 2.81.

9-Nitro-10-chlorobenzo(g)quinoline (VIII).—See preparation of (VI), above. Upon cooling, the alcoholic extract of the nitration product deposited a yellow solid; yellow crystals from ethanol; m. p. 209–211°; yield, 0.3 g. (12%).

(1) Parke, Davis and Company Fellow.

(2) Clem and Hamilton, THIS JOURNAL, **62**, 2349 (1940); Utermohlen and Hamilton, *ibid.*, **63**, 156 (1941); Barnum and Hamilton, *ibid.*, **64**, 540 (1942); Mueller and Hamilton, *ibid.*, **65**, 1017 (1943).

(3) Koeberle and Ploetz, U. S. Patent 2,003,596 (1935).

(4) Franzen and Staüble, *J. prakt. Chem.*, [2] **103**, 381 (1922).

(5) Phillips, *Ber.*, **27**, 1925 (1894); Braun and Gruber, *ibid.*, **55B**, 1711 (1922).

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Anal. Calcd. for $C_{13}H_7ClN_2O_2$: C, 60.36; H, 2.72. Found: C, 60.46, 60.61; H, 2.86, 2.92.

A mixture of some of this material and (VI) melted from 161–190°. However, these yellow crystals did not lower the melting point of the product obtained by subjecting (IV) to the same Skraup procedure used to prepare (V).

10-Morpholinobenzo(g)quinoline (IX).—In a sealed tube 2 g. (0.01 mole) of (V), 15 ml. (0.17 mole) of morpholine, and a few crystals of potassium iodide were heated at 150° for thirty-six hours. The reaction mixture was poured into 100 ml. of water and the resulting gummy precipitate dissolved in 5% hydrochloric acid. The acid solution was treated with charcoal and dilute sodium hydroxide added until the solution was barely acid. The unreacted (V) was removed by filtration and the filtrate made alkaline. The greenish-yellow solid was recrystallized twice from ethanol; bright yellow prisms; m. p. 160–161°; yield, 0.15 g. (6%).

Anal. Calcd. for $C_{17}H_{16}N_2O$: C, 77.24; H, 6.10. Found: C, 77.10, 77.34; H, 6.19, 6.16.

10-Piperidinobenzo(g)quinoline (X).—In a sealed tube 2 g. (0.01 mole) of (V) and 12 ml. (0.13 mole) of piperidine were heated at 150° for thirty-six hours. The reaction mixture was treated as in the preparation of (IX). Recrystallization of the product from ethanol gave bright-yellow needles; m. p. 97–99°; yield, 0.2 g. (8%).

Anal. Calcd. for $C_{18}H_{18}N_2$: C, 82.42; H, 6.91. Found: C, 82.27, 82.22; H, 7.07, 7.01.

5,10-Dichlorobenzo(g)quinoline (XI).—According to the procedure of Koeberle and Ploetz,[3] 3 g. of (V) was dissolved in chloroform and chlorine slowly bubbled in. The precipitate formed was treated with ammonium hydroxide and recrystallized twice from ethanol; yellow needles; m. p. 213–215°; yield, 2.5 g. (71%).

Anal. Calcd. for $C_{13}H_7Cl_2N$: C, 62.92; H, 2.84. Found: C, 62.86; H, 2.91.

In their patent[3] Koeberle and Ploetz neither characterized this chlorination product nor proved its structure. Refluxing (XI) with chromium trioxide in glacial acetic acid gave a tan solid which was recrystallized from benzene as tan needles; m. p. 278–280°. This product did not contain chlorine and its melting point agreed with that reported[5] for benzo(g)quinoline-5,10-dione. Hence, the chlorination product was 5,10-dichlorobenzo(g)quinoline.

6-Nitrobenzo(g)quinoline-5,10-dione (XII).—A mixture of 0.6 g. (0.002 mole) of (VI), 0.2 g. (0.002 mole) of chromium trioxide and 20 ml. of glacial acetic acid was refluxed for twenty-five hours. The reaction mixture was poured into water and the precipitate recrystallized twice from ethanol; pale tan crystals; m. p. 243–245°; yield, 0.25 g. (42%).

Anal. Calcd. for $C_{13}H_6N_2O_4$: C, 61.42; H, 2.34. Found: C, 61.52, 61.37; H, 2.35, 2.54.

6-Amino-10-chlorobenzo(g)quinoline (XIII).—Five grams (0.019 mole) of (VI), 3.2 g. (0.057 mole) of reduced iron powder, 80 ml. of glacial acetic acid, and 25 ml. of water were refluxed one hour. The mixture was diluted with about twice its volume of water, made alkaline, and extracted with three 100-ml. portions of chloroform. The combined extracts were washed with two 50-ml. portions of 5% hydrochloric acid and the acid solution treated with charcoal and neutralized with dilute sodium hydroxide. The precipitate was recrystallized from ethanol as orange needles; m. p. 181–183°; yield, 1.3 g. (30%).

Anal. Calcd. for $C_{13}H_9ClN_2$: C, 68.22; H, 3.97. Found: C, 68.09, 68.07; H, 3.94, 4.06.

6-Nitro-10-morpholinobenzo(g)quinoline (XIV).—One gram (0.004 mole) of (VI), 10 ml. (0.11 mole) of morpholine, and a pinch of copper bronze were refluxed five hours. The reaction mixture was poured into 300 ml. of water and the crude precipitate dissolved in 30 ml. of 5% hydrochloric acid. The acid solution was treated with charcoal and dilute sodium hydroxide added. The greenish precipitate which first appeared was rejected; the addition of more alkali to the filtrate precipitated a red solid. Recrystallization from ethanol gave red needles; m. p. 156–158°; yield, 0.06 g. (5%).

Anal. Calcd. for $C_{17}H_{15}N_3O_3$: C, 66.02; H, 4.88. Found: C, 66.25; H, 4.73.

7-Nitro-10-morpholinobenzo(g)quinoline (XV).—A mixture of 0.5 g. (0.002 mole) of (VII), 6 ml. (0.07 mole) of morpholine and a pinch of copper bronze was refluxed six hours. The reaction was worked up just as in the preparation of (XIV). The product was recrystallized from ethanol as tan platelets; m. p. 202–204°; yield, 0.02 g. (3%).

Anal. Calcd. for $C_{17}H_{15}N_3O_3$: C, 66.02; H, 4.88. Found: C, 66.24; H, 4.64.

Summary

10-Chlorobenzo(g)quinoline was condensed with morpholine and with piperidine. Nitration of 10-chlorobenzo(g)quinoline was found to give chiefly 6-nitro-10-chlorobenzo(g)quinoline, together with a small amount of 9-nitro-10-chlorobenzo(g)-quinoline.

6-Nitro-, 7-nitro- and 9-nitro-10-chlorobenzo-(g)quinoline were prepared from the new naphthalene intermediates, 1-chloro-5-nitro-, 1-chloro-6-nitro- and 1-chloro-8-nitro-2-acetamidonaphthalene, respectively.

6-Nitro- and 7-nitro-10-chlorobenzo(g)quinoline were condensed with morpholine. 6-Nitro-10-chlorobenzo(g)quinoline was reduced to 6-amino-10-chlorobenzo(g)quinoline.

LINCOLN, NEBRASKA RECEIVED NOVEMBER 22, 1943

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

Factors Determining the Course and Mechanism of Grignard Reactions. XIV. Replacement of Halogen Atoms of Aromatic Halides with Hydrogen Atoms by the Action of Grignard Reagents and Cobaltous Chloride

BY M. S. KHARASCH, D. C. SAYLES AND E. K. FIELDS

It is well established that aliphatic and aromatic Grignard reagents do not react, even at elevated temperatures, with monohalogenated and dihalogenated aromatic compounds. However, an energetic reaction occurs when cobaltous chloride is added to such a reaction mixture. Thus, butylmagnesium bromide reacts with phenyl bromide in the presence of 5 mole per cent. of cobaltous chloride to yield the following compounds:

Compound	Yields in % of amount calculated
Benzene	44
Butane and butylene	83
Butylbenzene	3
Biphenyl	3
Polyphenyls	11[1]

In order to ascertain the scope and general utility of this reaction, a number of dihalogenated aromatic compounds and monohalogenated polycyclic compounds were treated with Grignard reagents in the presence of cobaltous chloride.

TABLE I

REACTION OF GRIGNARD REAGENTS WITH ORGANIC HALIDES IN THE PRESENCE OF COBALTOUS CHLORIDE[a]

Grignard reagent[b]	Aromatic halide	Reaction,[c] %	Products identified[d] in %	
C_6H_5MgBr	*o*-$C_6H_4Cl_2$	48	C_6H_5Cl	12
	m-$C_6H_4Cl_2$	53	C_6H_5Cl	29
	p-$C_6H_4Cl_2$	30	C_6H_5Cl	10
	m-$C_6H_4Br_2$	81	C_6H_5Br	40
	p-$C_6H_4Br_2$	84	C_6H_5Br	45
CH_3MgBr	*p*-$C_6H_4Br_2$[e]	63	C_6H_5Br	37
	2,2′-$(C_6H_4Br_2)_2$[f]	66	$(C_6H_5)_2$	60
	2,2′-$(C_6H_4Br_2)_2$[g]	48	$(C_6H_5)_2$	20
			o-$C_6H_5C_6H_4Br$	8
C_6H_5MgBr	*o*-$C_6H_4Cl_2$	26	C_6H_5Cl	6
	m-$C_6H_4Br_2$	65	C_6H_5Br	44
	p-$C_6H_4Br_2$	87	C_6H_5Br	55
	2,4-$CH_3OC_6H_3Br_2$[h]	62	Anisole	10
			o- and *p*-bromoanisole	40
	o-$CH_3C_6H_4Br$	59	$C_6H_5CH_3$	33

[a] Five mole per cent. of cobalt chloride calculated on the basis of the organic halide used. [b] Five per cent. excess of Grignard reagent used. [c] These values are calculated from the halide ion titration of the aqueous solution (*cf.* ref. 1). [d] In all cases, some unreacted material and residue of polymeric substances were obtained. [e] An excess (130%) of the Grignard reagent was used. [f] Halide added to tenfold excess of Grignard reagent and 50 mole per cent. of cobalt chloride. [g] Tenfold excess of Grignard reagent and 11 mole per cent. cobalt chloride used. [h] Excess (150%) of Grignard reagent used.

(1) (a) Kharasch, Lewis and Reynolds, THIS JOURNAL, 65, 498 (1943); (b) Kharasch and Fields, *ibid.*, 63, 2316 (1941).

The results obtained with the dihalogenated aromatic compounds are summarized in Table I; those obtained with the monohalogenated polycyclic derivatives, in Table II.

TABLE II

REACTION OF GRIGNARD REAGENTS WITH POLYCYCLIC AROMATIC HALIDES IN THE PRESENCE OF COBALTOUS CHLORIDE

Grignard reagent	Mole % $CoCl_2$	Aromatic halide	% Reaction by aqueous layer titration	Products identified, %
n-BuMgBr	0	*p*-Bromo-	0	Biphenyl (52)
n-BuMgBr	5	biphenyl	65	Bixenyl (1.3)
PhMgBr	0	*p*-Bromo-	11	
PhMgBr	5	biphenyl	70	Biphenyl (52)
n-BuMgBr	0	2-Bromo-	0	
n-BuMgBr	5	naphthalene	60	Naphthalene (44)
PhMgBr	0	2-Bromo-	1	
PhMgBr	5	naphthalene	70	Naphthalene (47) Biphenyl (57)
n-BuMgBr	0	1-Bromo-	17	
n-BuMgBr	5	naphthalene	76	Naphthalene (62)
n-BuMgBr	0	9-Bromo-	5	
n-BuMgBr	5	phenan-	71	Phenanthrene (54)
PhMgBr	5	threne	96	Phenanthrene (55) Biphenyl (73)
n-BuMgBr	0	9-Bromoan-	1	
n-BuMgBr	5	thracene	53	Anthracene (49)
n-BuMgBr	0	2-Bromo-	0	
n-BuMgBr	5	fluorene	50	Fluorene (50)
n-BuMgBr	0	3-Bromoace-	0	
n-BuMgBr	5	naphthene	47	Acenaphthene (54)

Discussion

The results summarized in Tables I and II indicate that, although Grignard reagents do not react with aromatic halides (monohalogenated and dihalogenated hydrocarbons), a reaction leading to the replacement of a halogen atom by a hydrogen atom takes place in the presence of cobaltous chloride. The wide applicability of this method is indicated by the variety of halogenated substances which react as indicated. Thus, bromobenzene, *p*-bromobiphenyl, 1- and 2-bromonaphthalenes, 9-bromophenanthrene, 9-bromoanthracene, 2-bromofluorene, and 3-bromoacenaphthene give the corresponding hydrocarbons when treated with Grignard reagents in the presence of cobaltous chloride. Furthermore, ortho-, para- and meta-dichloro- and dibromobenzenes, 2,2′-dibromobiphenyl and 2,4-dibromoanisole give the corresponding monohalogen derivatives, or, if an excess of Grignard reagent is used, the corresponding hydrocarbons. The yields (40–55%) reported in the tables are not necessarily those that could be obtained under optimum experi-

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mental conditions; hence, no significance should be attached to slight variations in the figures recorded. However, the differences noted between dichloro- and dibromobenzenes are probably real; they indicate a greater resistance of the chloro compounds to reduction.

The replacement of the halogen atom by a hydrogen atom probably proceeds by a free radical chain mechanism in which the cobalt subhalide acts as the chain carrier.

R = Aliphatic radical; R′ = Aromatic radical

(a) $RMgX + CoCl_2 \longrightarrow RCoCl + MgXCl$
(b) $RCoCl \longrightarrow R\cdot + CoCl\cdot$
(c) $R'\cdot Br + CoCl\cdot \longrightarrow R'\cdot + CoClBr$
(d) $R'\cdot + C_2H_5OC_2H_5 \longrightarrow R'H$

The compounds formed from the aliphatic free radical R (produced in reaction b) and those formed from the ether molecule (reaction d) have already been discussed.[1a] Of interest, although fully expected, was the non-selective replacement of a halogen atom in 2,4-dibromoanisole by a hydrogen atom.

The dimerization of some aromatic radicals by the action of alkyl or aryl halides and cobaltous chloride on the Grignard reagents of these radicals has already been reported.[1b] It has now been found that *p*-biphenylmagnesium bromide,[2] and 9-phenanthrylmagnesium bromide, when treated with ethyl bromide and 5 mole per cent. of cobaltous chloride, give quantitative yields of bixenyl and biphenanthryl, respectively. These results taken in conjunction with those reported in Tables I and II substantiate a previous statement[1b] that the dimers of aromatic radicals are not formed in ether solution (or for that matter in other solvents) by the combination of the two free aromatic radicals; they are formed by some other mechanism which we hope to discuss in the near future. On the other hand, free radicals formed from weakly electronegative radicals do dimerize in ether solution.[3]

Experimental

Hydrocarbons.—The hydrocarbons used were purchased from the Eastman Kodak Company. They were purified by fractional distillation under reduced pressure and by crystallization from suitable solvents.

Bromohydrocarbons.—1-Bromonaphthalene and 2-bromonaphthalene were prepared in the usual manner. *p*-Bromobiphenyl was obtained from the Eastman Kodak Company. Phenanthrene dibromide was prepared by the procedure of Austin.[4] It was converted by heat into the 9-bromophenanthrene; this compound was purified first by distillation (b. p. 237–242° under 22 mm. pressure) and then by crystallization from ligroin (m. p. 63°). A similar procedure applied to anthracene yielded the 9-bromoanthracene (m. p. 100°). 2-Bromofluorene was prepared by the method of Clarkson and Gomberg.[5] 3-Bromoacenaphthene was prepared by the method of Compton and Walter.[6] 2,2′-Dibromobiphenyl was prepared according to the method of Schwechten.[7]

Reaction of Aryl Grignard Reagents with Ethyl Bromide in the Presence of Cobaltous Chloride; Preparation of Bixenyl and Biphenanthryl.—To 0.05 of a mole of the aryl Grignard reagent kept at 5°, five mole per cent. of cobaltous chloride was added. To this mixture, ethyl bromide (0.1 mole) dissolved in a small amount of ether, was slowly added in one and one-half to two hours. The reaction mixture was decomposed by ice and acidulated water (acetic acid), and then worked up in the usual way. Halide ion titrations of the water solution indicated 38% and 40% reactions, respectively. The yield of bixenyl (m. p. 302° after crystallization from nitrobenzene) calculated on the basis of the amount of Grignard reagent used was 60%. However, if this yield is corrected for the bixenyl (20%) present in the Grignard reagent, it is quantitative (40%). The yield of biphenanthryl (40%) was quantitative if calculated on the basis of the Grignard reagent that had reacted. The biphenanthryl thus obtained melted at 180° after crystallization from a mixture of chloroform and methanol.

Reaction of Grignard Reagents with Polycyclic Aromatic Halides in the Presence of Cobaltous Chloride (Table II).—The experimental technique was the same as described in previous papers.[1b] The cobaltous chloride (5 mole per cent.) was added to the Grignard reagent (0.05 mole) at low temperatures; then a solution of the organic halide (0.05 mole) in ether was added at a rate sufficient to maintain a gentle refluxing of the ether solution. The mixture was thoroughly agitated throughout the addition. After the addition was complete, the reaction mixture was refluxed for two hours on a water-bath; it was allowed to stand overnight, and was worked up in the usual way by pouring it onto ice, and extracting the mixture with ether. The aqueous layer was made up to 250 cc. volume; aliquot parts were withdrawn for halide ion titration. The ether solution was evaporated and worked up in the usual way. The results are recorded in Table II.

Reaction of Grignard Reagents with Dihalo Aromatic Compounds (Table I).—The Grignard reagents were prepared from ordinary magnesium turnings. In all cases, except where noted in Table I, the Grignard reagent was added to the halide in ether solution containing half of the total amount of the cobaltous chloride used in the experiment. After half of the Grignard reagent had been added, the other half of the cobalt chloride was added to the reaction mixture. Vigorous stirring and refluxing was maintained throughout the period of addition and for one hour thereafter. The reaction mixture was then treated in the usual manner; the products were separated by fractional distillation, or by crystallization from appropriate solvents.

Summary

1. In the presence of cobaltous chloride (5 mole per cent.), Grignard reagents reduce (a) dihalogenated aromatic compounds to the monohalogenated derivatives, (b) *o*-bromotoluene to toluene, (c) polycyclic aromatic halides to the corresponding hydrocarbons. In all cases some polymeric materials are obtained.

2. A mechanism for the replacement of the halogen atom by a hydrogen atom is suggested.

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(2) This reagent, as commonly prepared, contains about 20% bixenyl.

(3) For a fuller discussion, see Kharasch, Engelmann and Urry, THIS JOURNAL, 66, 365 (1944).

(4) Austin, *Trans. Chem. Soc.*, 93, 1763 (1908).

(5) Clarkson and Gomberg, THIS JOURNAL, 52, 2886 (1930).

(6) Compton and Walter, *Trans. Chem. Soc.*, 101, 958 (1912).

(7) Schwechten, *Ber.*, 65, 1605 (1932).

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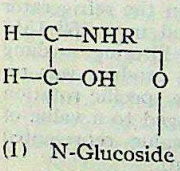
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF IOWA STATE COLLEGE]

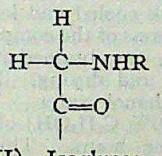
The Reaction of Glucose with Some Amines

BY ELEANOR MITTS AND R. M. HIXON

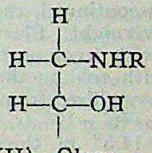
The phenylhydrazine derivatives were recently prepared from several corn sirup dextrins as a check on other methods of determining molecular weights of these large molecules. The ease of hydrolysis of these compounds indicated that they were of a glycosidic structure analogous to similar derivatives prepared by the reaction of phenylhydrazine in organic solvents with simple sugars. The tendency of the phenylhydrazine derivatives to form highly solvated molecules as well as the ease of isomerization detracts from their value for characterization of the dextrins. In connection with the synthesis of Vitamin B_2, detailed studies have been made of the reaction of aromatic amines with glucose. These compounds are N-glucosides (I) and undergo the Amadori rearrangement (II) to form amino ketones. A comparative study of the relative stability of the N-glucosides was made as an indication of nitrogen derivatives better suited for characterizing the dextrins. The data on glucosylalkylamines and their hydrogenation products (III) has been extended.



(I) N-Glucoside



(II) Isoglucosamine formed from (I) by Amadori Rearrangement



(III) Glucamines formed from (I) or (II) by hydrogenation

The available literature indicates that glucose and other monosaccharides react in non-polar solvents to give N-glucosides (I) with ammonia,[1] alkylamines,[1a,2] arylamines,[3] acid amides,[4] hydroxylamine[5] and phenylhydrazine.[6] As a general class, these compounds are labile and undergo rearrangement as well as hydrolysis. In many cases they crystallize with one or more molecules of water, of alcohol, or of amine. The difficulties of isolation or recrystallization seem to depend upon these solvation characteristics as well as upon hydrolysis or isomerization.

With the exception of the first member of the series, 1-aminoglucose or glucose ammonia, hydrolysis of the N-glucosides appears to parallel the basic dissociation constant (K_B) of the nitrogen substituent. The extent of hydrolysis depends upon concentration and temperature. Experiments with representative members of the various series indicate that for dilute aqueous solutions (2% or less) the alkylamines come to equilibrium in about twenty hours with approximately 40% of hydrolysis; in contrast, the glucosyl-*n*-arylamines after approximately ninety hours are only 8% hydrolyzed, while the amide derivatives are not hydrolyzed in water or even by dilute acids at room temperature.

The isomerization of N-glucosides to isoglucosamines (II, the Amadori rearrangement) has been observed with arylamines only. Weygand[7] suggests this type of rearrangement to explain the formation of osazones. The presence of the methoxy group in 2-methylglucose is not sufficient to prevent the formation of the osazone[8]; it is, however, sufficient to prevent rearrangement of the *p*-toluidide. Repeated attempts to induce the Amadori rearrangement in N-acyl and N-alkylamine glucosides met with negative results. In fact, the conditions used for the production of aryl isoglucosamines were found to be ideal for the production of the N-alkylamine glucosides. These conditions were used to prepare *n*-butyl, *n*-amyl and *n*-heptyl glucosylamines and the melting points found were identical to those reported previously by Votoček.[2b]

Catalytic hydrogenation of the N-glucosides of alkylamines has been previously reported.[9] It was found that good yields of N-alkyl glucamines (III) could be obtained in several cases where it was not possible to isolate the intermediate N-glucoside in crystalline form. The glucamines are crystalline solids, soluble in water and quite stable to heat. They may be titrated potentiometrically with dilute acid and are stable to both strong acid or alkali. These compounds, especially those from amines of intermediate molecular weight, lower the surface tension of water noticeably and are good wetting agents. Properties for a number of such compounds are reported in Table I.

Experimental

Glucosyl-*n*-butylamine.—To 10 g. (0.056 mole) of glucose and 2 ml. of 0.5 *N* hydrochloric acid, 9 g. (0.12 mole) of *n*-butylamine was added. This mixture was heated

(1) (a) Irvine, Thomsen and Garrett, *J. Chem. Soc.*, **103**, 238 (1913); (b) Levene, *J. Biol. Chem.*, **24**, 59 (1916); (c) Wayne and Adkins, THIS JOURNAL, **62**, 3314 (1940).

(2) Votoček and Valentin, *Coll. Czechoslov. Chem. Commun.*, **6**, 77 (1934).

(3) (a) Sorokin, *J. prakt. Chem.*, (2) **37**, 291 (1888); (b) Marchlewski, *ibid.*, (2) **50**, 95 (1894); (c) Strauss, *Ber.*, **27**, 1284 (1894); (d) Irvine and Gilmour, *J. Chem. Soc.*, **93**, 1429 (1908); (e) Kuhn and Dansi, *Ber.*, **69**, 1745 (1936); (f) Kuhn and Birhofer, *ibid.*, **71**, 621 (1938).

(4) (a) Schoorl, *Rec. trav. chim.*, **22**, 31 (1903); (b) Helferich and Kasche, *Ber.*, **59**, 69 (1926).

(5) Wolfrom and Thompson, THIS JOURNAL, **53**, 622 (1931).

(6) (a) Behrend and Lohr, *Ann.*, **362**, 78 (1908); (b) Behrend and Reinsberg, *ibid.*, **377**, 189 (1910).

(7) Weygand, *Ber.*, **73**, 1284 (1940).

(8) Brigl and Schinle, *ibid.*, **62**, 1716 (1929).

(9) (a) Karrer, Saloman, Kunz and Seebach, *Helv. chim. acta*, **18**, 1338 (1935). (b) Karrer and Harkenrath, *ibid.*, **20**, 83 (1937). (c) Flint and Saltzberg, U. S. Patent 2,016,962, Oct. 8, 1935; C. A., **29**, 8007 (1935).

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TABLE I

PROPERTIES OF SOME ALKYLGLUCAMINES

Alkyl-*d*-glucamine	Recrystd. from	M. p. uncor., °C.	% N Calcd.	% N Found		$[\alpha]^{25}D$[a]	% Carbon (micro) Calcd.	% Carbon (micro) Found	% Hydrogen (micro) Calcd.	% Hydrogen (micro) Found
N-Butyl-	Methanol	127–128	5.91	6.02	5.87	−14	50.59	50.4	9.77	9.7
N-Amyl-	Methanol	129–130	5.57	5.42	5.52	−13.8	52.55	52.3	10.03	9.9
N-Heptyl-	Methanol	126–127	5.02	5.08	4.99	−14	55.86	55.5	10.47	10.4
N-Cyclohexyl-	Methanol	145–146	5.32	5.18		−11	...	...	...	..
N,N′-Ethylene-	Methanol–water	136–137	7.22	7.17		−15.5	43.26	43.0	8.3	8.3
N-Hexadecyl-	....	123–124[b]	3.45	3.42	3.25	..				
N-Octadecyl-	....	118–119[b]	3.23	3.19	3.14	..				
N-Isopropyl-	Methanol–ethyl acetate	126–127[b]	6.27	5.71	5.64	−13				
N-2-Octyl-	Ethyl acetate	107–108[b]	4.77	4.63		..				
N,N′-Propylene	Methanol–water	135–137	6.97	6.92		..				

[a] One per cent. solution in 50% ethanol. [b] Softened earlier.

under reflux on a water-bath at 70° until the glucose went into solution and for ten minutes thereafter. The solution was cooled and 20 ml. of ethanol, then 100 ml. of ether, was added. The needle-like crystals that formed were filtered by suction and washed repeatedly with ether; yield 11 g. The compound was recrystallized from dioxane and washed with petroleum ether. Recrystallization from alcohol and ether usually resulted in the formation of a gelatinous precipitate rather than the desired crystals. The product was dried over phosphorus pentoxide under reduced pressure. The melting point of the crystals was usually about 86–87° but, after repeated crystallization, the melting point was raised to 96–97°. The specific rotation after five minutes was $(\alpha)^{25}D$ −22° (*c*, 2; C_2H_5OH); this changed to a constant value of −7.8° in less than one hour.

Anal. Calcd. for $C_{10}H_{23}O_6N$: N, 5.53. Found: N, 5.48, 5.49.

Glucosyl-*n*-amylamine.—The same procedure as given above was used; yield 11 g. The melting point of the compounds after thorough drying was 96–97°, which was not changed after recrystallization from alcohol–ether. The specific rotation after twelve minutes was $(\alpha)^{25}D$ −22°; this changed to a constant value of −8° (*c*, 2; C_2H_5OH).

Anal. Calcd. for $C_{11}H_{25}O_6N$: N, 5.25. Found: N, 5.28, 5.28.

Glucosyl-*n*-heptylamine.—The same procedure was used for the preparation of this glucosylalkylamine as was employed for the preparation of the *n*-butyl compound. Thirteen grams of white needles, recrystallized from a butanol–Skelly D mixture, was obtained. The compound could also be recrystallized from methanol or methanol–water mixtures, or from water alone if the solution were cooled rapidly enough to preclude appreciable hydrolysis; m. p. 97–98°, $(\alpha)^{25}D$ −13° after ten minutes, changing to a constant value of −7° (*c*, 2; C_2H_5OH).

Anal. Calcd. for $C_{13}H_{29}O_6N$: N, 4.74. Found: N, 4.70, 4.63.

Glucosyldicyclohexylamine.—To 9 g. (0.09 mole) cyclohexylamine was added 10 g. (0.056 mole) of glucose and 2 ml. of 0.5 *N* hydrochloric acid. This mixture was heated on the water-bath at 75° until the solution became homogeneous and for ten minutes thereafter. After the solution was cooled, 20 ml. of ethanol and 100 ml. of ether were added. After thirty-six hours in the refrigerator, 6 g. of crystals was obtained. The compound melted at 97–98°, with softening early. The specific rotation after four minutes was $(\alpha)^{25}D$ −23.5°; this changed to −11.6° in six hours (*c*, 2; C_2H_5OH). On analysis, it was found that two molecules of the amine had combined with the hexose and one molecule of water had been eliminated.

Anal. Calcd. for $C_{18}H_{36}O_5N_2$: N, 7.77. Found: N, 7.60, 7.75.

Efforts to obtain a condensation product from one molecule of glucose and one molecule of the amine were not successful. The second molecule of cyclohexylamine could not be removed by heating the compound at the boiling point of acetone for three hours under reduced pressure. Heating at 100° resulted in the darkening of the compound and after several hours 20.44% of the total weight was lost. Upon analysis, the nitrogen content was found to be 8.26%, indicating that water was removed from the glucosylalkylamine more easily than a cyclohexylamine molecule.

Diglucosylethylenediamine.—To 3.5 g. (0.06 mole) of ethylenediamine in 50 ml. of methanol, 21 g. (0.12 mole) of glucose was added. This mixture was refluxed gently on a water-bath until the glucose went into solution. The refluxing was continued and soon a precipitate appeared on the side of the flask. After two hours, the refluxing was discontinued, the flask cooled and left in the refrigerator overnight. Eleven grams of the compound, m. p. 152–154° (with decomposition), was obtained after filtering, washing with cold methanol, and drying. The product was recrystallized from methanol–water. The specific rotation $(\alpha)^{25}D$ −17° (*c*, 2; 50% C_2H_5OH) changed to a value of +14.5° in thirty-nine hours. This value represented partial hydrolysis as well as mutarotation.

Anal. Calcd. for $C_{14}H_{28}O_{10}N_2$: N, 7.29. Found: N, 7.35, 7.35.

Glucosyl-*n*-hexadecylamine.—Twenty-four grams (0.10 mole) of *n*-hexadecylamine was dissolved by warming in 50 ml. of ethanol and to this was added 18 g. (0.10 mole) of glucose and 50 ml. of ethanol. After the mixture was refluxed for several minutes, the glucose went into solution and the refluxing was continued for fifteen minutes. The precipitate that formed on cooling was filtered and washed with alcohol and ether; yield 31 g., m. p. 106–107° with softening somewhat earlier. The compound was purified by precipitation from hot ethanol. The specific rotation was not determined since the compound was not appreciably soluble in ordinary solvents at room temperature.

Anal. Calcd. for $C_{22}H_{47}O_6N$: N, 3.32. Found: N, 3.28, 3.26.

Glucosyl-*n*-octadecylamine.—Twenty-seven grams (0.10 mole) of *n*-octadecylamine was dissolved in 100 ml. of ethanol, and 18 g. (0.10 mole) of glucose added. This mixture was refluxed until the glucose went into solution and for fifteen minutes thereafter. The precipitate (37.5 g.) that formed on cooling the red-brown liquid was filtered and washed with alcohol and ether, then dried; m. p. 104–105° with softening earlier. The specific rotation was not determined.

Anal. Calcd. for $C_{24}H_{51}O_6N$: N, 3.12. Found: N, 3.01, 3.06, 3.01.

Attempted Condensations of Other Amines with Glucose.—Repeated attempts using the different methods of preparation for glucosylalkylamines were made to obtain pure crystalline condensation compounds from isopropylamine, 2-aminoöctane, and propylenediamine. Solid

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compounds were obtained by precipitation of the glucose–isopropylamine solution with ether, and by precipitation of the methanol or ethanol solution of propylenediamine and glucose, but the nitrogen analysis was high in all cases and the preparation melted over a range of several degrees. The compounds could not be recrystallized from any of the ordinary solvents. Evidence of reaction of all these amines with glucose was shown by the ease of solution of the sugar in the alcohol containing the anhydrous amine as well as by the analysis of the amorphous products obtained.

Reduction of the Glucosyl-*n*-alkylamines.—All of the glucosyl-*n*-alkylamines prepared were hydrogenated in a Parr type bomb using activated Raney nickel as a catalyst.[10] The physical constants and nitrogen analyses of the compounds are given in Table I. Ten grams of the glucosyl-*n*-alkylamines was dissolved in 200 ml. of solvent (methanol, ethanol or alcohol–water mixtures). The reduction was carried out below 100° (most often 70–83°) at pressures of 800 to 1300 lb. of hydrogen. The amount of catalyst was varied from 2.5 to 9 g. and the time of reaction from seven to fourteen hours. No effort was made to determine the minimum conditions necessary for complete reduction. Good yields were obtained except from glucosyl-*n*-hexadecylamine and glucosyl-*n*-octadecylamine which, after reduction and partial removal of the solvent, gelatinized and were difficult to obtain as solids.

N-Isopropyl-*d*-glucamine, N,N′-propylenediglucamine and N-2-octyl-*d*-glucamine were prepared, even though the corresponding glucosyl derivatives were not isolated in the pure state. A solution of the glucoside of 2-aminoöctane and of isopropylamine was obtained by the same method used for the preparation of the glucosyl-*n*-butylamine, except that after the solution was homogeneous, 75 ml. of ethanol was added and the solutions refluxed for one-half hour. In the reduction of diglucosylpropylenediamine, 12 g. (0.067 mole) of glucose was refluxed with 2.5 g. (0.034 mole) of propylenediamine in 60 ml. of methanol for one hour. Before reduction 150 ml. of 50% methanol was added. Although complete reduction of the diglucosylpropylenediamine occurred, only a very small amount of the reduced compound was isolated.

N-Isopropyl-*d*-glucamine was not pure as was shown by the nitrogen analysis. The compound gelatinized on attempted recrystallization from alcohol, but precipitated from a methanol-ethyl acetate mixture. Since the nitrogen value of the compound was still somewhat low, the impurity was believed to be sorbitol.

Hydrolysis of Glucosyl-*n*-alkylamines.—Glycosyl-*n*-butylamine was selected as a representative compound of this series, and the equilibrium of 0.5000 g. of the compound in 25 ml. of water was followed. From the change in optical rotation, it was evident that equilibrium was reached in twenty-two hours at room temperatures. On the assumption that only one form of the glucosylamine was present, and that it dissociated into glucose and the amine, the amount of the compound that had dissociated was calculated to be 56.9%. Potentiometric titration of the solution at equilibrium indicated that 39.5% of the compound had hydrolyzed. By extraction with ether an amount of the amine equivalent to 44% of the glucosyl-*n*-alkylamine was recovered. It was evident that mutarotation as well as hydrolysis occurred in aqueous solution. In methanol solution, mutarotation but no hydrolysis occurred. The other glucosyl-*n*-alkylamines behaved in much the same manner, the amount of hydrolysis depending upon the concentration and the temperature.

Hydrolysis of Other Amine Derivatives of Glucose.—Glucosyl-*n*-arylamine as well as the N-aryl-isoglucosamines were prepared by the method given by Weygand.[11] The change in rotation of *p*-toluidine-*d*-glucoside in aqueous solution was followed, and the amount of amine liberated after ninety hours was determined by extracting and weighing the extracted amine. Extraction of the 0.008 molar solution of the N-glucoside in water indicated only 8% hydrolysis. The isoglucosamine did not hydrolyze.

1-Aminoglucose was prepared by the method of Ling and Nanji.[12] The compound, after recrystallization from 95% methanol, appeared to be the hydrated compound, m. p. 120–121°, $(\alpha)^{24}D$ +19.1° (0.1001 g. in 1.694 ml. water, 1-dm. tube). Values found in the literature for the melting point of glucose ammonia and 1-aminoglucose vary from 120 to 131°, the rotation from +19.5 to +22.6°.

Anal. Calcd. for $C_6H_{15}O_6N$: N, 7.10. Found: N, 7.01.

1-Aminoglucose is remarkably stable in aqueous solution at ordinary temperatures as evidenced by the very slight change in rotation. This stability was confirmed by potentiometric titration of 1-aminoglucose with dilute acid, and titration of the amine in the presence of a known amount of ammonium hydroxide. After seventy-three hours, no measurable amount of ammonia had been liberated. However, slight acidity or higher temperatures cause immediate hydrolysis.

1-Aminoglucose pentaacetate was prepared from 1-aminoglucose and N-acetyl-1-aminoglucose was obtained from this compound according to the method of Brigl and Keppler.[13] This amide derivative was not hydrolyzed in aqueous solution or in dilute acid. It was hydrolyzed, however, by heating with 1 *N* acid.

Attempted Condensation of Acetamide with Glucose and Acetobromoglucose.—Two grams (0.034 mole) of acetamide was added to 6 g. (0.033 mole) of glucose in 100 ml. of methanol; after a few minutes refluxing on a water-bath, all of the glucose went into solution. The refluxing was discontinued after two hours and most of the solvent was removed under reduced pressure. Although no N-acetyl-1-aminoglucose was obtained even on seeding, the solution of the glucose in the alcohol and the inability to extract with hot chloroform more than one-third of the amide from the solvent-free residue indicated that a reaction had taken place. Such a reaction would be expected, in analogy to the glycosides of urea which have been reported.[4b]

When 10 g. (0.024 mole) of acetobromoglucose prepared by the method of Fischer[14] was refluxed with 4.0 g. (0.068 mole) of acetamide in 20 ml. of chloroform, crystals appeared in the solution after approximately thirty minutes. On analysis for bromine it was found that the crystals were diacetamide hydrobromide that sublimed 95–100° and melted 138–139°. No crystals of pentaacetyl-1-aminoglucose were obtained when the filtrate was seeded.

The Amadori Rearrangement.—Although this rearrangement was easily effected on N-glucosides of the arylamines, neither the alkylamine nor acylamine derivatives of glucose formed the rearranged product. In fact, the best method of preparation of the glucosylalkylamines from the low molecular-weight alkylamines was a procedure that was used for the preparation of the isoglucosamines in the aryl series. A further attempt to effect the rearrangement or partial rearrangement of the glucosylalkylamines was made by refluxing 1 g. of glucose in 10 g. of *n*-butylamine for three hours. Although the resulting gold-colored solution reduced methylene blue fairly rapidly (rapid reduction of methylene blue was used as evidence for the formation of isoglucosamine), only impure crystals of glucosyl-*n*-butylamine could be obtained after rapid removal of excess amine and precipitation with alcohol-ether. No evidence of any kind was obtained to indicate that the N-acyl derivative underwent even partial rearrangement.

Amine Derivatives of 2-Methylglucose.—The phenylhydrazine derivative of 2-methylglucose was prepared by allowing 1.65 g. of phenylhydrazine in 1 ml. of water to stand overnight in the presence of 0.55 g. of the monosaccharide (m. p. 150–155°) and one drop of glacial acetic acid. This derivative melted 176–177° and had a methoxyl content 11.1% as compared to the calculated value of 10.93%. Glucose phenylosazone was obtained by refluxing the phenylhydrazine derivative of 2-methylglucose with phenyl-

(10) Mozingo in "Organic Syntheses," Editor, N. L. Drake, John Wiley and Sons, Inc., New York, N. Y., 1941, Vol. 21, p. 15.

(11) Weygand, *Ber.*, **72**, 1663 (1939); **73**, 1259 (1940).

(12) Ling and Nanji, *J. Chem. Soc.*, **121**, 1682 (1922).

(13) Brigl and Keppler, *Z. physiol. Chem.*, **180**, 38 (1929).

(14) Fischer, *Ber.*, **49**, 584 (1916).

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hydrazine and glacial acetic acid in aqueous solution as had been reported by Brigl and Schinle.[8] The analysis for the glucose phenylosazone is as follows.

Anal. Calcd. for $C_{18}H_{22}O_4N_4$: N, 15.64; OCH_3, 0.00. Found: N, 15.93; OCH_3, 0.40.

The *p*-toluidide of 2-methylglucose was prepared by heating 1.04 g. of the monomethyl sugar (OCH_3, 15.27%) with 0.72 g. of *p*-toluidine and 0.30 ml. of water. The mixture was heated on a water-bath until the solution became homogeneous and for ten minutes thereafter to insure complete reaction. After cooling, 2 ml. of 95% ethanol and 4 ml. of ether was added. Cooling in the refrigerator yielded a precipitate (0.15 g.) that was identified as unchanged 2-methylglucose. The mother liquor was evaporated to 1.5 ml. and left overnight; needle-like crystals (0.55 g.), m. p. 150–151° after purification, were obtained.

Anal. Calcd. for $C_{14}H_{21}O_5N$: OCH_3, 10.95. Found: OCH_3, 10.7.

Prolonged refluxing in the water–ethanol solvent with dilute acetic acid and with dilute hydrochloric acid gave no evidence for the Amadori rearrangement; crystals of the glucoside were isolated in all cases.

Summary

Physical properties are reported for a number of glucosylalkylamines and the corresponding glucamines.

The glucamines formed from primary amines of intermediate molecular weight are good wetting agents.

An approximation of the degree of hydrolysis of the various N-substituted glucosides was made by comparison of changes in rotation, by potentiometric titration and by extraction of the hydrolyzed amine. With the exception of the first member of the series, 1-aminoglucose, ease of hydrolysis appears to parallel the K_B of the nitrogen substituent.

An attempt was made to effect the Amadori rearrangement of the glucosylalkylamines and the acyl derivatives of 1-aminoglucose. No rearranged product could be isolated in either case.

The *p*-toluidide and phenylhydrazine derivative of 2-methylglucose were prepared. The methoxyl group on the second carbon atom prevented rearrangement of the *p*-toluidide, but glucose phenylosazone was prepared from the phenylhydrazine derivative of 2-methylglucose.

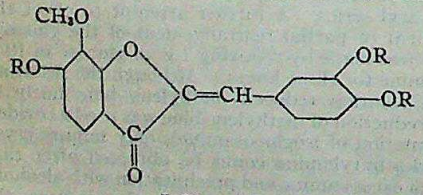
AMES, IOWA RECEIVED AUGUST 23, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

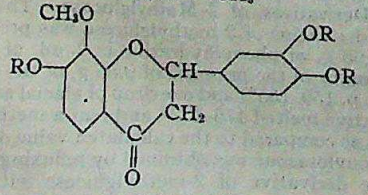
Anthochlor Pigments. V. The Pigments of *Coreopsis grandiflora*, Nutt. II

BY T. A. GEISSMAN AND CHARLES D. HEATON

In the preceding paper of this series,[1] structures were proposed for leptosin, leptosidin and a flavanone, constituents of the flower petals of *Coreopsis grandiflora*, Nutt. Leptosin and leptosidin are related as glycoside and aglycon, and to the latter was assigned the structure of 7-methoxy-3′,4′,6-trihydroxybenzalcoumaranone (I). The position of the sugar residue (presumably glucose) in leptosin was assumed to be 6, on the basis of certain distinctive color reactions of the glycoside. The structure of the flavanone was considered to be II, both because of the correspondence in the positions of the hydroxyl and methoxyl groups in this structure and in that chosen for leptosidin, and because of the similarity between certain color reactions of the flavanone and those of butin (3′,4′,7-trihydroxyflavanone).



I, R = H
III, R = CH_3



II, R = H
IV, R = CH_3

We have synthesized 3′,4′,6,7-tetramethoxybenzalcoumaranone (III) by the condensation of veratraldehyde with 6,7-dimethoxycoumaranone. The product, crystallizing in bright yellow needles, did not depress the melting point of fully methylated leptosidin. This establishes for the first time the occurrence in nature of a substance possessing the benzalcoumaranone nucleus.

3′,4′,7,8-Tetramethoxyflavanone (IV) has been described by Kostanecki and Rudse,[2] who reported its melting point as 144°. While the trimethyl ether of the naturally-occurring flavanone analyzed correctly for this structure and showed color reactions which left no doubt that it was a flavanone and pointed strongly to the probability that it had structure IV, it melted at 139–140°, a fact which left some doubt as to its identity with the flavanone described by Kostanecki and Rudse. The synthesis of IV has shown that the trimethyl ether of the naturally-occurring flavanone is indeed 3′,4′,7,8-tetramethoxyflavanone. The condensation of gallacetophenone 3,4-dimethyl ether with veratraldehyde yielded 2′-

(1) Geissman and Heaton, THIS JOURNAL, 65, 677 (1943).

(2) Kostanecki and Rudse, *Ber.*, 38, 937 (1905).

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hydroxy-3′,4′,3,4-tetramethoxychalcone, and this was isomerized to the flavanone by treatment with dilute alcoholic hydrochloric acid. The product melted at 137–139° even after repeated recrystallization from dilute alcohol, and retained a pale yellow color. It did not depress the melting point of the natural substance and gave the same blue-violet color when reduced with magnesium and alcoholic hydrochloric acid. Further study showed that it was contaminated with a small amount of the chalcone, and when this was removed the pure flavanone, m. p. 143.5–144°, was obtained. A mixture of this material and that obtained from the natural source melted at 142.5–143°.

The position of the methoxyl group in leptosidin and in the flavanone, and the point of attachment of the sugar residue in leptosin still rest upon the inferences drawn from the observations previously reported.[1] These inferences carry additional weight in view of the establishment of the disposition of the oxygen atoms in these compounds, but direct proof is still needed and will be the object of further work.

Experimental

6,7-Dimethoxycoumaranone.—To a suspension of 4.0 g. of α-chlorogallacetophenone[3] in 30 ml. of hot water was added 12 g. of sodium carbonate, followed by 10 ml. of dimethyl sulfate, with stirring. After the reaction was complete, an additional 6 g. of sodium carbonate and 3 ml. of dimethyl sulfate were added and the mixture warmed for a few minutes longer. The semi-solid mixture was filtered and the solid removed and stirred with warm alcohol to remove inorganic salts. Upon cooling the alcoholic solution the product separated as reddish crystals. Recrystallized from alcohol, the compound formed light pink crystals, m. p. 122–123°[4] (literature,[5] m. p. 122°).

3′,4′,6,7-Tetramethoxybenzalcoumaranone (III).—A solution of 0.5 g. of veratraldehyde and 0.5 g. of 6,7-dimethoxycoumaranone in 10 ml. of warm alcohol was treated with 3 ml. of 30% aqueous sodium hydroxide solution. Yellow crystals began to form at once and in less than a minute the reaction mixture had set to a crystalline mass. The product (0.68 g., 84%) was collected and recrystallized from aqueous alcohol. The bright yellow needles melted at 156–157° and further recrystallization did not change the melting point. A mixture of the synthetic material with leptosidin trimethyl ether (m. p. 156–157°) melted at 156–157°.

2′-Hydroxy-3′,4′,3,4-tetramethoxychalcone.—A solution of 0.5 g. of gallacetophenone 3,4-dimethyl ether[6] and 0.45 g. of veratraldehyde in 4 ml. of warm alcohol was treated with 2 g. of hot 50% sodium hydroxide solution. The mixture was shaken and kept hot for fifteen minutes, cooled and poured into dilute hydrochloric acid. The oily precipitate solidified on standing. It was recrystallized from dilute alcohol, yielding 0.51 g. of yellow-orange needles, m. p. 121–122° (literature,[2] 119°).

3′,4′,7,8-Tetramethoxyflavanone (IV).—A solution of 0.25 g. of the chalcone in a mixture of 20 ml. of alcohol, 8 ml. of concentrated hydrochloric acid and 25 ml. of water was refluxed for four hours, evaporated to half its volume and poured into dilute hydrochloric acid. The yellow oil which separated soon solidified. After seven recrystallizations from dilute alcohol the flavanone was still pale yellow in color and melted at 137–139° (literature,[2] 144°). A mixed melting point with the fully methylated naturally-occurring flavanone, m. p. 139–140°, was 138–140°. The two substances gave identical colors when reduced side by side with magnesium and alcoholic hydrochloric acid.

The synthetic material was recrystallized from carbon disulfide, and careful examination of the product showed that it was a mixture of yellow-orange rosets and pale yellow needles. A partial mechanical separation of these two substances, followed by recrystallization of the nearly colorless material from carbon disulfide, afforded nearly colorless needles of the pure flavanone, m. p. 143.5–144°. A mixture of this material with the natural substance (m. p. 139–140°) melted at 142.5–143°.

Anal. Calcd. for $C_{19}H_{20}O_6$: C, 66.26; H, 5.86. Found: C, 66.10; H, 5.92.

Summary

Leptosidin trimethyl ether and the trimethyl ether of the flavanone accompanying leptosidin in the flower petals of *Coreopsis grandiflora*, Nutt, have been identified as 3′,4′,6,7-tetramethoxybenzalcoumaranone and 3′,4′,7,8-tetramethoxyflavanone, respectively.

The proof of the structure of leptosidin trimethyl ether establishes for the first time the occurrence in nature of a compound possessing the benzalcoumaranone nucleus.

LOS ANGELES, CALIFORNIA RECEIVED AUGUST 19, 1943

(3) Nencki, *J. Russ. Phys.-Chem. Soc.*, **25**, 182 (1883).

(4) Melting points are uncorrected.

(5) Felix and Friedländer, *Monatsh.*, **31**, 63 (1910).

(6) Baker, Jukes and Subrahmanyam, *J. Chem. Soc.*, 1682 (1934).

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF BROOKLYN COLLEGE]

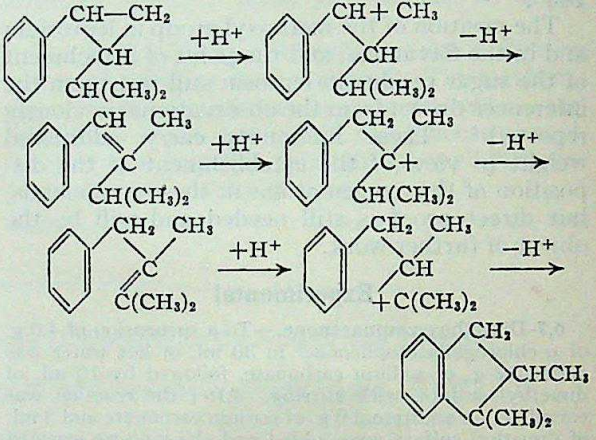
The Action of Sulfuric Acid on 1-Phenyl-2-alkylcyclopropanes[1,2]

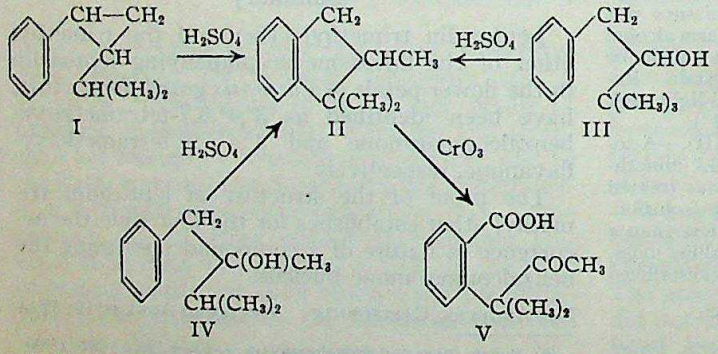
BY DAVID DAVIDSON AND JULIAN FELDMAN

Since the chemistry of the cyclopropane ring resembles that of the olefinic double bond it was of interest to compare the behavior of certain monophenylated cyclopropanes toward sulfuric acid with that of monophenylated olefins, which, if not polymerized, are converted to indans or tetralins.[3]

In the case of 1-phenyl-2-isopropylcyclopropane (I), the action of 90% sulfuric acid produced a low yield of 1,1,2-trimethylindan (II), a product previously obtained by the cyclodehydration of 1-phenyl-3,3-dimethyl-2-butanol (III)[4] and of 1-phenyl-2,3-dimethyl-2-butanol (IV).[5] This product is readily identified by its oxidation to the ketone acid (V). Treatment of 1-phenyl-2-methylcyclopropane[6] and of 1-phenyl-2-ethylcyclopropane with 90% sulfuric acid yielded gummy polymers and only traces of volatile oils.[7]

The foregoing results suggest that the attack on the 1-phenyl-2-alkylcyclopropanes by sulfuric acid begins with the opening of the cyclopropane ring by the addition of a proton to the least substituted carbon atom.[8] The resulting carbonium ion, which may also be obtained from olefins or alcohols, may then undergo its characteristic reactions; *i. e.*, addition to an unsaturated molecule (*polymerization*), decomposition to a smaller carbonium ion and an unsaturated molecule (*depolymerization*), isomerization to another carbonium ion (*rearrangement*), or decomposition into an olefin and a proton (*protolysis*). In the case of 1-phenyl-2-isopropylcyclopropane the changes shown below may be postulated.





Preliminary tests with higher homologs and with milder acid (85% phosphoric acid) indicate that isomerization to olefins actually does occur. Only with the isopropyl derivative are conditions very favorable for cyclization[3]; hence, in the other cases polymerization results.

Experimental

1-Phenyl-2-alkylcyclopropanes.—These hydrocarbons (Table I) were prepared by Kishner's method.[6,7,9] This involves the decomposition of certain pyrazolines in the presence of platinized asbestos and solid potassium hydroxide, the pyrazolines themselves resulting from the condensation of α,β-unsaturated ketones with hydrazine hydrate. The required unsaturated ketones were prepared by condensing benzaldehyde with methyl alkyl ketones in the presence of aqueous sodium hydroxide.[10] Good yields (75–80%) were obtained in each step.

TABLE I

1-PHENYL-2-ALKYLCYCLOPROPANES

R	B. p., °C.	d^{20}_4	$n^{20}D$	Reference
H	174	0.940	1.5316	7
CH_3	186	.920	1.5208	6
	184–186	.925	1.5237	This paper
CH_3CH_2	203–205	.918	1.5162	This paper
$(CH_3)_2CH$	213–216	.899	1.5072	This paper

(1) Presented before the Division of Organic Chemistry at the 100th meeting of the American Chemical Society held at Detroit, Michigan, September, 1940.

(2) This article is based on the thesis presented by Julian Feldman in partial fulfillment of the requirements for the degree of Master of Arts, Brooklyn College, 1940.

(3) Roblin, Jr., Davidson and Bogert, THIS JOURNAL, **57**, 151 (1935).

(4) Price, Davidson and Bogert, *J. Org. Chem.*, **2**, 540 (1938).

(5) Bogert and Davidson, THIS JOURNAL, **56**, 185 (1934).

(6) Kishner, *J. Russ. Phys.-Chem. Soc.*, **44**, 862 (1912); *C. A.*, **6**, 2915 (1912).

(7) Kishner, *J. Russ. Phys.-Chem. Soc.*, **45**, 950 (1913); *C. A.*, **7**, 3965 (1913), found that phenylcyclopropane was polymerized by sulfuric acid.

(8) Compare the modernized version of Markovnikov's rule (Fuson and Snyder, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1942, p. 19). The applicability of Markovnikov's rule to cyclopropanes was shown by Kishner,[6] who found hydrogen bromide to add to 1-phenyl-2-methylcyclopropane to form 1-phenyl-1-bromo-2-methylpropane.

(9) Kishner, *J. Russ. Phys.-Chem. Soc.*, **61**, 781 (1929); *C. A.*, **23**, 4698 (1929).

(10) Harries and Müller, *Ber.*, **35**, 966 (1902).

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The Conversion of 1-Phenyl-2-isopropylcyclopropane to 1,1,2-Trimethylindan.—While stirring, 14.4 g. of 1-phenyl-2-isopropylcyclopropane was run into 30 ml. of 90% sulfuric acid. Within a half hour the temperature rose to 40° after which it was maintained at 35° for one hour. The residual oil was removed by adding 25 ml. of ligroin, separating from the acid, washing the ligroin layer twice with 5-ml. portions of cold, concentrated sulfuric acid, steam distilling, separating the volatile oil, removing the ligroin by distillation through a short Widmer column, and distilling the residue. This gave 3.2 g. of 1,1,2-trimethylindan, b. p. 208°, d^{20}_4 0.919, $n^{20}D$ 1.5137.

Analyses.[11] Calculated for $C_{12}H_{16}$: C, 89.9; H, 10.1. Found (1-phenyl-2-isopropylcyclopropane): C, 89.7; H, 10.1. Found (1,1,2-trimethylindan): C, 89.7; H, 10.2.

Oxidation of 0.46 g. of the product obtained above by the method of Price, Davidson and Bogert[4] yielded 0.30 g. of the ketone acid (V) which when recrystallized from water melted at 156°. This did not depress the melting point of an authentic sample of the acid melting at 158°. Both samples gave iodoform when treated with sodium hypoiodite.

(11) These analyses were performed by Mr. Saul Gottlieb, Columbia University.

Summary

1. 1-Phenyl-2-isopropylcyclopropane is rearranged by 90% sulfuric acid to 1,1,2-trimethylindan.

2. Under similar conditions 1-phenyl-2-methylcyclopropane and 1-phenyl-2-ethylcyclopropane undergo polymerization.

3. Cyclopropanes obey the modernized Markovnikov rule.

BROOKLYN, N. Y. RECEIVED DECEMBER 30, 1943

[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE OF AGRICULTURE AND APPLIED SCIENCE]

The Isolation of Stigmasterol and β-Sitosterol from the Common Bean, *Phaseolus vulgaris*

BY ARNOLD C. OTT[1] AND CHARLES D. BALL

The content of the "crude fat" of the common or navy bean, *Phaseolus vulgaris*, has been reported by various workers[2] to be between 1.4 and 2.36%. Grimme[3] submitted values for certain physical and chemical constants of the oil among which was an unsaponifiable matter percentage of 5.85. Likiernik[4] appeared to be the only worker to have isolated sterols from any part of the bean. He obtained from the seed coats two substances named by him paraphytosterol and phasol. In harmony with the work of Anderson and Shriner[5] paraphytosterol would appear to be γ-sitosterol, while phasol, m. p. 189–190°, $[\alpha]_D$ + 30.6°, is either a mixture or has not been identified with any of the better known sterols. Attention has been focused on the ether soluble portion of the navy bean by the recent observation of Bowman,[6] who maintains that the bean oil retards the digestion of soluble starch by pancreatic amylase *in vitro*.

In the present work the bean oil, "ether extract," has been found to represent about 2.6% of the bean, of which 5.0 to 6.0% was unsaponifiable matter. This unsaponifiable matter consisted of 55 to 60% crude sterols. Stigmasterol made up about one-fourth of the sterols, while β-sitosterol was found to be present to the extent of 5 to 7% of the total sterols. The separation of the stigmasterol was based on the insolubility of the tetrabromide while the β-sitosterol was obtained from the mother liquors after debromination and fractional crystallization as acetates. No sterols corresponding to α-sitosterols appeared to be present in any appreciable amount. After irradiation the unsaponifiable matter had a vitamin-D activity of about 700 U. S. P. units per g. of unsaponifiable matter, thus indicating the presence in very small amount or amounts of irradiatable sterol or sterols.

(1) Present address: Hercules Powder Co., Wilmington, Del.

(2) (a) Atwater and Bryant, *U. S. Dept. Agr. Off. Exp. Sta. Bul.*, 28 Rev. (1906); (b) Peterson and Churchill, THIS JOURNAL, **43**, 1180 (1921); (c) Eichelberger, *ibid.*, **44**, 1407 (1922).

(3) Grimme, *Pharm. Zentr.*, **52**, 1141 (1911).

(4) (a) Likiernik, *Ber.*, **24**, 187 (1891); (b) Likiernik, *Z. physiol. Chem.*, **15**, 426 (1891).

(5) Anderson and Shriner, THIS JOURNAL, **48**, 2976 (1926).

(6) Bowman, *Science*, **98**, 308 (1943).

Experimental

1. Extraction of the Beans.—Forty kg. of the common bean, *Phaseolus vulgaris*, was ground in a hammer mill and extracted six times by cold ethyl ether. The extract was filtered and the solvent distilled off in an atmosphere of carbon dioxide. The yield was 0.83 kg. of yellow oil, which represented 1.9% of the original beans.

2. Saponification.—To the entire lot of the oil 4 liters of ethanol and 1 liter of 50% potassium hydroxide were added. The mixture was stirred on the steam-bath for two hours. Water was then added and the unsaponifiable matter was exhaustively extracted from the soaps with "Skellysolve B." The combined extracts were concentrated to 50% concentration of oil and then washed free from alkali. The remainder of the solvent was evaporated; yield, 48.7 g. of a yellow, semi-solid oil. This quantity represented about 5.9% of the crude oil.

3. Preparation of Crude Sterols.—The entire lot of unsaponifiable material was taken up in petroleum ether, b. p. 40–60°, and steam passed into the solution until saturation nearly occurred. The solution was then allowed to stand overnight. The first fraction of crystals, designated Fraction I, consisted of 22.5 g. of colorless crystals; m. p. 138–144°; $[\alpha]^{27}D$ −44.0° (35.4 mg., 2.1 ml. chloroform, l = 1 dm., $\alpha^{27}D$ −0.742°, *average* reading). The Liebermann–Burchard reaction was strongly positive. The mother liquor was evaporated to 300 ml. and allowed to stand for twenty-four hours in the cold. The result was Fraction II, which consisted of 7.2 g. of crystals, m. p. 128–131°; $[\alpha]^{26}D$ −38.0° (38.6 mg., 2.1 ml. chloroform, l = 1 dm., $\alpha^{26}D$ −0.698°, *average* reading). A third fraction of about 2 g. was obtained from the mother liquors of

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fraction II. The total crude sterols amounted to 29–30 g. or about 60% of the unsaponifiable matter.

4. Separation of Sterols.—An unsuccessful attempt was made to separate the sterols as azobenzenemonocarboxylic esters according to the chromatographic method of Ladenburg, Fernholz and Wallis.[7] From their work the separability of sterols on alumina depends primarily upon differences between the number of double bonds, and not upon their position or upon the nature of the side chains. Inference might be implied that the sterols of the common bean are all of the same general type.

One and one-half g. portions from each of Fractions I and II were combined, and acetylated with 60 ml. of acetic anhydride, by refluxing for one and one-half hours. The mixture was concentrated to saturation and after cooling for one hour at 12°, the crude acetates were filtered off. The acetates were brominated by solution in 30 ml. of ethyl ether and the addition of 38 ml. of bromine–acetic acid solution (5 g. bromine in 100 ml. of glacial acetic acid) following the procedure of Windaus and Hauth.[8] After refrigeration the insoluble bromides were filtered and washed with cold ethyl ether. A yield of 1.4 g., m. p. 190–194°, was obtained. Six recrystallizations of the bromides from chloroform–methanol gave a product with a m. p. of 194–196°.

Stigmasteryl Acetate.—To a solution of 1.2 g. of the recrystallized bromides in 12 ml. of glacial acetic acid 1.2 g. of zinc dust was added. The mixture was refluxed for one and one-half hours, filtered hot, diluted with water, and extracted with ethyl ether. The ether layer was washed with dilute sodium sulfite, then with water, and the ether removed by evaporation. The product obtained weighed 580 mg. It was recrystallized four times from ethanol, and twice from 2–1 methanol–chloroform; m. p. 139–140°; $[\alpha]^{25}D$ −54.0° (37.4 mg., 2.1 ml. chloforoform, l = 1 dm., $\alpha^{25}D$ −0.962°, *average* reading).

Anal.[9] Calcd. for $C_{31}H_{50}O_2$: C, 81.88; H, 11.09. Found: C, 81.18; H, 10.73.

Stigmasterol.—Four hundred mg. of the above acetate was hydrolyzed for one hour with 10% alcoholic potassium hydroxide. Water was added and the mixture extracted with ethyl ether. The ether solution was washed with dilute sodium carbonate, and then with water. After removal of the ether, the residue was recrystallized three times from 95% ethanol, m. p. 168–169°; $[\alpha]^{29}D$ −47.3° (28.6 mg., 2.1 ml. chlofororm, l = 1 dm., $\alpha^{29}D$ −0.644°, *average* reading).

Anal. Calcd. for $C_{29}H_{48}O$: C, 84.40; H, 11.72. Found: C, 83.47; H, 11.70.

Stigmasteryl Benzoate.—About 300 mg. of the free sterol was dissolved in 2 ml. of dry pyridine; then 0.6 ml. of benzoyl chloride was added. The mixture was heated for two and one-half hours in a glass-stoppered flask on the steam-bath and allowed to cool. The contents were poured into ice-cold 5% sulfuric acid. The solution was extracted with ethyl ether, washed with dilute sodium carbonate, and then with 10% ethanol. The extract was evaporated on the steam-bath and the residue recrystallized three times from ethanol and once from methanol–chloroform; m. p. 160.5–161.5°; $[\alpha]^{24}D$ −24.5° (152.3 mg., 2.1 ml. chloroform, l = 1 dm., $\alpha^{24}D$ −1.779°, *average* reading).

Anal. Calcd. for $C_{36}H_{52}O_2$: C, 83.65; H, 10.14. Found: C, 83.95; H, 9.83.

β-Sitosteryl Acetate.—The remainders of Fractions I and II were combined with the small amount of the third fraction. This combined fraction was converted into acetates by treatment with 250 ml. of acetic anhydride and refluxing for two and one-half hours. On cooling, a yellow, wax-like cake appeared on the surface, while suspended below colorless crystals were observed. The colorless crystals were dissolved by warming the solution to about 40°, and the colored, wax-like cake removed by filtration. The filtrate was reduced in volume to effect a more complete crystallization, cooled in the refrigerator for one hour, filtered and washed with cold glacial acetic acid. The product obtained (about 10 g.) was brominated as previously described, the brominated products filtered off, and the derivatives in the filtrate debrominated in the usual manner with zinc dust. The debrominated acetates were taken up in sufficient 1–1 acetone–chloroform to effect a solution about one-half saturated. After standing overnight, the solid acetates were removed by filtration. The acetates were subjected to a triangular fractionation[10] first with a 3–1 acetone–methanol mixture and subsequently with a 3–1 ethanol–benzene mixture. From this fractionation appeared: (1) a wax-like material, insoluble in cold concentrated sulfuric acid, with a m. p. of 65–66.5° after thirteen recrystallizations from ethanol–benzene and (2) β-sitosteryl acetate; m. p. 123–124°; $[\alpha]^{28}D$ −38.5° (40.5 mg., 2.1 ml. chloroform, l = 1 dm., $\alpha^{28}D$ −0.744°, *average* reading).

Anal. Calcd. for $C_{31}H_{52}O_2$: C, 81.52; H, 11.47. Found: C, 81.59; H, 10.96.

The first material was no further characterized.

β-Sitosterol.—The above acetate was saponified with 10% alcoholic potassium hydroxide, extracted and washed as usual. The product was crystallized three times from methanol–chloroform; m. p. 136–138°; $[\alpha]^{25}D$ −37.8° (19.2 mg., 2.1 ml. chloroform, l = 1 dm., $\alpha^{25}D$ −0.346°, *average* reading).

Anal. Calcd. for $C_{29}H_{50}O$: C, 83.99; H, 12.15. Found: C, 83.41; H, 11.25.

β-Sitosteryl Benzoate.—Fifty mg. of the free sterol was treated with 0.2 ml. of benzoyl chloride in 1.5 ml. of dry pyridine. The mixture was heated for one and one-half hours on the steam-bath and allowed to stand. The contents of the reaction were poured into cold 5% sulfuric acid and the mixture extracted with ethyl ether. The residue obtained from the ether extraction was crystallized four times from ethanol; m. p. 145–146°; $[\alpha]^{25}D$ −13.5° (19.4 mg., 2.1 ml. chloroform, l = 1 dm., $\alpha^{25}D$ −0.125°, *average* reading).

In Table I are presented the data on the properties of stigmasterol and β-sitosterol and their derivatives as obtained or derived from the common bean, together with a comparison of the corresponding products as obtained from other sources by other investigators.

TABLE I

	M. p., °C.	$[\alpha]_D$ in $CHCl_3$
Stigmasterol (isolated from the common bean)	168–169	−47.3
acetate	139–140	−54.0
benzoate	160.5–161.5	−24.5
Stigmasterol[11]	169–170	−44.7 to 51.0
acetate[11]	141 to 144	−55.6
benzoate[11]	160	
β-Sitosterol (isolated from the common bean)	136–138	−37.8
acetate	123–124	−38.5
benzoate	145–146	−13.5
β-Sitosterol[11]	139–140	−36.1
acetate[11]	127–128	−39.1[12]
Unknown sterol (isolated from the common bean)	155–157	−55.8
acetate	134–135	
dinitrobenzoate	222–223	−17.3

Attempted Isolation of α-Sitosterols.—From the crystallization by triangulation as described under the isolation of

(7) Ladenburg, Fernholz and Wallis, *J. Org. Chem.*, **3**, 294 (1938).

(8) Windaus and Hauth, *Ber.*, **39**, 4378 (1906).

(9) Microanalyses are by Dr. T. S. Ma, University of Chicago.

(10) Morton, "Laboratory Techniques in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1938, p. 162.

(11) Sobotka, "The Chemistry of the Sterids," The Williams and Wilkins Co., Baltimore, Md., 1938, pp. 224 and 239.

(12) Gardner, this Journal, **48**, 2987 (1926).

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β-sitosteryl acetate, the fraction containing the soluble acetates was obtained by evaporation of the solvent on the steam-bath. The residue obtained was taken up in ethanol and hydrolyzed by the addition of alcoholic potassium hydroxide in the manner previously described. The solution obtained was worked up in the same manner as given for β-sitosterol. The product was dried and treated with sufficient 3,5-dinitrobenzoyl chloride in order to yield the corresponding esters. Triangular fractionation was again used in an attempt to isolate one of the three known "α-sitosterols," which according to Wallis and Fernholz[13] differ greatly in the solubilities of their 3,5-dinitrobenzoates. The most insoluble of the 3,5-dinitrobenzoates obtained had a m. p. of 222–223°; $[\alpha]^{28}D$ −17.3° (23.6 mg., 2.1 ml. chloroform, l = 1 dm., $\alpha^{28}D$ −0.195°, *average* reading). The regenerated free sterol melted at 155–157°; $[\alpha]^{28}D$ −55.8° (15.6 mg., 2.1 ml. chloroform, l = 1 dm., $\alpha^{28}D$ −0.415°, *average* reading). The acetate of the free sterol was prepared; m. p. 134–135°. The Liebermann–Burchard reaction was positive. Since all the derivatives of all the "α-sitosterols" have a positive value of relatively high magnitude for their optical rotations, the absence of any appreciable amounts of α-sitosterols is indicated, and the presence of an unknown sterol is indicated. A summary of the properties of this unknown sterol is also included in Table I.

5. Irradiation of the Unsaponifiable Matter.—A portion of the unsaponifiable matter was dissolved in ethyl ether and irradiated with ultraviolet light. Aliquots of this stock solution were taken for assay by the standard biological method. The results of the assay indicated an activity of 700 U. S. P. units per g. of crude unsaponifiable matter.[14]

(13) Wallis and Fernholz, THIS JOURNAL, **58**, 2446 (1936).

Summary

1. The total unsaponifiable matter of the common bean, *Phaseolus vulgaris*, is about 5.9%, or about 0.15% of the air-dry bean.

2. About 60% of the unsaponifiable matter is represented by crude sterols.

3. Stigmasterol and β-sitosterol have been isolated and characterized, the former representing about 25%, and the latter about 6% of the crude sterols.

4. An unidentified sterol with a high negative optical rotation has been isolated.

5. Neither α-sitosterols nor γ-sitosterol, the apparent paraphytosterol of Likiernik, have been found, although the presence of small amounts of these sterols is not precluded.

6. The unsaponifiable matter of the common bean after irradiation has a Vitamin-D activity of 700 U. S. P. units per g.

(14) The authors wish to thank Dr. C. A. Hoppert, Professor of Biological Chemistry, for the Vitamin-D assay.

EAST LANSING, MICH. RECEIVED JANUARY 3, 1944

[CONTRIBUTION FROM THE DEPARTMENTS OF CHEMISTRY OF THE UNIVERSITY OF TEXAS AND SOUTHWESTERN LOUISIANA INSTITUTE]

Studies in the Biphenyl Series. IV. The Iodination of the Acetate, Benzoate and Benzenesulfonate of 4-Hydroxybiphenyl[1]

BY HAROLD R. SCHMIDT, CORA MAY SAVOY[2] AND JOHN LEO ABERNETHY

In connection with an investigation of the bactericidal activity of certain halo-4-hydroxybiphenyls, it was of interest to find a more convenient route to 4-hydroxy-4′-iodobiphenyl than had been used previously. Since it is known that chlorination[3,4,5] and bromination[6,7] of certain esters of 4-hydroxybiphenyl give rise to substitution in the 4′-position of the biphenyl nucleus, and subsequent hydrolysis gives the desired 4′-chloro and 4′-bromo compound, it seemed that iodination of these esters might give rise to the corresponding iodo compounds. Hence, 4-acetyloxybiphenyl, 4-benzoyloxybiphenyl and 4-benzenesulfonyloxybiphenyl were subjected to iodination.

Iodination of 4-acetyloxybiphenyl (I) with iodine in the presence of nitric acid gave rise to 4-acetyloxy-4′-iodobiphenyl (II) when either carbon tetrachloride or glacial acetic acid was used as the solvent. Hydrolysis of the ester gave rise to 4-hydroxy-4′-iodobiphenyl (III) which did not depress the melting point of the known compound prepared from benzidine (IV), by converting IV to 4-amino-4′-iodobiphenyl (V) and then to III, according to the method of van Alphen.[8] Furthermore, acetylation of III produced an ester which did not depress the melting point of the product of iodination of I. It was found that a better yield of the iodinated ester (II) was obtained if nitric acid was added immediately to the reaction mixture rather than dropwise over a period of several hours. The latter procedure gave rise to a considerable amount of nitrated product, along with the iodinated ester.

By means of a similar reaction, 4-benzoyloxybiphenyl (I) was converted to 4-benzoyloxy-4′-iodobiphenyl (II). Benzoylation of III gave rise to this same ester. Hydrolysis of II yielded III. Similarly, iodination of 4-benzenesulfonyloxybiphenyl (I) yielded 4-benzenesulfonyloxy-4′-iodobiphenyl (II), which was proved by benzenesulfonation of III. Hydrolysis of II yielded III.

(1) A portion of this paper was abstracted from a thesis presented by Harold R. Schmidt to the Graduate Faculty of the University of Texas in partial fulfillment of the requirements for the degree of Master of Arts, August, 1943, and was presented before the Texas Academy of Science, November, 1943, in Austin, Texas.

(2) Present address: Department of Chemistry, Southwestern Louisiana Institute, Lafayette, Louisiana.

(3) Savoy and Abernethy, THIS JOURNAL, **64**, 2219 (1942).

(4) Savoy and Abernethy, *ibid.*, **64**, 2719 (1942).

(5) Schmidt, Savoy and Abernethy, *ibid.*, **65**, 296 (1943).

(6) Hazlet, *ibid.*, **59**, 1087 (1937).

(7) Hazlet, Alliger and Tiede, *ibid.*, **61**, 1447 (1939).

(8) van Alphen, *Rec. trav. chim.*, **50**, 1111 (1931).

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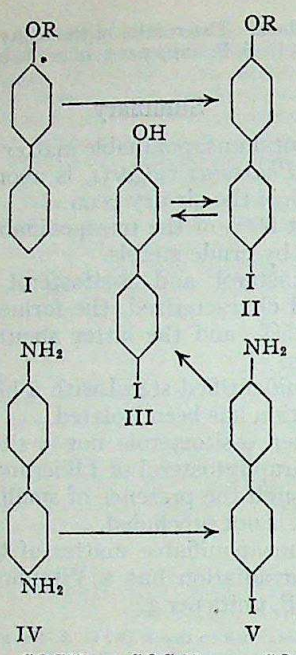
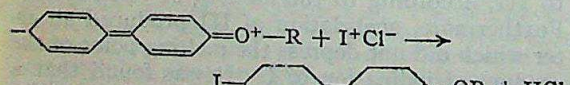


R = —$COCH_3$, —COC_6H_5 or —$SO_2C_6H_5$

Iodine monochloride has been found to be a suitable iodinating agent for many organic compounds which contain strong ortho-para directing substituents. Since iodine monochloride has a very high dipole moment, even in solvents of very low dielectric constant,[9] its ability to make an electrophilic attack on positions of relatively high electron density in aromatic compounds is readily explained. As there would be considerable resonance between the benzene rings of the biphenyl nucleus, particularly when the 4-position contains an acetyloxy, benzoyloxy or benzenesulfonyloxy substituent, and as the 3- and 5-positions are hindered by the ester linkages, it was anticipated that substitution by means of this incipiently ionized iodine monochloride would take place with relative ease. Such was found to be the case when either carbon tetrachloride or glacial acetic acid was used as the solvent.



R = —$COCH_3$, —COC_6H_5 or —$SO_2C_6H_5$.

Substituted esters identical with the ones prepared by iodination with iodine and nitric acid were formed.

Acknowledgment.—The authors are indebted to the Research Institute of the University of Texas for a grant which made this investigation possible.

Experimental

Iodination of 4-Acetyloxybiphenyl.—(a) A mixture of 10 g. of 4-acetyloxybiphenyl, prepared from 4-hydroxybiphenyl, 13.1 g. of iodine (10% excess), 100 ml. of carbon tetrachloride and 3 ml. of concentrated nitric acid was refluxed on a steam-bath for five hours and allowed to cool. The solvent was removed by distillation under reduced pressure, and the solid residue was crystallized from ethanol. After purification by recrystallization from ethanol, the pure 4-acetyloxy-4′-iodobiphenyl, which was obtained as lustrous white plates melting at 155° (cor.), weighed 6.1 g. (38.3% yield).

(b) Ten grams of 4-acetyloxybiphenyl and 13.1 g. of iodine were suspended in 100 ml. of glacial acetic acid, and a solution of 3 ml. of concd. nitric acid in 25 ml. of glacial acetic acid was added dropwise over a period of four hours. The mixture was refluxed during the addition of the nitric acid, and for one hour after. The product was cooled, poured into 800 ml. of ethanol, and recrystallized from ethanol. Pure 4-acetyloxy-4′-iodobiphenyl (2.2 g.) (13.8% yield) with m. p. 155° resulted. The rapid addition of nitric acid yielded a product of yellow needles (m. p. 201°) in greater quantity than the iodo compound. Nitration of 4-acetyloxybiphenyl in glacial acetic acid gave rise to the same yellow needles, m. p. 201°.

(c) Fifteen grams of 4-acetyloxybiphenyl was dissolved in 60 ml. of glacial acetic acid. To this solution 14.5 g. of iodine monochloride (Eastman Kodak Co. grade), dissolved in 20 ml. of glacial acetic acid, was added slowly over a period of one-half hour. The mixture was heated gently on a steam-bath during the addition. After all the iodine monochloride had been added the mixture was heated for three hours with constant stirring. Hydrogen chloride was liberated slowly.

At the end of the reaction period the mixture was cooled and poured into a large quantity of ice water. The oil which separated was dissolved in chloroform and the resultant solution was washed thoroughly with sodium bisulfite solution to remove the free iodine and then with water. After drying over anhydrous sodium sulfate, approximately one-third of the chloroform was removed under reduced pressure. Petroleum ether (b. p. 30–35°) was added to the remainder of the solution and 2.5 g. (10.5% yield) of pale yellow crystals separated. These were found to melt at 155–156° and proved to be 4-acetyloxy-4′-iodobiphenyl.

The remaining solution was concentrated further by the above procedure, yielding another precipitate. This solid was found to be soluble in ethanol which indicated that hydrolysis had taken place during the procedure. An attempt was made to benzoylate this solid. An oil formed which could not be solidified, which suggested that a mixture of several different substances was present. Further attempts to separate these products were unsuccessful.

Hydrolysis of 4-Acetyloxy-4′-iodobiphenyl.—Ten grams of 4-acetyloxy-4′-iodobiphenyl, prepared by the iodination of 4-acetyloxybiphenyl, was suspended in a solution of 50 ml. of water, 50 ml. of ethanol, and 10 g. of potassium hydroxide. The mixture was refluxed for one-half hour, cooled, and poured into 250 ml. of water. The solution was acidified, and the white precipitate which formed was filtered and washed with 2 liters of water. This product, obtained in quantitative yield (8.8 g.), melted at 202° (cor.) and did not depress the melting point of 4-hydroxy-4′-iodobiphenyl prepared from benzidine.

4-Hydroxy-4′-iodobiphenyl.—According to the method of van Alphen,[8] 25 g. of benzidine was tetrazotized, and the product obtained was allowed to stand with an additional 25 g. of benzidine at 15° for three days. The 4-amino-4′-biphenyldiazoic acid formed was treated with potassium iodide and subsequently diazotized and heated. The product was extracted from the reaction mixture with a dilute solution of sodium carbonate. Acidification of the solution yielded 3.5 g. (4.4% yield) of 4-hydroxy-4′-iodobiphenyl, which melted at 202° after crystallization from chloroform and petroleum ether (b. p. 35–55°).

Acetylation of 4-Hydroxy-4′-iodobiphenyl.—To a mixture of 2 g. of 4-hydroxy-4′-iodobiphenyl and 3 ml. of acetic anhydride, 5 drops of sirupy phosphoric acid was added. The mixture was refluxed for five minutes on a steam-bath. Water was added slowly to the hot solution until the excess acetic anhydride had decomposed. The

(9) Fairbrother, *Trans. Faraday Soc.*, **33**, 1507 (1937).

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warm solution was poured into ice water whereupon a precipitate separated. Filtration and recrystallization of the precipitate from ethanol yielded 1.8 g. (79% yield) of pure ester[8] melting at 155–156°. The melting point of a mixture of equal amounts of the above prepared ester and the product obtained on iodination of 4-acetyloxybiphenyl caused no depression.

Iodination of 4-Benzoyloxybiphenyl.—(a) A mixture of 10 g. of 4-benzoyloxybiphenyl, prepared from 4-hydroxybiphenyl, 10.1 g. of iodine (10% excess), 10 ml. of concentrated nitric acid, and 100 ml. of carbon tetrachloride was heated on a water-bath for eight hours. After the solvent was removed by distillation under reduced pressure, the solid residue was crystallized three times from glacial acetic acid. Pure 4-benzoyloxy-4′-iodobiphenyl (10.5 g.) (72% yield) was obtained as white plates which melted at 207° (cor.). When glacial acetic acid was used as the solvent for the iodination the yield was reduced to 45%.

(b) To a warm solution of 14.5 g. of 4-benzoyloxybiphenyl in 80 ml. of glacial acetic acid, 15 g. of iodine monochloride in 40 ml. glacial acetic acid was added in fifteen minutes. The mixture was placed on a steam-cone and heated to a temperature at which hydrogen chloride was liberated. Any iodine monochloride which vaporized was condensed in the lower part of the water-cooled condenser. The reaction was allowed to proceed for three hours, at the end of which time it was cooled and poured into ice water. A gummy mass separated. It was taken up in chloroform, washed with sodium bisulfite and water, and dried over anhydrous sodium sulfate.

When the solution was dry it was filtered and the chloroform removed by distillation under reduced pressure until a solid began to separate. The remaining portion was removed from the flask and white plates were caused to precipitate by the addition of petroleum ether. The solid was suspended and digested in hot ethanol. On filtration, 14.2 g. (67.2% yield) of solid was obtained. Recrystallization from acetic acid raised the melting point of 4-benzoyloxy-4′-iodobiphenyl to 207°.

Anal. Calcd. for $C_{19}H_{13}O_2I$: I, 31.75. Found: I, 31.30.

Hydrolysis of 4-Benzoyloxy-4′-iodobiphenyl.—4-Benzoyloxy-4′-iodobiphenyl (5 g.) was suspended in a solution containing 40 ml. of ethanol, 10 ml. of water and 5 g. of potassium hydroxide. The mixture was refluxed for eight hours, cooled, and diluted with an equal volume of water. After the ethanol had been removed by distillation, the solution was chilled and saturated with carbon dioxide. The white solid which separated was extracted with ether. The ether extract was dried with anhydrous sodium sulfate, and the solvent removed by distillation under reduced pressure. The solid residue was crystallized from a mixture of carbon tetrachloride and petroleum ether (b. p. 35–55°). This product, which weighed 2.9 g. (78% yield), melted at 202°. A mixture of the compound thus formed and 4-hydroxy-4′-iodobiphenyl prepared from benzidine melted at 202°.

The aqueous solution previously saturated with carbon dioxide was acidified and again extracted with ether. After the ether extract had been dried with anhydrous sodium sulfate, the ether was removed by distillation under reduced pressure. Upon recrystallization of the residue from water, 0.7 g. (44% yield) of benzoic acid, m. p. 121.5°, resulted.

Benzoylation of 4-Hydroxy-4′-iodobiphenyl.—A mixture of 1 g. of 4-hydroxy-4′-iodobiphenyl, 10 ml. of pyridine and 1 ml. of benzoyl chloride was refluxed for ten minutes. The solution was allowed to cool to room temperature and poured into 100 ml. of ice water. A precipitate separated which was filtered and digested with ethanol. The yield of 4-benzoyloxy-4′-iodobiphenyl was 1.1 g. (82% yield) and its melting point was 206–207°. A mixture of the product obtained by the action of iodine monochloride on 4-benzoyloxybiphenyl and the above ester did not cause a depression of the melting point.

Iodination of 4-Benzenesulfonyloxybiphenyl.—(a) A mixture of 10 g. of 4-benzenesulfonyloxybiphenyl and 8.9 g. (10% excess) of iodine was suspended in 100 ml. of carbon tetrachloride containing 10 ml. of conc. nitric acid. The suspension was heated on a water-bath for eight hours and allowed to cool. After the solvent had been removed by distillation under reduced pressure, the solid residue was crystallized three times from methanol. The 4-benzenesulfonyloxy-4′-iodobiphenyl, obtained as white needles which melted at 93.5° (cor.), weighed 8.5 g. (60% yield).

Iodination of 4-benzenesulfonyloxybiphenyl was carried out as described above, except that glacial acetic acid was used as the solvent. The same product, 4-benzenesulfonyloxy-4′-iodobiphenyl, resulted in a yield of 51%.

(b) 4-Benzenesulfonyloxybiphenyl (16.7 g.) was suspended in 50 ml. of glacial acetic acid and heated gently on a steam-bath, which caused the ester to dissolve. Fifteen grams of iodine monochloride, dissolved in 20 ml. of glacial acetic acid, was added slowly to the above solution. The reaction was allowed to run for three hours with constant heating and stirring. At the end of this time the solution was cooled and poured into ice water, whereupon a solid separated. The solid was taken up in chloroform after which the iodine was removed with sodium bisulfite solution. The chloroform solution was washed with water and distilled under reduced pressure until approximately one-third of the original volume remained. To this mixture petroleum ether was added causing a precipitate to separate. The solid was recrystallized three times from ethanol, and yielded 5.4 g. (23% yield) of pure 4-benzenesulfonyloxy-4′-iodobiphenyl. The melting point of the above white needle-like crystals was 92–93° (cor.).

Anal. Calcd. for $C_{18}H_{13}SO_3I$: I, 29.10. Found: I, 28.95.

Hydrolysis of 4-Benzenesulfonyloxy-4′-iodobiphenyl.—A suspension of 10 g. of 4-benzenesulfonyloxy-4′-iodobiphenyl in 160 ml. of ethanol, 40 ml. of water, and 10 g. of potassium hydroxide was refluxed for twelve hours, cooled, and diluted with an equal volume of water. The solution was acidified, and the white precipitate which separated was crystallized from a mixture of carbon tetrachloride and petroleum ether (b. p. 35–55°). Six and six-tenths grams of purified product (97% yield), melting point 202°, resulted. A mixture of this compound and 4-hydroxy-4′-iodobiphenyl prepared from benzidine melted at 202°.

Benzenesulfonation of 4-Hydroxy-4′-iodobiphenyl.—Two grams of 4-hydroxy-4′-iodobiphenyl was dissolved in 20 ml. of pyridine and cooled by means of an ice-bath. To this cooled solution, 3 ml. of benzenesulfonyl chloride was added. After the addition the mixture was heated gently on a hot-plate for fifteen minutes, cooled to room temperature and poured into 100 ml. of ice water. The precipitate which separated was filtered and recrystallized from ethanol. The pure product, melting at 93.5° (cor.), weighed 2.7 g. (93% yield). A mixture of the product obtained on iodination of 4-benzenesulfonyloxybiphenyl and the ester as prepared above caused no depression in the melting point.

Summary

Iodination of the acetate, benzoate and benzenesulfonate of 4-hydroxybiphenyl gave rise to substitution in the 4′-position. Both iodine monochloride and iodine and nitric acid were used as iodinating agents. Proof of the structure of these esters was afforded by hydrolysis to the known 4-hydroxy-4′-iodobiphenyl, prepared from benzidine. Furthermore, acetylation, benzoylation and benzenesulfonation of 4-hydroxy-4′-iodobiphenyl gave rise to these same esters.

The ease of iodination of these esters with iodine monochloride has been explained on the basis of

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the high dipole moment of iodine monochloride and the resonance between the benzene rings of the biphenyls.

It would appear in each case that iodination with iodine and nitric acid in a carbon tetrachloride solution is the best procedure for iodination of the esters studied.

AUSTIN, TEXAS RECEIVED NOVEMBER 26, 1943

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY, BUREAU OF AGRICULTURAL AND INDUSTRIAL CHEMISTRY, AGRICULTURAL RESEARCH ADMINISTRATION, UNITED STATES DEPARTMENT OF AGRICULTURE]

Pyrolysis of Lactic Acid Derivatives. Production of Phenyl and *o*-Tolyl Acrylate*

BY E. M. FILACHIONE, J. H. LENGEL AND C. H. FISHER

In recent years considerable interest has been shown in the production of acrylic esters by the pyrolysis of esters of acetoxypropionic acid. These esters can be made from lactic acid by the reactions

$$CH_3CHOHCOOH + ROH \longrightarrow CH_3CHOHCOOR + H_2O$$

$$CH_3CHOHCOOR + (CH_3CO)_2O \longrightarrow CH_3CH(OCOCH_3)COOR$$

Methyl acetoxypropionate[1,2] has been pyrolyzed to give high yields of methyl acrylate. Satisfactory yields of acrylic esters have been obtained also by pyrolysis of the benzyl[1] and tetrahydrofurfuryl[3] esters of acetoxypropionic acid. Other esters of acetoxypropionic acid, including the ethyl,[1] butyl,[1] allyl,[4] and methallyl[4] esters, have been pyrolyzed, but the yields of the corresponding acrylic esters are low, since a predominant side reaction takes place, *i. e.*, the aliphatic alcohol radical is decomposed into the corresponding olefin. For example, ethylene, carbon monoxide, acetaldehyde and acetic acid are formed when ethyl acetoxypropionate is pyrolyzed. Because of this or other side reactions, the satisfactory preparation of acrylic esters by the pyrolytic method appears limited to acetoxypropionic esters that have relatively stable alkyl groups.

Recent work[5] has shown that α-acetoxyisobutyric esters can be converted by pyrolysis into methacrylic esters more readily than α-acetoxypropionic esters can be transformed into acrylic esters.

Phenol is thermally stable, and because of their structure phenyl and substituted phenyl esters of acetoxypropionic acid would be expected to be incapable of the side reaction that occurs with ethyl acetoxypropionate and related esters. Results given in the present paper demonstrate that this expectation was reasonable.

Phenyl and *o*-tolyl acetoxypropionates were prepared by the following series of reactions and also by the methods described in the experimental section: (1) Aqueous 80% lactic acid was acetylated with acetic acid, benzene being used as an entraining agent to remove the water of esterification continuously.[6] The yields of acetoxypropionic acid were as high as 77%. (2) Acetoxypropionic acid was converted by means of thionyl chloride into acetoxypropionyl chloride in 80 to 82% yields. (3) Acetoxypropionyl chloride was converted by treatment with phenol (or *o*-cresol) into phenyl (or *o*-tolyl) acetoxypropionate in yields of almost 90%. (4) Pyrolysis of phenyl acetoxypropionate (or the corresponding *o*-tolyl ester) produced the aryl acrylate (75 to 80% yields).

Phenyl α-acetoxypropionate was pyrolyzed at temperatures and contact times that ranged from 440 to 600° and from 0.77 to 20 seconds. A pressure of 18 to 19 mm. was used in one experiment, atmospheric pressure for the others (Table I). The yield of acetic acid was always higher than the yield of phenyl acrylate. Carbon monoxide and carbon dioxide were formed in some experiments in considerable amounts. Styrene, obtained in yields as high as 20%, presumably was formed prior to decomposition of phenyl acetoxypropionate into phenyl acrylate since it has been reported by Skraup and Nietzen[7] that phenyl acrylate yields phenol, acetylene, and carbon monoxide on pyrolysis.

o-Tolyl acetoxypropionate was pyrolyzed at temperatures ranging from 500 to 591° (Table II). *o*-Tolyl acrylate was obtained in yields as high as 75%; the yields of acetic acid were even higher. No real attempt was made to detect *o*-methylstyrene in the reaction products.

Possibly because of the presence of small amounts of phenol or some other inhibitor, the phenyl acrylate purified by distillation showed little tendency to polymerize. Samples of phenyl acrylate that had been washed with dilute sodium

* Not copyrighted. This paper was presented before the Division of Industrial and Engineering Chemistry of the 106th meeting of The American Chemical Society at Pittsburgh, Pa., Sept., 1943.

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TABLE I

PYROLYSIS OF PHENYL α-ACETOXYPROPIONATE

Expt.	Amount pyrolyzed, g.	Temp., °C.	Contact time, sec.	Ester dec. %	Yields, moles per mole of ester decomposed: Acetic acid	Phenyl acrylate	Styrene	CO_2	CO
77	37	500	18	60	0.65	0.50	..	0.08	0.26
81	49	550	14	96	.81	.64	..	.12	.24
82	39	550	20	100	.88	.66	0.16	.21	.28
84	57	600	10	100	.91	.54	.07	.27	..
90	56	600	6	100	.90	.61	.12	.18	.21
102	56	583	3.7	95	.75	.64	.21	.07	.07
128	45	594	5.5	100	.86	.72	.07	.08	.08
H-170	82	522	19	65	.94	.76	.04	.07	.10
H-172	116	531	12	55	.94	.76	.03	.05	.09
H-173	123	548	15	73	.98	.76	.08	.08	.10
H-174	114	565	12	78	.97	.76	.11	.10	..
H-176	92	440	20	13	.64	.32	..	.01	.14
360[a]	78	541	0.77	34	.88	.80	..	..	..

[a] A pressure of 18 to 19 mm. was used.

TABLE II

PYROLYSIS OF o-TOLYL α-ACETOXYPROPIONATE

Expt.	Amount pyrolyzed, g.	Temp., °C.	Contact time, sec.	Ester dec., %	Yields, moles per mole of ester decomposed: Acetic acid	o-Tolyl acrylate	CO_2	CO
134	49	500	15	61	0.83	0.72	0.03	0.09
141	40	547	21	100	.90	.67	.04	.05
363	122	591	7	71	.64	.55	..	..
368	111	542	11	67	.97	.66	..	..
370[a]	76	549	2.3	82	.97	.75	..	..

[a] A pressure of 18 to 20 mm. was used.

hydroxide solution, however, polymerized readily (mass polymerization at 75°) in the presence of 1% benzoyl peroxide, forming a transparent product that was hard at room temperature but became soft at approximately 60°.

When a sample of *o*-tolyl acrylate isolated from the pyrolysis products by distillation was heated with approximately 1% benzoyl peroxide, a soft and viscous polymer was formed. Samples of the *o*-tolyl ester that had been washed with alkali polymerized readily (mass polymerization at 67°) when treated with 1% benzoyl peroxide. The polymer thus obtained, which was hard at room temperature, softened at approximately 60°.

The authors gratefully acknowledge the assistance of Dr. W. P. Ratchford, under whose direction the pyrolyses were carried out, and also the assistance of the other members of the Carbohydrate Division and of the Analytical and Physical Chemistry Division.

Experimental

Preparation of Acetoxypropionyl Chloride.—A mixture of 4 moles of lactic acid (80%), 28.0 moles of glacial acetic acid, 200 ml. of benzene, and 1 ml. of concentrated sulfuric acid was refluxed, with the continuous removal of water by means of a modified Dean and Stark tube. After twenty-one hours the mixture was neutralized with 4.0 g. of sodium acetate and distilled in vacuum. A 77% yield of acetoxypropionic acid resulted. By heating the acetoxypropionic acid with thionyl chloride (1.1 mole) gradually for approximately two hours to a final temperature of 95°, followed by distilling in vacuum, an 82% yield of acetoxypropionyl chloride was isolated.

Preparation of Phenyl α-Acetoxypropionate.—Phenyl acetoxypropionate was prepared by heating equimolar quantities of phenol and acetoxypropionyl chloride on a steam-bath until evolution of hydrogen chloride ceased. The ester was then isolated in 86 to 88% yields by distillation in vacuum: b. p. 110 to 111° (2 to 3 mm.) and 143° (12 mm.); $n^{20}D$ 1.4860; d^{20}_4 1.134. *Anal.* Calcd. for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81; M_R, 52.70. Found: C, 62.63; H, 6.05; M_R, 52.65.

Phenyl acetoxypropionate was prepared also by (a) the reaction of acetoxypropionyl chloride with aqueous sodium phenolate (65% yield); (b) the interaction of acetoxypropionyl chloride, phenol, and phosphorus oxychloride (30%); and treatment of phenyl acetate with acetoxypropionic acid in the presence of a small amount of concentrated sulfuric acid (45% yield on the basis of unrecovered acetoxypropionic acid).

Preparation of o-Tolyl α-Acetoxypropionate.—A mixture of 1.0 mole of *o*-cresol and 1.0 mole of α-acetoxypropionyl chloride was heated on the steam-bath until evolution of hydrogen chloride ceased. The mixture was then distilled in vacuum, a Claisen flask being used. The *o*-tolyl α-acetoxypropionate boiled at 112 to 113° below 1 mm.; $n^{20}D$ 1.4860; d^{20}_4 1.124. *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35; saponification equivalent, 111.1. Found: C, 64.01; H, 6.56; saponif. eq., 111.2.

Pyrolysis.—The pyrolysis of the acetoxypropionates was carried out by allowing the liquid to run into a Pyrex glass tube having a bore of 30 mm. and heated over a length of 13 inches. The vertical tube, packed with short lengths of Pyrex glass tubing, was heated by an electric furnace[2] controlled automatically. The apparatus[2] was swept with nitrogen before the pyrolysis started and also after all the ester had been added. A small amount of hydroquinone was added to the condensate to prevent premature polymerization.

Titration of the crude pyrolysis product showed the amount of acetic acid present. The acrylate and undecomposed acetoxypropionate were isolated by vacuum

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distillation of the crude pyrolysis product. Styrene was also formed in the pyrolysis of phenyl acetoxypropionate. It was collected with the acetic acid fraction in the distillation and was isolated by adding salt water to the acetic acid fraction.

Further data on the pyrolysis of phenyl and *o*-tolyl acetoxypropionate are given in Tables I and II.

Properties of Phenyl Acrylate and *o*-Tolyl Acrylate.—Phenyl acrylate[7] as obtained by the pyrolysis of phenyl α-acetoxypropionate was a virtually colorless liquid that boiled at 63 to 64° at 1- to 2-mm. pressure and 87 to 94° at approximately 12 mm.; $n^{20}D$ 1.5210; d^{20}_4 1.0762. *Anal.* Calcd. for $C_9H_8O_2$: C, 72.97; H, 5.44; M_R, 41.35. Found: C, 72.77; H, 5.66; M_R, 41.92. Neither the phenyl nor the *o*-tolyl acrylate polymerized readily until it had been washed with dilute alkali.

The *o*-tolyl acrylate was a virtually colorless liquid: b. p. 55 to 57° at 0.5 mm.; 78 to 79° at 3 mm.; $n^{20}D$ 1.5160; d^{20}_4 1.050; MR (calcd.) 45.96; MR (obs.) 46.59.

Summary

1. Satisfactory methods have been developed for converting lactic acid into α-acetoxypropionyl chloride, phenyl α-acetoxypropionate and *o*-tolyl α-acetoxypropionate.

2. Pyrolysis of the phenyl and *o*-tolyl esters of acetoxypropionic acid yielded phenyl and *o*-tolyl acrylate, respectively. Styrene also was formed in the pyrolysis of phenyl acetoxypropionate.

3. Relatively hard resins were obtained by polymerizing phenyl and *o*-tolyl acrylate.

PHILADELPHIA, PA. RECEIVED DECEMBER 17, 1943

NOTES

Polarographic Behavior of Aniline Oxidation Products

BY DAVID LESTER AND LEON A. GREENBERG

A recent paper by Levitan, Kolthoff, Clark and Tenenberg[1] describes the polarographic behavior of some of the oxidation products of sulfanilamide. For some time we have been interested in the possible use of the polarograph for the analysis of the intermediary products of the metabolism of aniline and therefore investigated the behavior of β-phenylhydroxylamine, *p*-aminophenol, and azoxybenzene at the dropping mercury electrode. Since we concluded at that time that this method of analysis was better replaced by specific and more sensitive colorimetric methods in the case of the first two compounds, our study was not pursued further.

Our study, however, yielded results which appear to be at variance with those published on the hydroxylamino derivative of sulfanilamide. We find that in 0.07 *M* phosphate buffer (*p*H 6.3) β-phenylhydroxylamine does not give a cathodic wave but does give an anodic oxidation wave with an $E^1/_2$ *vs.* the S. C. E. of −0.02 volt. Levitan, Kolthoff, Clark and Tenenberg do not mention an anodic wave but do find a cathodic wave in 0.1 *M* sodium hydroxide. It has been our experience with β-phenylhydroxylamine that in the presence of alkali it is converted quite completely and rapidly to the azoxybenzene derivative, which then exhibits a cathodic wave; it is therefore impossible to polarograph alkaline β-phenylhydroxylamine solutions. It would be noteworthy if hydroxylaminobenzenesulfonamide, through the presence of a sulfonamide group, would not undergo this same transformation. This point is supported by the fact that the half-wave potentials for the hydroxylamino and azoxy derivatives of sulfanilamide are practically identical. It is unfortunate that the electrode reduction of the azoxy compound had to be carried out in 50% methanol, thus making impossible comparisons of the diffusion currents.

With our apparatus (Fisher Scientific Co. Electropode) and capillary an anodic diffusion current of 5.23 μa. per 0.001 *M* solution was found for hydroquinone and *p*-aminophenol with the 0.07 *M* phosphate buffer (*p*H 6.3). Since it is known that two electrons are involved in this reaction, two electrons are probably also involved in the anodic oxidation of β-phenylhydroxylamine, which gives a diffusion current of 5.3 μa. per 0.001 *M* solution. We have found that with the same buffer, but containing 20% ethanol, the diffusion current of azoxybenzene is 7.5 μa. per 0.001 *M* solution, with an $E^1/_2$ *vs.* the S. C. E. of −0.63 volt. Since the addition of alcohol decreases the diffusion current, it is quite likely that four electrons or more may be involved in the reduction: thus $C_6H_5NONC_6H_5 \rightarrow C_6H_5NHNHC_6H_5 + H_2O$, that is, the reduction to hydrazobenzene and water.

LABORATORY OF APPLIED PHYSIOLOGY
YALE UNIVERSITY, NEW HAVEN, CONN.
RECEIVED JANUARY 7, 1944

Alkylcyanopyruvic Esters from Aliphatic Nitriles

BY GLENN S. SKINNER, J. H. TAYLOR AND J. L. ERNST

It was reported[1] that mixtures of sodium and potassium are more effective than sodium alone in

(1) N. I. Levitan, I. M. Kolthoff, W. G. Clark and D. J. Tenenberg, THIS JOURNAL, 65, 2265 (1943).

(1) Skinner, THIS JOURNAL, 59, 322 (1937).

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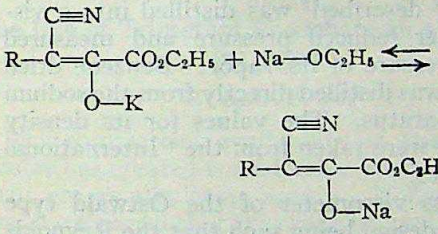
TABLE I

Ethyl alkylcyanopyruvate		Equivs. alkoxide	Yield, %	B. p., °C.	Mm.	Nitrogen, % Found	Calcd.
Methyl	$C_7H_9O_3N$	50% Na:50% K.	79	119–21	14		
Ethyl	$C_8H_{11}O_3N$	K	65	127–9	15	8.25	8.28
n-Propyl	$C_9H_{13}O_3N$	K	55	137–9	15	7.58	7.65
n-Propyl		90% Na:10% K.	31	135–7	15		
n-Propyl		Na	13	135–9	15		
n-Propyl		Na ribbon (ether)	15	132–5	13		
n-Butyl	$C_{10}H_{15}O_3N$	K	58	148–50	15	6.87	7.10

Melting points: methyl, 68° (Wislicenus gives 68°); ethyl, 46–48°. Densities: *n*-propyl, 1.073 (20°), 1.068 (25°); *n*-butyl, 1.050 (20°), 1.046 (25°). Refractive indices: *n*-propyl, 1.477 (20°), 1.476 (25°); *n*-butyl, 1.479 (20°), 1.478 (25°).

causing the condensation of ethyl phenylacetate with ethyl carbonate or ethyl oxalate. Accordingly mixtures of sodium and potassium ethoxides have been applied to nitriles that do not satisfactorily condense with ethyl oxalate under the influence of sodium ethoxide alone, there being the possibility that once the potassium derivative is formed it might undergo double decomposition with sodium ethoxide and thus avoid to some extent the use of potassium.



Fleischauer[2] was unable to isolate cyanopyruvic ester from the condensation products formed by the action of sodium ethoxide on a mixture of methyl cyanide and ethyl oxalate although he did show that a small amount had been formed. Wislicenus and Silberstein[3] using potassium ethoxide obtained an 83% yield of cyanomethylpyruvic ester from propionitrile. Later investigators[4] have used potassium ethoxide. Thus it would appear that the activation of the α-hydrogen in aliphatic nitriles by the nitrile group alone is not sufficient to permit a satisfactory reaction if sodium ethoxide is the condensing agent.

In phenylacetonitrile, which readily condenses,[5] this hydrogen is also in the reactive position with respect to the double bond in the ring. It is significant also that ethylene cyanide reacts readily with two moles of oxalic ester to give a fair yield of the diketo ester while trimethylene cyanide reacts with only one mole.[6] This difference may be understood if one considers that the hydrogen of the second methylene group in the case of ethylene cyanide is activated also by the double bond of the enolic form present as the salt. In the case of trimethylene cyanide these two influences activate different hydrogen atoms.

(2) Fleischauer, *J. prakt. Chem.*, [2] **47**, 375 (1893).
(3) Wislicenus and Silberstein, *Ber.*, **43**, 1825 (1910).
(4) Borsche and Manteuffel, *Ann.*, **512**, 97 (1934).
(5) Erlenmeyer, Jr., *Ber.*, **22**, 1483 (1889).
(6) Michael, *Am. Chem. J.*, **30**, 156 (1903).

The results of our experiments indicate that with valeronitrile a very poor yield (13%) of cyano-*n*-propylpyruvic ester is obtained with sodium ethoxide as the sole condensing agent, that if one-tenth of the sodium ethoxide is replaced by potassium ethoxide the yield is raised to 31% and that the yield is 55% if potassium ethoxide is the sole condensing agent. On this basis the yield should be increased to approximately 17% by the substitution of the equivalent weight of potassium for 10% of the sodium, whereas the yield is actually increased to 31%. An equimolecular mixture of sodium and potassium ethoxides gave a 79% yield of cyanomethylpyruvic ester which is almost as good as that obtained by Wislicenus and Silberstein who used potassium ethoxide. According to the procedure we employed the greater solubility of the sodium enolate causes no error in isolating the product. The ethylation of cyanopropylpyruvic ester yields the ether of the enol form which confirms more recent results.[4,7]

Preparation of Alkylcyanopyruvic Esters.—In a typical experiment, 14.0 g. of sodium was caused to react with absolute alcohol (182 cc.) dissolved in 805 cc. of absolute ether. The potassium (23.8 g.) was then added to the cooled mixture. After all of the metal had reacted a solution of 67.1 g. of propionitrile in 178.1 g. of ethyl oxalate was added at once and the whole was thoroughly mixed. A deep red color developed within a half hour. The amount of precipitate appearing after standing for four days was much less than it was when the equivalent amount of potassium ethoxide was used. The reaction mixture was then quickly mixed with a freezing mixture prepared from 115 cc. of hydrochloric acid (d. 1.19) and 440 g. of finely crushed ice. The ether layer was dried over sodium sulfate and distilled, finally under diminished pressure. Upon standing several months in a closed container the esters partially decomposed to a yellow oil. Redistillation of such a sample gave oxalic ester, the alkylcyanopyruvic ester and a high boiling residue that did not contain nitrogen. The sample for the analysis of cyanoethylpyruvic ester was prepared by cooling an ether–ligroin solution in an ice–salt mixture.

Ethyl 3-Cyano-2-ethoxy-2-hexenoate.—This compound was prepared in 52% yield by alkylating cyano-*n*-propylpyruvic ester in alcohol with sodium ethoxide and ethyl sulfate. The unalkylated ester was removed by extraction with sodium carbonate solution; b. p. 137–139° (9.3 mm.); 114° (1 mm.).

Anal. Calcd. for $C_{11}H_{17}O_3N$: N, 6.63; OC_2H_5, 42.66. Found: N, 6.48; OC_2H_5, 42.76.

UNIVERSITY OF DELAWARE
NEWARK, DELAWARE RECEIVED NOVEMBER 22, 1943

(7) Skinner and Green, THIS JOURNAL, **62**, 2882 (1940).

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Reaction of Potassium Chromate with an Indium Salt

BY M. F. STUBBS[1]

The yellow precipitate formed by adding a chromate to a solution of an indium salt first described by Winkler[2] has been assumed to be indium chromate,[3] although Friend[4] points out that indium chromate does not appear to have been analyzed. In view of the present availability of indium, we have now carried out this precipitation and have made observations on the resulting changes in the *p*H of the solution.

Pure indium sulfate was prepared by the method of Seward[5] using 99.98% pure indium[6] and other reagents of analytical reagent quality. To the indium sulfate at 0.02 *M* concentration having an initial *p*H of approximately 2.5 as measured with a Model No. 3 *p*H Electrometer (Coleman), calibrated against the buffer solution furnished by the manufacturer, standard 0.2222 *M* potassium chromate solution was added at room temperature in small amounts from a buret with stirring.

A definite yellow turbidity appeared at *p*H 3.30, complete flocculation of the yellow precipitate taking place at 3.36–3.42, further additions of the chromate resulting in a steady rise in the *p*H. A typical titration curve is shown in Fig. 1. The results are in agreement with the observation of Moeller[7] that attempts to bring a simple indium salt to the neutral point result in the precipitation of hydrous indium hydroxide at *p*H 3.41–3.43.

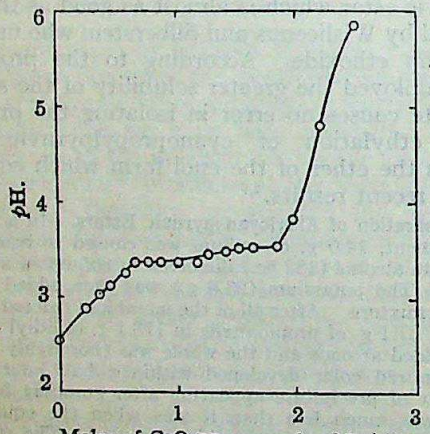

Fig. 1.

The yellow precipitate was then filtered and washed repeatedly until free of chromate. Prolonged washing, however, failed to remove the yellow color. After drying overnight at 110° to convert any hydrous indium hydroxide to indium hydroxide,[8] the precipitate was analyzed for indium by dissolving in dilute sulfuric acid and precipitating with ammonium hydroxide. This process was repeated and the indium hydroxide ignited to oxide. The combined filtrate was analyzed for chromium by acidifying with sulfuric acid, adding excess ferrous ammonium sulfate and back-titrating with standard potassium dichromate in the presence of phosphate ion with diphenylamine sodium sulfonate as indicator.

Anal. Calcd. for $In_2(CrO_4)_3$: In, 39.74; Cr, 27.02. Calcd. for $In(OH)_3$: In, 69.23. Found: In, 63.74, 63.55, 63.48; Cr, 2.16, 2.87, 2.94.

These observations indicate either that the precipitate originally formed is a mixture of indium hydroxide with indium chromate (or a basic indium chromate), or that the indium chromate as precipitated is very largely hydrolyzed during the washing process.

DEPARTMENT OF CHEMISTRY
CARTHAGE COLLEGE
CARTHAGE, ILLINOIS
RECEIVED NOVEMBER 12, 1943

(1) Present address: Tennessee Polytechnic Institute, Cookeville, Tennessee.
(2) Winkler, *J. prakt. Chem.*, **102**, 289 (1867).
(3) J. W. Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Vol. 5, Longmans, Green and Co., 1924, p. 395.
(4) Friend, "Textbook of Inorganic Chemistry," Vol. 4, Chas. Griffin and Co., Ltd., 1917, p. 162.
(5) Seward, THIS JOURNAL, **55**, 2740 (1933).
(6) From the Indium Corporation of America, Utica, New York.
(7) Moeller, THIS JOURNAL, **63**, 2626 (1941).
(8) Carnelley and Walker, *Trans. Chem. Soc.*, **53**, 74 (1888).

The Viscosities of Dimethyl and Trimethylamine at 15, 25 and 35°

BY ELIJAH SWIFT, JR., AND DEXTER LEIGH WOLFE[1]

The viscosities of dimethyl- and trimethylamine have been measured at three different temperatures using benzene as a standard.

Procedure.—A sample of the amine purified as previously described[2] was distilled into a viscometer under reduced pressure and measured under the pressure of its vapor. Benzene dried over sodium was distilled directly from the sodium into the apparatus. The values for its density and viscosity were taken from the "International Critical Tables."

An all-glass viscometer of the Ostwald type was used, its design being such that the Reynolds number was well below the critical value, and the surface tension correction[3] was minimized. The viscometer was sealed during measurements, so the upper bulb was filled by inverting the instrument beneath the surface of the water in the thermostat. It was not possible to get the same volume each time, so a correction was made for the working volume,[2] as calculated from the weight of material in the instrument and its density[1] at each temperature. At least three measurements of the time of efflux were made at each temperature, using a stop watch calibrated against a standard clock. The temperature was controlled[1] to ±0.02°. Two fillings with different material were made with each compound and with benzene.

The average difference in time between the two runs made on a liquid at the same temperature was 0.2% and the greatest difference 0.5%. The equation used to calculate the viscosities was

$$\eta = \eta_0 \frac{dt}{d_0 t_0} + \frac{mV}{8\pi l} \frac{d}{t} \left(\frac{t^2}{t_0^2} - 1 \right)$$

where the symbols have the usual meanings. The value of m was taken as 1.12,[4] the correction

(1) At present with the Armed Forces.
(2) E. Swift, Jr., THIS JOURNAL, **64**, 115 (1942).
(3) G. Jones and J. H. Fornwalt, *ibid.*, **60**, 1683 (1938).
(4) E. C. Bingham, "Fluidity and Plasticity," McGraw-Hill Book Co., New York, N. Y., 1922. E. Hatschek, "Viscosity of Liquids." D. Van Nostrand, Co., New York, N. Y., 1928.

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amounting to about 4% at the greatest. Because of uncertainty in the value of m for this particular instrument, the calculated viscosities are probably reliable to only 1%.

The results obtained are given in Table I.

TABLE I

VISCOSITIES OF COMPOUNDS IN MILLIPOISES

	15°	25°	35°
Dimethylamine			
Viscosity	2.07	1.86	1.67
KE Corr.	− .06	− .06	− .07
Trimethylamine			
Viscosity	1.94	1.77	1.61
KE Corr.	− .06	− .06	− .07

LAWRENCE COLLEGE
APPLETON, WISCONSIN, and
INDIANA UNIVERSITY
BLOOMINGTON, INDIANA RECEIVED OCTOBER 25, 1943

The Use of Trimethyl Phosphate as a Methylating Agent

BY A. D. F. TOY

The commercial availability of trialkyl phosphates has created considerable interest regarding their use as alkylating agents. Noller and Dutton[1] have shown that they may be used to alkylate phenols, and more recently Billman, Radike and Mundy[2] have applied them successfully to the alkylation of amines.

The present paper reports the methylation of aliphatic alcohols with trimethyl phosphate.

The reaction proceeds readily on heating, but the yield of methyl ether is only 50–60% based on the alcohol used, and not all of the available methyl groups of the phosphate ester are utilized. A fraction of the alcohol is converted into olefins and another part appears in the form of mixed alkyl acid phosphates. By employing an excess of the alkylating agent the yield of methyl ether may be increased.

With the procedures used the method is limited to alcohols boiling above 160°, because with lower boiling compounds the reaction proceeds too slowly.

(1) Noller and Dutton, THIS JOURNAL, 55, 424 (1933).
(2) Billman, Radike and Mundy, *ibid.*, 64, 2977 (1942).

TABLE I

ALKYL METHYL ETHERS[a]

Alcohol used	Moles phosphate per mole alc.[a]	Method	Time, hr.	Yield, %	B. p., °C. (uncor.)	Ref.
2-Ethyl-	0.350	I	23	56.6	159–160	*b*
hexanol-1	.350	II	5	57.8	159–160	
	.500	II	4.5	62.0	159–160	
	.667	II	6.0	68.0	159–160	
Octanol-1	.667	II	2.0	69.5	173–174	*c*
Octanol-2	.350	I	27	56.7	159–160	*d*
Heptanol-2	.600	I	20	54.3	139–140	*e*
Hexanol-1	.350	II	9	52.7	124–125	*f*
Ethylene						
glycol	.333	I	5.3	37.2	122–123	*g*

[a] One and one-half moles of alcohol used in all cases. [b] Calcd. for $C_9H_{20}O$: C, 75.0; H, 13.9. Found: C, 74.4; H, 13.6. [c] Dobriner, *Ann.*, 243, 3 (1888). [d] Cerchez, *Bull. soc. chim.*, [4] 43, 767 (1928). [e] Calcd. for $C_8H_{18}O$: C, 73.8; H, 13.85. Found: C, 73.6; H, 14.0. [f] Lespieau, *Bull. soc. chim.*, [4] 43, 1190 (1928). [g] The compound obtained is ethylene glycol monomethyl ether: Palomaa, *Ber.*, 35, 3300 (1902).

Experimental Part

Two general procedures were followed, both employing commercial grade trimethyl phosphate.

Method I.—The alcohol and the trimethyl phosphate were boiled under reflux until the temperature of the liquid phase reached a constant minimum. The volatile components were distilled, the last portions being removed under reduced pressure, and the desired methyl ether was isolated by careful fractionation of the distillate. The time required for the reaction was twenty to thirty hours.

Method II.—The reactants were boiled in a Claisen flask connected to a water-cooled receiver, and the temperature of both the liquid and the vapor phase was measured. After one hour the temperature of the liquid was 15–20° below the initial temperature. More heat was applied, so that the ether distilled as it was formed, and the temperature of the liquid phase was maintained 3–10° below the initial temperature. The reaction was complete when distillation ceased or when the residue began to decompose. The last traces of volatile material were removed by distillation under reduced pressure and the product was isolated as above.

The results of runs with various alcohols are listed in the table. Analyses were by Mr. Russell Bell of this Laboratory.

Among the volatile by-products, small amounts of olefins, methyl alcohol and unchanged starting material were found. The non-volatile residue was an alkali-soluble mixture of alkyl acid phosphates resembling those obtained by the action of phosphorus pentoxide on alcohols.[3]

RESEARCH LABORATORY
VICTOR CHEMICAL WORKS
CHICAGO HEIGHTS, ILLINOIS RECEIVED DECEMBER 9, 1943

(3) Adler and Woodstock, *Chem. Industries*, 51, 516 (1942).

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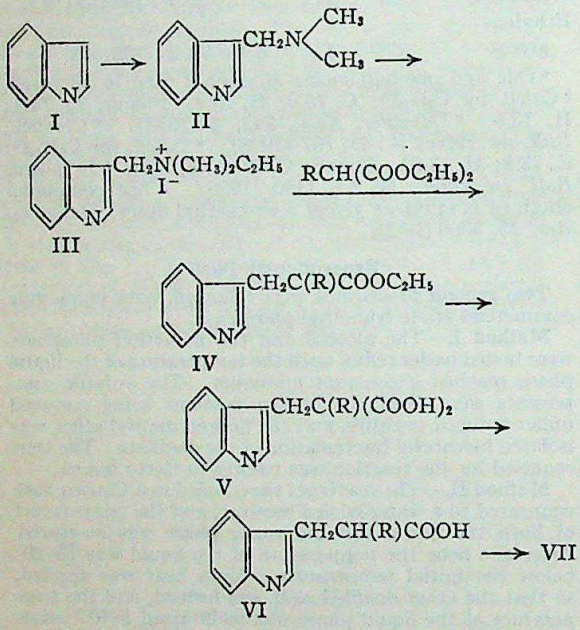
COMMUNICATIONS TO THE EDITOR

A NEW SYNTHESIS OF TRYPTOPHAN

Sirs:

In view of the recent communication of Snyder, *et al.*,[1] on the use of gramine methiodide as an alkylating agent, we wish at this time to record our experience in this field.

Tryptophan (VII) was synthesized by the procedure outlined in the following equations



The condensation was carried out successfully when R = H, $HNCOCH_3$ or $HNCOC_6H_5$. The ethyl α-carbethoxy-β-(3-indolyl)-propionate, (R = H), was hydrolyzed to the malonic acid which melted at 187–189° when pure.[2] The free acid was easily converted to β-(3-indolyl)-propionic acid, which melted at 128–130°.[2]

Ethyl α-carbethoxy-α-acetamido-β-(3-indolyl)-propionate, (R = $HNCOCH_3$), melted at 157° (Calcd. N, 8.09. Found: N, 8.27). Ethyl α-carbethoxy - α - benzamido - β - (3 - indolyl) - propionate, (R = $HNCOC_6H_5$), melted at 142° (Calcd. N, 6.86. Found: N, 7.20).

Hydrolysis of IV in sodium hydroxide solution proceeded quite smoothly. The free acetamido and benzamidomalonic acids (V), m. p. 135–137° (dec.), 85–90° (dec.), respectively, were used inthe crude form since some decarboxylation accompanied purification, thus rendering the preparation of analytical samples difficult. Complete decarboxylation was effected by heating at 180–200° until the evolution of carbon dioxide ceased.[2] The structures of the acetyl and benzoyltryptophan so prepared were confirmed by direct comparison with authentic specimens. The free amino acid was obtained from the above derivatives by hydrolysis according to procedures described in the literature. The over-all yield of tryptophan based on indole as the starting material was as high as 35% of the theoretical. Details of the procedure will be published at some future date.

N. F. Albertson
S. Archer
C. M. Suter
Winthrop Chemical Company
Rensselaer, New York

Received February 21, 1944

(1) Snyder, Smith and Stewart, This Journal, **66**, 200 (1944).

(2) Maurer and Moser, *Z. physiol. Chem.*, **161**, 131 (1926). The authors report 188° as the m. p. for the malonic acid and 134° for the decarboxylated product.

LOW ANGLE X-RAY SCATTERING FROM CHRYSOTILES

Sir:

It is becoming increasingly evident that studies of low angle scattering of monochromatic X-rays will prove valuable in the study of sub-optical–microscopic structures. Bernal and Fankuchen in their virus studies,[1] Bear in his collagen studies,[2] Warren for carbon black[3] and Kratky in studies of proteins and of fibers,[4,5] found such significant small angle scattering. We have now studied various chrysotiles with X-rays using a standard technique for the wide angle scattering and the apparatus and technique employed in the study of dry gels of tobacco mosaic virus[1] for the low angle work. Copper characteristic radiation filtered through nickel foil was used. In the low angle work a fine slit system to define the X-ray beam and a 30 cm. specimen to film distance permitted the study of the small angle scattering down to angles corresponding to 500 Å. The specimens were stationary thin slabs of chrysotile mounted so that the X-rays passed through the thin direction of the specimen. The wide angle diagrams are substantially alike and all showed an undifferentiated low angle equatorial scattering. The use of a fine slit system[1] resolved this scattering into clearly differentiated lines. In each of the four samples studied to date, at least two lines were always visible, the ratio of their Bragg spacings being $\sqrt{3}$. This suggests strongly that these chrysotiles are composed of parallel fundamental fibrils—hexagonally packed in cross section. The diameters of the fibrils can be computed from the Bragg spacings (on the hypothesis

(1) Bernal and Fankuchen, *J. Gen. Physiol.*, **25**, 111–165 (1941).

(2) Bear, This Journal, **64**, 727 (1942).

(3) Biscoe and Warren, *J. Applied Phys.*, **13**, 364–371 (1942).

(4) Kratky, Sekora and Treer, *Z. Elektrochem.*, **48**, 587–601 (1942).

(5) Kratky and Sekora, *Naturwissenschaften*, **31**, 46–47 (1943).

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of hexagonal packing) and prove to be significantly different.

TABLE I

	Diam. of fibrils in Å.
Canadian chrysotile	195
"harsh" chrysotile (U. S. A.)	250
"soft" chrysotile (U. S. A.)	226
Chrysotile (Italy)	218

It seems possible that the explanation of the variations in mechanical properties of the chrysotiles can be explained on the basis of the differences in their low angle scattering (and consequently on differing fundamental fibril diameter). An extensive survey of asbestos-like materials is now in progress.

DEPARTMENT OF CHEMISTRY
POLYTECHNIC INSTITUTE OF BROOKLYN I. FANKUCHEN
BROOKLYN, NEW YORK M. SCHNEIDER

RECEIVED JANUARY 28, 1944

GLIOTOXIN, THE ANTIBIOTIC PRINCIPLE OF *GLIOCLADIUM FIMBRIATUM*[1]

Sir:

We find that the antibiotic substance gliotoxin is produced by at least three different organisms.

Professor Harold Raistrick of the London School of Hygiene and Tropical Medicine has isolated from a species of *Penicillium* (as yet not completely identified) a crystalline substance which appeared to be identical with gliotoxin from *Gliocladium fimbriatum*.[1] He had independently reached the conclusion that it should be represented by the formula $C_{13}H_{14}N_2O_4S_2$ (private communication to J. R. J., London, October 11, 1943). Professor Raistrick has kindly furnished us a sample of his crystalline material and a comparison with our gliotoxin has shown that the two substances are identical.

The sample from Professor Raistrick on examination with a polarizing microscope was monoclinic hemimorphic, crystallizing as flattened rods elongated parallel to the "b" axis. It showed the forms: basal pinacoid, 001; orthopinacoid, 100; hemiclinodomes, 011 and $01\bar{1}$, and hemiprisms, $\bar{1}10$ and 110. The crystallographic angle β is 79° with the interfacial angle, $011:01\bar{1}$, equal to 109°. The optic axial plane is perpendicular to 010 with α, the obtuse bisectrix, 34° from "a" in the obtuse angle β. The optic axial angles are $2V = 53°$ and $2E = 90°$. The refractive indices are α, 1.644 ± 0.001; β, 1.658 ± 0.001; β' (component of β in the plane 100), 1.655 ± 0.002; and γ, 1.708 ± 0.001. This description agrees in every respect with the previously published crystal structure of gliotoxin[1]; hence Professor Raistrick's material is identical with gliotoxin.

Determination of the decomposition point[2] showed 218° (uncor.), and a mixed decomposition point with gliotoxin, melting with decomposition at 219°, was 218°. In a determination of specific rotation, a very characteristic constant of gliotoxin, 6.1 mg. of the sample in 1 ml. of chloroform gave $\alpha = -1.71 \pm 0.06°$, $[\alpha]^{20}D$ $-280 \pm 10°$. This is in reasonably good agreement with the values previously found for gliotoxin: $[\alpha]^{19}D$ -239 (C, 0.51 in $CHCl_3$)[2]; $[\alpha]^{26}D$ $-255 \pm 15°$ (C, 0.103 in $CHCl_3$).

Furthermore, identification of gliotoxin as a product of the fungus *Aspergillus fumigatus* has been accomplished by Dr. O. Wintersteiner.[3]

Since gliotoxin has been isolated from cultures of *Gliocladium fimbriatum*, *Aspergillus fumigatus* and a species of *Penicillium* not yet identified, it may prove to be an antibiotic product of still other fungi.

BAKER LABORATORY OF CHEMISTRY JOHN R. JOHNSON
CORNELL UNIVERSITY WALTER C. MCCRONE, JR.
ITHACA, NEW YORK WILLIAM F. BRUCE

RECEIVED FEBRUARY 9, 1944

(1) Johnson, Bruce and Dutcher, THIS JOURNAL, **65**, 2005 (1943).

(2) Weindling and Emerson, *Phytopathology*, **26**, 1069 (1936).

(3) In press; private communication to W. F. B., March, 1943.

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NEW BOOKS

Dictionary of Science and Technology in English–French–German–Spanish. By MAXIM NEWMARK. Philosophical Library, Inc., 15 E. 40th St., New York, N. Y. 1943. viii + 386 pp. Price, $6.00.

Like a four-color mechanical pencil, a four-language dictionary creates at first sight an impression of ingenuity, compactness, and efficiency, but after a little use one begins to wonder whether a set of old-fashioned single-purpose pencils or dictionaries is not generally more convenient. The present dictionary is constructed in four parts, of which the first is a *numbered* alphabetical list of English words, each followed by its approximate equivalent in French, German, and Spanish. Then come three alphabetical lists of French, German, and Spanish words, respectively, each followed by the *number* of the English word to which it corresponds. Thus compactness is obtained at the expense of convenience, for in order to find the meaning of a foreign word (the most frequent purpose for which such a dictionary is wanted) it is necessary to look in two places. It appears that additional compactness is obtained at the expense of reasonable completeness. As a test, a single sentence of four lines was selected at random from a standard German text on a physico-chemical subject, and found to contain three words not in the Dictionary—verlaufen, darstellen, bestätigen, by no means rare words. In fairness it should be said that the author is particularly interested in achieving up-to-date coverage of technological terms.

It would seem that this book might be useful where for some reason compactness is at a premium, or where there may be occasional need to translate from one foreign language to another.

A. S. COOLIDGE

The Chemistry of Large Molecules (Frontiers in Chemistry, Volume I). By R. E. BURK, Director of Research, The Standard Oil Co., Cleveland, Ohio, and OLIVER GRUMMITT, Morley Chemistry Laboratory, Western Reserve University, Cleveland, Ohio. Published under the Auspices of Western Reserve University. Interscience Publishers, Inc., New York, 1943. 313 pp. 26 figs. 15.5 × 23.5 cm. Price, $3.50.

The chapters of this book represent lectures presented during 1942 as one of the Frontiers in Chemistry series sponsored by Western Reserve University. This is the first of these series to be published. Other volumes will follow. It is the purpose of these lectures to bring together reports summarizing progress in related fields of research.

This volume consists of eight chapters. In the first chapter, "The Mechanism of Polyreactions" by Professor H. Mark, mechanisms of various types of polymerization are discussed. The second chapter, "The Investigation of High Polymers with X-Rays," also by Professor H. Mark, reviews broadly the occurrence, origins and effects of crystallinity in chain polymers. Diffusion, dialysis and viscosity of dilute polymer solutions and the dependence of these on molecular size and shape are discussed by the late Dr. E. O. Kraemer under the title "The Colloidal Behavior of Organic Macromolecular Materials." The fourth chapter on "The Ultracentrifuge and its Application to the Study of Organic Macromolecules," also by Dr. Kraemer, presents an excellent summary of the essentials of ultracentrifuge methods and the results which have been obtained on proteins and on filamentous molecules. "Elastic-Viscous Properties of Matter" by Drs. A. Tobolsky, R. E. Powell and H. Eyring is rather more diversified than other chapters. The statistical mechanics of chain configuration and of mixing of long chains with small molecules are included as well as applications of the transition state theory of viscous flow to the flow of polymer molecules by segments, theory of rubber elasticity, creep in metals, viscosity of suspensions and polymer solutions and thixotropic phenomena. In 27 pages Dr. R. M. Fuoss presents the most significant results of recent investigations carried out chiefly by Fuoss and collaborators on "The Electrical Properties of High Polymers" and their relationship to chemical structure and mechanical properties. Similarly, Professor C. S. Marvel summarizes recent work for which he and his associates are largely responsible on "Organic Chemistry of Vinyl Polymers." The final chapter (65 pp.) by Dr. Emil Ott on "Chemistry of Cellulose and Cellulose Derivatives" represents an exceptionally well organized, concise summary of a very broad field.

In view of the scope and purpose of these lectures, it is clear that the book is to be regarded neither as a text nor as a reference work. From the point of view of the casual reader who desires to be informed on recent accomplishments and current problems, but who cannot (or at least does not) find the time to become an expert on all phases of the subject, this may be looked upon as a point of merit. Too often scientific books strive to be either comprehensive of the entire field or to be complete in all details. This book can be recommended to readers desiring to be brought up to date on the broader aspects of recent developments in the phases of the subject covered by these eight chapters. The book should find a welcome place among the current flood of books which continue to appear on high polymers.

The bibliographies at the end of each chapter should be useful to readers who will want to delve farther into the subject. Numerous diagrams and figures are included. The editing and printing are well done and errors are few. A subject index is given at the end of the volume.

P. J. FLORY

Physical Biochemistry. By HENRY B. BULL, Ph.D., Associate Professor of Physiological Chemistry, Medical School of Northwestern University. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y., 1943. iv + 347 pp. Illustrated. 14.5 × 22 cm. Price, $3.75.

This book represents "an attempt to reorient to some extent" the character of "instruction in physical chemistry for premedical and for graduate students in the biological sciences." The general pattern of the presentation is indicated by the chapter headings: Atoms and Molecules, Energetics, Reaction Kinetics, Electrostatics and Dielectrics, Ions in Solution, Electromotive Force Cells, Acids and Bases, Oxidation-Reduction, Electrical Conductance, Electrokinetics, Surface Activity, Colloidal Solutions, Viscosity and the Flow of Liquids, Diffusion, The Ultracentrifuge, Osmotic Pressure, Membranes and Cell Penetration, Colloidal Structures. Under these headings are found discussions of a number of topics which I have not seen previously treated in comparable detail in any book addressed to a similar audience. These include: the transition state theory of reaction kinetics; some aspects of electrostatics, including dielectric constants, dipole moments, and dielectric increments; semiquinones; a very full discussion of electrokinetics, including the Tiselius electrophoresis apparatus; the relation between viscosity and molecular asymmetry in solutions of large molecules; streaming birefringence; sedimentation and diffusion in their relation to molecular size and shape; and the evaluation of pore size in membranes. The chapter on surface activity goes into much detail, and covers nearly forty pages. Numerous references to the original literature, often to very recent papers, are given as footnotes to the

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text; and the student is urged to read at least a few of them.

All of these topics are interesting and important, and are in the forefront of interest to many investigators today. For the teacher who is presenting important topics in physical chemistry to biological and premedical students, however, the question of relative emphasis remains a difficult problem. In the opinion of this reviewer, it is essential that the student should obtain a firm grasp of the fundamentals of chemical thermodynamics, the significance of the mass law, acid–base equilibria and oxidation–reduction potentials, and the elements of reaction kinetics especially in relation to enzyme action. All these topics are treated by Bull, but in some cases with a brevity which might leave most students without a firm grasp of the subject. It would seem essential to supplement the use of the text, and the recommended outside reading, by the working of numerous quantitative problems requiring the application of the fundamental principles. A set of such problems might be a valuable addition to the book in future editions. For instance, the extensive table of free energies of formation in Chapter II is excellent in itself, but the student is not likely to appreciate it unless he uses it in solving problems. The discussion of thermodynamics in this chapter would benefit from considerable amplification, with fuller explanation of the fundamental concepts, if the student is really to acquire the ability to use thermodynamics effectively in his thinking. The exposition of the activity concept (p. 26), which occupies less than a page, is one example of this; and the short paragraph on entropy and probability (p. 19) may mystify the student more than it enlightens him.

Raoult's law is not introduced until p. 293; in view of its importance, it might be well to place it near the beginning, in Chapter II (Energetics); and also to place Chapter XVI (on osmotic pressure and colligative properties) immediately after Chapter II.

Some equations, such as those involving electrokinetic potentials (p. 157 ff.), and the Langmuir adsorption equation (p. 206), are derived step by step, while others, sometimes simpler and more fundamental, are given without derivation. This is true for instance of the equation for the osmotic work involved in concentrating a component of a system (p. 20), or the Michaelis–Menten equation for enzyme kinetics (pp. 54–55). The student ought certainly to understand the derivation of such equations, if he is to obtain full educational value from a course of this sort.

Occasionally the discussion leaps suddenly from quite simple to much more complicated topics. For instance, on p. 60, a very simple discussion on the elements of electrostatics is followed abruptly by Poisson's equation. I fear that most students will fail to see the significance of the latter when so presented.

It is easy to find points for criticism in a book of this type, for the choice of topics and the manner of their presentation offer most formidable difficulties to an author who attempts to present physical chemistry to biologists and students of medicine. Bull's treatment has broken new ground in several respects, and I believe that it will have a definite influence on the character of instruction of this sort in the future.

JOHN T. EDSALL

A Text-Book of Inorganic Chemistry. By FRITZ EPHRAIM. English Edition by P. C. L. THORNE and E. R. ROBERTS. Fourth Edition, Revised and Enlarged. Interscience Publishers, Inc., 215 Fourth Avenue, New York, N. Y., 1943. (Gurney and Jackson, London, W. C. 1, England, and Oliver and Boyd, Ltd., Tweeddale Court, Edinburgh.) 924 pp. $8.75.

Earlier editions of this book have been reviewed in THIS JOURNAL, **57**, 593 (1935), and **63**, 1171 (1941). This edition differs only slightly from the preceding one. It contains ten additional pages and the revisions have been relatively minor.

The popularity of this text is shown by the increasing frequency with which new editions have appeared, only four years having elapsed since the publication of the last edition. This popularity is easily understood, for to the student familiar only with the usual order of presentation of the bewildering array of the facts of inorganic chemistry, it is certainly illuminating to have them presented in the less usual order adopted here.

ARTHUR B. LAMB

Industrial Chemistry. By WILLIAM THORNTON READ, Dean of the School of Chemistry, Rutgers University, 3rd ed., John Wiley & Sons, Inc., New York, N. Y.; Chapman & Hall, Ltd., London, 1943. 631 pp. 92 illus. 14 × 20 cm. $5.00.

This book gives a general descriptive survey of the more important chemical industries. It is intended primarily for students in their junior or senior year in college who are specializing in chemistry and assumes a knowledge of chemistry which may be expected of a student who has taken introductory courses in general descriptive, analysis, physical, and organic chemistry. At this stage of his career the most important problems facing such a student are the selection of his future wife and a decision as to the kind of job he would like to hold twenty or thirty years later. Shall it be Mary, Sue, or Betty, and shall he go into medicine, or electronics, or sanitary engineering, or chemistry? If we assume that he has selected Betty and has decided to become a professional chemist he is now ready to begin serious work in preparation of his career. He will tentatively set his ambition on the future title of Professor, Research Director, Chief Chemist, Factory Superintendent, Sales Manager, Purchasing Agent, or President of a chemical manufacturing company. This book is designed as a textbook in a course which should help him to reach a wise decision and start the process of fitting himself for an executive position where he will have the responsibility and authority to make decisions on matters of policy. Such an official must make his decisions and put them into effect on the basis of foresight and then a year or a decade later the wisdom of his decisions will be judged by hindsight. A good batting average requires exceptional ability and training, and a little luck may not come amiss.

The success of a factory built to manufacture chemicals is not assured merely by a simple and direct chemical process with good yields and good machine design. It is not enough to make a chemical efficiently but it must also be salable at a profit. The factory may succeed technically but fail financially because it is built in a poor location or it is too big for its markets and therefore cannot operate steadily. A suit for patent infringement may result in an injunction stopping all operations. A foreign war may cut off an imported raw material or a change in tariff make it too expensive. A new scientific discovery or a new invention may make the process of manufacture, or the product itself, obsolete. Persistent disloyalty among employees may outweigh the most skillful chemical engineering. Therefore the young chemist who hopes to rise to positions of executive responsibility should train himself to be a broad man capable of understanding, weighing and anticipating the significance of many outside influences upon the industry with which he is connected. A good knowledge of chemistry and chemical engineering is not enough. He may need some sound knowledge of thermodynamics, electronics, geology, biology, marketing, law, foreign relations, psychology and labor relations. His college course should give him a good start on his education and above all get him in the habit of reading and thinking on many subjects. A textbook of industrial chemistry should, therefore, not be too narrowly confined to chemistry and chemical engineering and should stimulate the student to think on broad lines. This book of Read's meets these specifications to a substantial degree but misses many good opportunities to give practice in con-

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sidering the comparative advantages and disadvantages of alternative procedures or methods. Thus, for example, it is mentioned that both platinum and vanadium oxide are used as catalysts in the contact process of making sulfuric acid but the student is not encouraged to think about the comparative advantages of these catalysts. Similarly, there are now two competing methods of making caustic soda—the electrolytic, and the treatment of Solvay soda with lime—but these are described in different chapters without any discussion of this interesting competitive situation.

The dramatic interest, significance and pedagogic effectiveness of the book could be appreciably increased by more attention to the historical development of the chemical industries. In the chapter on sulfuric acid, the contact process is discussed first, followed by the lead chamber process. Why not follow the historical order by discussing the chamber process first and then the contact process and thus give more realism to the half page devoted to the "Comparison of Contact and Lead Chamber Processes?"

In the chapter on Fixed Nitrogen the order of discussion is: fractional distillation of liquid air, helium, by-product ammonia from coal, ammonia synthesis, calcium cyanamide, the arc process, nitric acid from ammonia, nitric acid from Chile saltpeter, and sodium nitrate from caliche. This horrible scrambling of the historical sequence of development of these processes sacrifices much of the interest and significance. The ammonia synthesis is discussed without mentioning Haber's name or any allusion to the fact that this process was available to Germany during World War I and in combination with the Ostwald Process made Germany independent of Chilean saltpeter whereas England, France and the United States were compelled to rely upon Chilean saltpeter, which was dangerously threatened by the German submarines. The frantic efforts to escape this menace by the construction of the Muscle Shoals plant or the reasons for the choice of the cyanamide process do not rate even a mention. The later controversies over the disposal of this plant and the dam which eventually resulted in the great T. V. A. projects are ignored although they have had great influence on the development of the chemical industries in America. And why discuss the making of nitric acid from ammonia, then from Chilean nitrate and finally the recovery of Chilean nitrate from caliche?

The American potash industry is described before the German. There is no adequate presentation of the industrial difficulties created in America when German potash was cut off in 1915. Why was it that with potash prices averaging more than ten times the previous level for the four years of World War I the U. S. production in 1918 was only 20% of the prewar imports and all except two of the eighty-eight producers in 1918 have gone out of the potash business? And yet in the interval before World War II an American potash industry has arisen which can now care for every need. This extremely interesting and significant story is entirely missing.

The chapter on rubber contains no allusion to the acute situation created by the Japanese capture of Singapore or to the revolutionary changes which are being forced on the American rubber industry. There is no reference to the Baruch–Conant–Compton Report itself, or to its subject matter, or to subsequent developments. The discussion of synthetic rubber is extremely weak for a book dated August, 1943. Why not encourage the students to form an opinion on the prospects of survival of this new industry?

The author avoids mentioning the name of companies so completely that it shows a definite policy. Trade names of materials and even names of great inventors or personalities are used extremely sparingly. He does mention the name of Goodyear, Solvay, Baekeland, Acheson, Hall, and a few others. Glover and Gay-Lussac are towers rather than men. He avoids mentioning Liebig, Nobel, Perkin, Baeyer, Ostwald, Knietsch, Haber, Bergius, Hyatt, Sabatier, Onslager, Burton, Wesson, Dow, and Carothers.

It is perhaps unavoidable that at the time they graduate from college young chemists will be more familiar with the personalities of professional baseball players than of the great chemists and know more about the achievements of football teams than of teams of chemists and engineers representing our great chemical companies. But why encourage this weakness in our educational system? Why describe Neoprene and Nylon without mentioning the du Pont Company? Or the recovery of bromine and magnesium from the ocean without mentioning the Dow Chemical Company?

These criticisms refer to relatively minor matters since they concern missed opportunities rather than actual blunders. The book contains a great deal of information clearly and accurately presented. Any young chemist, whether still a student or at the beginning of his industrial career can broaden his knowledge and substantially improve his prospects of professional advancement by a study of this book.

A comparison of the third edition with the second shows that the changes are relatively minor and are scattered throughout the book.

GRINNELL JONES

Inorganic Qualitative Analysis. Semi-micro Technique. By HAROLD A. FALES, Ph.D., Professor of Chemistry at Columbia University, and FREDERIC KENNY, Ph.D., Professor of Chemistry at St. Francis College, Brooklyn. D. Appleton–Century Company, Inc., 35 West 32nd St., New York, N. Y., 1943. ix + 237 pp. 15 × 22 cm. Price, $2.65.

This book, which is intended for a one-semester course, follows much the same pattern as most contemporary texts in this field. The first 150 pages deal with theoretical topics, and the remaining 75 pages are devoted to systematic schemes of analysis employing semi-micro technique.

The usual theoretical topics are discussed, including types of compounds, strong and weak electrolytes, hydrolytic equilibria, solubility product, complex ions, and oxidation–reduction theory. The characteristics of electrolyte solutions and of various types of ionic equilibria are thoroughly and clearly presented. Each of the theoretical chapters concludes with a comprehensive set of problems, which in general appear to be well chosen. Among the few exceptions may be noted the fictitious equation $S = \sqrt[5]{K/108}$ on p. 72 for the relation between the molar solubility S in pure water and the solubility product K of lead phosphate, which is unrealistic and misleading because it ignores the extensive hydrolysis of the phosphate ion. Fortunately, there appear to be few synthetic examples of this sort; most of them display excellent didactic judgment.

In the reviewer's opinion the chapter on oxidation–reduction theory is outstandingly good, particularly the sections on pp. 139–145 which discuss a number of examples of oxidation–reduction equilibria that are important in qualitative analysis.

The semi-micro laboratory procedure provides for the detection of the usual twenty-four metallic elements, and the scheme of analysis adheres closely to the classical Noyes and Bray system with a few minor modifications. The various group analyses are summarized in clearly executed tabular diagrams. Equations are given for all reactions, and happily these have been written with a realistic appreciation of the ionic or molecular states of the substances involved.

Unfortunately the analytical chemistry of the non-metallic elements is almost completely ignored, and all that one finds is tests for four anions (chloride, sulfate, nitrate, and carbonate) on pages 221–222. The reviewer fails to appreciate the point of view which this neglect implies; certainly the importance of the analytical chemistry of the non-metallic elements warrants the inclusion of systematic schemes for anion analysis in even a one-semester course in qualitative analysis. It is true that in the past the laborious and time-consuming features of the classical macro procedures provided a more or less cogent argument for

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limiting one-semester courses to cation analysis, but surely the development of relatively rapid semi-micro techniques has invalidated this argument. Also the fact that anion analysis is somewhat less systematized and generally presents chemically more complex situations than cation analysis cannot be denied, but these attributes are actually more advantageous than disadvantageous from a didactic viewpoint. A student cannot be expected to acquire even a modicum of critical chemical sense, or a true perspective toward analytical chemistry, unless he is given an opportunity to wrestle with a few difficulties. It is hoped that in future editions of this otherwise sound text anion analysis will receive the attention it deserves.

JAMES J. LINGANE

Manometric Methods as Applied to the Measurement of Cell Respiration and Other Processes. By MALCOLM DIXON, Ph.D., Sc.D., F.R.S., University Lecturer in Biochemistry in the University of Cambridge. Second edition. The Macmillan Company, 60 Fifth Avenue, New York, N. Y., 1943. xiv + 155 pp. Illustrated. 13 × 19.5 cm. Price, $1.75.

This useful and standard manual gives an up-to-date account of all the most common methods in use in biochemical laboratories for following the time course of oxygen uptake and carbon dioxide output by cell and tissue enzyme systems. The author writes "It has of course not been possible to include every modification of manometer which has been described in the literature: my aim has been to select those forms which are already in fairly general use or likely to become so." In this aim he has been extremely successful. The book contains full instructions for, and precautions in, the use of the chief biochemical manometers, *i. e.*, the Barcroft and the Warburg apparatus and their various adjuncts and accessories. It also describes in detail the various methods of calibration, including an original theoretical treatment of the author not published elsewhere.

In the edition just published the main new features consist of short descriptions of (i) the beautiful, but rather special, ultra-micro-methods introduced since 1933, (ii) the recently developed modifications of the standard types, (iii) further applications of the methods. The older features have been thoroughly revised and brought up-to-date, and the list of references expanded. The book can be confidently recommended to all biochemists and might also be of occasional service in "pure" chemical departments.

F. J. W. ROUGHTON

Organic Chemistry. By C. W. PORTER AND T. D. STEWART, Members of the Faculty of the College of Chemistry in the University of California. Ginn and Company, Statler Office Building, Park Square, Boston, Mass., 1943. v + 577 pp. 15.5 × 23 cm. Price, $4.00.

All text-books for a year's instruction in elementary organic chemistry will necessarily present certain essential facts in the subject. The chief interest is in how the facts are presented. The beginning of this text is a preview of the whole subject in the first chapter. The student is hurriedly introduced to hydrocarbons of all kinds, alcohols, aldehydes, ketones, acids, esters, amines, amino acids, halogen-containing compounds and ten varieties of sulfur compounds. The tetrahedral atom, atomic dimensions, optical isomers, physical properties, solubility, chemical reactivity, atomic structure, isotopes, radioactive and heavy atoms, and the electronic valence pass rapidly in these first twenty-six pages. The object of this generalized survey is, to some extent, to overcome "the practical difficulty of learning an enormous number of new names and facts in a short time" by presenting the more commonly used new ideas "in anticipation of more detailed treatments."

There may be many, including the reviewer, who will question whether such an aerial photograph will mean much to a student who is unacquainted with any part of the detailed view; or doubt whether reference to the fact that sulfur is present in thiamine or vitamin B, or that Nylon is an amino acid, will have any real significance to a student when these subjects are not mentioned again until the latter half of the text. For those who favor such a method of instruction, however, the authors have given a very good preview.

The remainder of the text follows the more conventional order of hydrocarbons, alcohols, ethers, halides, aldehydes and ketones, acids, etc. The current interest in hydrocarbons as sources of organic compounds is stressed. The trend toward compounds of biological interest receives due attention by a considerable amount of space allotted to pyrimidines, purines, sulfa drugs, alkaloids, sterols, vitamins and enzymes.

The book is divided into 489 pages of discussion, 26 of supplementary notes and appendix, and forty-one pages of very good problems. The chapters are not numbered, but otherwise clearly indicated. The work is relatively free from errors, though the omission of a bond in the formula for quinine is unfortunate. In general the work is a very satisfactory addition to the collection of texts available for elementary organic chemistry.

AVERY A. MORTON

Plants and Vitamins. By W. H. SCHOPFER, Director of the Botanical Institute, University of Bern, authorized translation by NORBERT L. NOECKER. Chronica Botanica Company, Waltham, Mass., and G. E. Stechert and Co., New York, N. Y., 1943. xiv + 293 pp. Illustrated. 18 × 27 cm. Price, $4.75.

As may be guessed from the title, this book covers a relatively large field including the synthesis of vitamins by plants and the responses of plants including microörganisms to vitamins.

Some of the chapters (24 in number) have to do with specific organisms, *e. g.*, yeasts, lactic acid bacteria, etc.; others have to do with specific vitamins, and others deal with more general topics. The author has not been signally successful in the organization of the material.

It is unfortunate, due primarily no doubt to war conditions, that the literature has been reviewed completely only up until 1941, and that from this point on the review is incomplete. Inasmuch as the field covered by this book has undergone very active investigation in recent years, and many important matters have been clarified during the interval involved in its translation and publication, this book cannot be recommended as a critical and up-to-date summary.

For those whose interests are in plant physiology and to whom the vitamin field is largely unfamiliar, Professor Schopfer's book will be especially valuable.

ROGER J. WILLIAMS

BOOKS RECEIVED

January 10, 1944–February 10, 1944

HAROLD SIMMONS BOOTH and VIVIAN RICHARD DAMEREL. "Quantitative Analysis." Second Edition. McGraw-Hill Book Company, Inc., 330 West 42nd Street, New York, N. Y. 303 pp. $2.50.

PAUL H. DAUS, JOHN M. GLEASON and WILLIAM M. WHYBURN. "Basic Mathematics for War and Industry." The Macmillan Company, 60 Fifth Avenue, New York, N. Y. 277 pp. $2.00.

H. G. DEMING. "General Chemistry." Fifth Edition. John Wiley and Sons, Inc., 440 Fourth Avenue, New York (16), N. Y. 706 pp. $3.75.

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HENRY EYRING, JOHN WALTER AND GEORGE E. KIMBALL. "Quantum Chemistry." John Wiley and Sons, Inc., 440 Fourth Avenue, New York (16), N. Y. 394 pp. $5.00.

BENJAMIN HARROW. "Laboratory Manual of Biochemistry." Second Edition. W. B. Saunders Company, West Washington Square, Philadelphia, Penna. 132 pp. $1.50.

GLENN L. JENKINS AND WALTER H. HARTUNG. "The Chemistry of Organic Medicinal Products." Second Edition. John Wiley and Sons, Inc., 440 Fourth Avenue, New York (16), N. Y. 675 pp. $6.50.

W. A. KOEHLER. "Principles and Applications of Electrochemistry." In Two Volumes. Vol. II. "Applications." Second Edition. John Wiley and Sons, Inc., 440 Fourth Avenue, New York (16), N. Y. 573 pp. $5.00.

MARTINDALE. "The Extra Pharmacopoeia." Twenty-second Edition in Two Volumes. Published by direction of the Council of the Pharmaceutical Society of Great Britain. The Pharmaceutical Press, 17 Bloomsbury Square, W. C. 1, London, England. 1217 pp. 27/6. Postage 6d. extra.

CHESTER MERLE SUTER. "The Organic Chemistry of Sulfur." John Wiley and Sons, Inc., 440 Fourth Avenue, New York (16), N. Y. 858 pp. $10.00.

"Abridged Scientific Publications from the Kodak Research Laboratories." Vol. XXIV., 1942. Eastman Kodak Company, Rochester, New York. 391 pp.

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NOTICE TO AUTHORS OF PAPERS

Manuscripts for THIS JOURNAL should be submitted to the Editor ready for publication, typewritten (double space), with 2–3 cm. margins, on a good quality, durable paper, preferably of 8.5″ × 11″ size. In addition to the original typewritten copy, one or more carbon copies should be submitted so that the time required for examination by the Editorial Board may thus be considerably shortened. Care should be taken that all pages in a manuscript, including tables (but not the diagrams) be numbered consecutively. In preparing manuscripts authors are requested to observe, for reasons of economy, the utmost conciseness consistent with clarity of presentation. The manuscripts should be addressed to specialists in their particular field rather than to the general reader. Extensive reviews of the literature cannot be accepted. When well-known or previously published procedures have been followed in the experimental work they should only be designated or referred to.

Form of Presentation.—There should be one or more introductory paragraphs setting forth the occasion, significance and main objectives of the investigation and the method of attack. This should be followed by the experimental results and a discussion of them, either *seriatim* or at their conclusion. Finally, there should be a brief summary of the main achievements of the investigation. Sometimes, particularly when the subject matter is involved and there are many details which, though essential for a successful repetition of the experiments, are unnecessary for the main account of the investigation, these details can with advantage be relegated to an appendix or supplement, just preceding the Summary. In intermediate cases it is often advisable to retain a single, straightforward presentation but to intercalate sections in fine print giving the experimental details of procedure. This has the great advantage of keeping the experimental details close to the more general statements based upon them and yet at the same time permitting the reader if he wishes to pass over this section without inconvenience.

It will be of great assistance to the Editor's Office if the style, arrangement and orthography of the manuscripts are made to conform to the usages of the JOURNAL as exemplified in its recent issues and as set forth in the following paragraphs.

Center headings should be employed sparingly; side headings should be indented and run into the text to which they apply, using period and dash. References to the literature and all footnotes regardless of their nature (except those in tables) should be numbered in one consecutive series, repetition of notes being avoided by using simply the superscript number corresponding to the original reference. They should follow immediately in separate lines the line of text containing the text words to which they refer, and may be set off by short rules above and below. The items in the references to the literature should conform to the uniform usages of the Journal as regards order and punctuation, and to the abbreviations as given by *Chemical Abstracts* in its "List of Periodicals Abstracted." The names of all simple compounds rather than their formulas should be used whenever they occur in the text. Periods of time (unless fractional) should be written in words and quantities of material in Arabic numerals, unless occurring at the beginning of a sentence. Letters used to represent quantities in mathematical expressions should be underscored to indicate that they are to be printed in italics, and Greek or other unusual characters should be written plainly or should be explained by annotations. Simple fractional expressions should be written with a slant line rather than in the conventional manner, so that only a single line of type is required. All subscripts and superscripts should be carefully made and placed (the degree sign ° or a small o should not be used to represent zero). For economy, except in unusual circumstances the abbreviations %, °A., cm., cc., ml., g., Å., m. p., f. p., b. p., cal., kcal., expt. and Fig., should be used rather than the words.

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Formulas and Equations.—Empirical and structural formulas and mathematical and chemical equations should be arranged to fill adequately the width of a single column. This will often require a continuation of the equation in additional lines, and although this is a disadvantage it is in general preferable to intrusion into the adjoining column. Subscripts and superscripts, especially the latter, should be written with care and the conventional fractional arrangements should not be used in exponents. Organic structural formulas should be arranged to fill the space economically, and arrows should be used horizontally or vertically, not diagonally, wherever possible.

Notes do not differ fundamentally from Articles. They describe fragmentary or less complete studies and hence particular attention must be given to brevity and conciseness of presentation. Summaries are not included. They are collected in a special section near the end of each number of the Journal.

New Compounds.—This department is for brief accounts of new substances which do not appear of sufficient importance to justify separate publication and cannot be described appropriately as part of any other Article or Note. These accounts should report the preparation of the new compound succinctly, yet fully enough so that the operations can be duplicated. Significant properties, formulas and analytical data to establish the identity and purity of the substance should be given. Material appearing in this classification will not be accepted for subsequent publication.

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JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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[CONTRIBUTION FROM THE DEPARTMENT OF VITAL ECONOMICS OF THE UNIVERSITY OF ROCHESTER]

Thiamine Inactivation by the Chastek-Paralysis Factor. Inhibition[1] of Thiamine Inactivation

BY ROBERT R. SEALOCK AND RUTH L. GOODLAND

Evidence of the enzymatic nature of the destruction of thiamine by the fish principle or Chastek-paralysis factor has been presented previously.[2] In an effort to obtain more conclusive evidence concerning the enzyme hypothesis, the effect of the usual enzyme inhibitors on the fish principle was studied. Included among the substances used were heavy metal ions, iodine, pyrophosphate, sulfite and cyanide. In the concentrations commonly employed with enzyme reactions several of these were found to interfere[3] with the determination of thiamine by the diazotized aminoacetophenone method of Melnick and Field.[4] Further analysis[3] of the interference indicated that only a few of the inhibitors might be used in the thiamine-fish principle experiments, and in some instances it is evident (Table I) that inhibition of thiamine destruction did occur. On the other hand, it was also apparent that the interference with the analytical method limited the usefulness of these reagents.

TABLE I

INHIBITION OF THIAMINE DESTRUCTION

Inhibitor	Concentration, moles/liter × 10^3	Inhibition, %
Cupric sulfate	1.0	50.0
Zinc chloride	1.0	41.3
Ferric chloride	1.0	45.6
Potassium cyanide	1.0	23.8
Sodium fluoride	1.0	13.1
Iodoacetic acid	1.0	4.3
Cysteine	0.1	56.7
	.01	9.9
Sodium sulfite	.01	9.5

The inhibition of enzyme reactions, however, is not limited to reagents of this type for there are numerous classical examples of inhibition with compounds whose chemical structures are similar to those of the substrate molecules. The effect of various compounds, resembling the thiamine molecule in one or more features, on the destruction of thiamine by the fish principle was therefore investigated. In Table II in which the compounds are listed it is evident that certain ones

TABLE II

INHIBITION OF THIAMINE DESTRUCTION

Compound	Concentration, moles/liter × 10^4	Inhibition, %
4-Methyl-thiazolium chloride derivatives		
3-*o*-Aminobenzyl-[a,b]	5.0	100
3-*o*-Nitrobenzyl-[a,b]	0.5	1.8
	5.0	0
	50.0	0
3-β-Aminoethyl-[a,b]	0.5	47.9
	5.0	56.4
	20.0	74.6
3-β-Phthalimidoethyl-[a,b]	0.5	5.7
	5.0	18.4
	20.0	30.2
3-Ethyl-[a,c]	10.0	9.3
3-Phenyl-[a,c]	5.0	2.3
	10.0	4.9
3-Ethyl-2-methyl-[a,c]	5.0	0
	10.0	0
	40.0	10.0
3-Phenyl-2-methyl-[a,c]	5.0	0
3-Methyl-5-β-hydroxyethyl-[c,d]	5.0	0
	15.0	0

(1) Presented in part before the Division of Biological Chemistry of the American Chemical Society at the annual fall meeting at Buffalo, N. Y., Sept. 10, 1942.

(2) Sealock, Livermore and Evans, THIS JOURNAL, **65**, 935 (1943).

(3) Sealock and Goodland, unpublished data.

(4) Melnick and Field, *J. Biol. Chem.*, **127**, 515 (1938).

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TABLE II (*Concluded*)

Compound	Concentration, moles/liter × 10^4	Inhibition, %
2-Methyl-4-aminopyrimidine derivatives		
5-Bromomethyl-[d]	0.5	0
	5.0	34.8
	20.0	48.6
5-Methylenesulfonic acid	0.5	10.6
	10.0	19.7
	20.0	22.7
5-Ethoxymethyl-[d]	0.5	9.4
	5.0	13.2
	20.0	18.8

[a] These compounds were very kindly made available by Dr. H. T. Clarke. [b] Clarke, THIS JOURNAL, **66**, 652 (1944). [c] Clarke and Gurin, *ibid*, **57**, 1876 (1935). [d] Obtained through the courtesy of the Medical Department of Merck and Co., Inc. The authors are also indebted to this company for a generous supply of thiamine for these studies.

possess the property of greatly retarding the destruction of the vitamin.

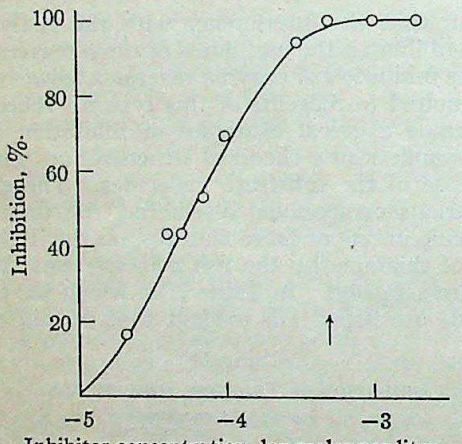
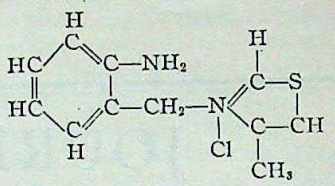


Fig. 1.—Inhibition of thiamine destruction: inhibitor, *o*-aminobenzyl-4-methylthiazolium chloride; the arrow indicates thiamine concentration (5×10^{-4} *M*).

Comparison of the results obtained with the aminobenzyl- or aminoethyl-thiazolium compounds and the corresponding nitro- and phthalimido- derivatives emphasizes the importance of the amino group even though it is attached to the thiazole ring by three carbons in the one case and by two in the other. That this group is not the sole decisive point in the inhibition is evidenced by the distinctly lessened effect obtained with the aminopyrimidines. It appears more likely from the data of Table II that the amine in combination with the thiazolium portion of the molecule furnishes the stronger inhibition. This point will be considered in more detail in a later communication.

Since the most pronounced inhibition occurs with *o*-aminobenzyl-4-methylthiazolium chloride (I) and because of the similarity of its structure to that of thiamine (II)[5] the effect of the former compound was investigated in greater detail.



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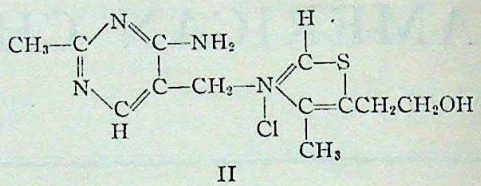

II

Experiments with a wider range of concentrations yielded the results shown in Fig. 1, in which is plotted the per cent. inhibition of thiamine destruction against concentration of the aminobenzyl compound. The character of the curve obtained is suggestive of the fundamental relationship involved.

For the purpose of further experimentation the assumption was made that the disappearance of thiamine in the presence of the fish principle occurs by a mechanism similar to that adopted for the majority of enzyme reactions.[6] In these it is believed that the substrate (in this case thiamine) combines with the enzyme (fish principle) to form an active complex which decomposes to yield the products of the reaction and the regenerated enzyme, the velocity of the reaction being directly proportional to the concentration of the active complex. In addition, inhibitor compounds resembling the substrate molecule are believed to combine in the same way with the enzyme protein in the place of the substrate and thus competitively retard the enzyme reaction. It may also be assumed that a similar situation applies with the aminobenzyl derivative with the consequent decrease in thiamine destruction. The validity of these assumptions may be tested by the use of methods originally derived from the law of mass action by Michaelis and Menten.[7] Representation of the formation of the enzyme-substrate complex by the expression

$$E + S \rightleftarrows ES \qquad (1)$$

leads to the Michaelis–Menten equation

$$v = V(S)/(K_S + (S)) \qquad (2)$$

where v is the initial velocity of the reaction, V the maximal velocity, S the substrate concentration and K_S the dissociation constant. The last term (K_S) corresponds to the substrate concentration of half-maximal velocity and is commonly known as the Michaelis constant.

(5) The similarity in spatial arrangement is even more striking when the comparison is made with atomic models.

(6) Haldane, "Enzymes," Longmans, Green and Co., London, 1930.

(7) Michaelis and Menten, *Biochem. Z.*, **49**, 333 (1913).

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By inversion of the above equation Lineweaver and Burk[8] obtained the form

$$1/v = K_S/V(S) + 1/V \qquad (3)$$

with which, by plotting $1/v$ against $1/(S)$, the more exacting linear treatment of the data is possible. With the slope and intercept values so obtained, the Michaelis constant and maximal velocity are readily calculated.

The latter authors, representing the case with an inhibitor present by the expression

$$2E + S + I \rightleftharpoons EI \text{ (Inactive)} + ES \text{ (Active)} \qquad (4)$$

have derived a second equation similar to the first and also of linear form

$$1/v = \frac{1}{V}\left(K_S + \frac{K_S(I)}{K_I}\right)\frac{1}{(S)} + \frac{1}{V} \qquad (5)$$

Included are the additional terms for inhibitor concentration, (I), and the enzyme-inhibitor dissociation constant, K_I. It is evident from equation (4) that the enzyme of the inactive enzyme-inhibitor complex is no longer able to catalyze the reaction involving the substrate. Again, by plotting the values of $1/v$ and $1/(S)$ of the inhibitor experiment, one may obtain, as Lineweaver and Burk have shown, a straight line the intercept of which is identical with that of the experiment without the inhibitor, but the slope of which is increased by the term, $K_S(I)/VK_I$ of equation (5). In this case the inhibition may be considered competitive. On the other hand, if in the two cases the slope remains the same but the intercept is increased in the presence of the inhibitor then non-competitive inhibition is occurring.

In order to determine whether the decreased thiamine loss in the presence of the aminobenzyl thiazole was due to competition between the former and the latter for the fish principle molecule, an experiment was designed so that the analytical treatment of Lineweaver and Burk might be applied. From solutions containing five different concentrations of thiamine and the same amount of fish principle, aliquots were removed at intervals for thiamine analysis. Similar solutions to which the inhibitor had been added were also analyzed, the over-all time in both cases being sufficiently short so that a plot of the thiamine destruction yields a straight line. From the amounts of thiamine destroyed at the different times the initial velocity of destruction (slope of best straight line through each set of values) in each solution was calculated using the method of least squares. Comparison of the initial velocities recorded in Table III again demonstrates the decreased activity of the fish principle in the presence of the aminobenzyl compound. Also recorded are the values for the amount of thiamine destroyed in each solution at sixty minutes. These may be compared to the values for the same time obtained by calculation. The decreased inhibition (increased destruction) with decreasing ratio of inhibitor to thiamine concentration apparent in Table III further confirms the fundamental relationship suggested by the results shown in Fig. 1.

TABLE III

INHIBITION OF THIAMINE DESTRUCTION

Thiamine concentration, moles/liter × 10^4 Without inhibitor	Destruction: Initial velocity, v, moles/liter/min. × 10^8	Destruction: At 60 minutes, moles/liter × 10^6 Obs.	Destruction: At 60 minutes, moles/liter × 10^6 Calcd.
1.0	0.746	42.8	44.8
2.5	.992	56.6	59.5
5.0	1.12	68.0	67.4
10.0	1.26	74.0	75.6
20.0	1.36	70.0	81.6
With 0.2 × 10^{-4} *M* inhibitor			
1.0	0.136	9.2	8.2
2.5	.285	18.0	17.1
5.0	.618	44.0	37.1
10.0	.758	46.0	45.5
20.0	1.29	76.0	77.4

The reciprocals of the initial velocities and substrate concentrations were plotted as shown in Fig. 2, the best straight lines being calculated by the method of least squares. From the calculation, the values of slopes and intercepts recorded in Table IV were obtained. Since the intercepts of the two straight lines coincide and the slopes are widely divergent, we may consider in the terms of Lineweaver and Burk that the inhibitory action of the aminobenzylthiazole is specific and competitive rather than general and non-specific. In addition, it is evident that the reaction involving thiamine and the fish principle exhibits features previously encountered only in the case of enzymatic reactions.

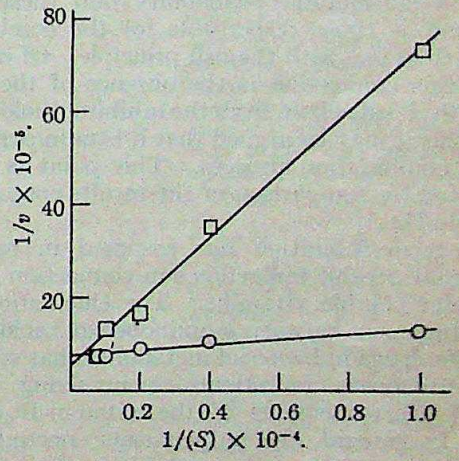

Fig. 2.—Inhibition of thiamine destruction: v, initial velocity, moles/l./minute; (S), substrate (thiamine) concentration, moles/l.; O, no inhibitor; □, with 0.2 × 10^{-4} *M* inhibitor (*o*-aminobenzyl-4-methylthiazolium chloride).

From the above slope and intercept values the maximal velocity, the Michaelis constant for the thiamine-fish principle complex and the corre-

(8) Lineweaver and Burk, THIS JOURNAL, 56, 658 (1934).

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TABLE IV

SUMMARY OF CONSTANTS

	Inhibitor Absent	Inhibitor Present
Slope	62.0	693
Increase in slope, $K_S(I)/VK_I$		631
Intercept	7.47×10^5	4.90×10^5
Maximal velocity, V[a]	0.134×10^{-5}	0.204×10^{-5}
Michaelis constant, K_S[b]	0.831×10^{-4}	
Inhibitor constant, K_I[b]		0.0197×10^{-4}
Affinity constants		
$1/K_S$	1.20×10^4	
$1/K_I$	50.7×10^4	

[a] Moles/liter/minute. [b] Moles/liter.

sponding constant for the inhibitor-fish principle complex have been calculated (Table IV). The reciprocals of the latter may be regarded as affinity constants. The ratio of $1/K_I$ to $1/K_S$ is 42.2, from which it is reasonable to believe that the inhibitor compound combines somewhat more firmly with the fish principle than does thiamine.

It may be further concluded from the above results that *o*-aminobenzyl-4-methylthiazolium chloride possesses the functional groups which allow its combination with the fish principle. There is considerable probability that these are the same as those responsible for the combination of thiamine with the fish principle. Of interest in this connection is the absence of the hydroxyethyl- side chain from the inhibitor molecule. From this it may be argued that it is unimportant in the combination process. This point is also supported by comparison of the results contained in Table II.

The term inhibition has assumed in recent times considerable importance in connection with the water soluble vitamins. The elucidation of the antagonism between *p*-aminobenzoic acid and the sulfa drugs in bacterial metabolism has stimulated numerous investigations involving analogs of other members of the vitamin-B complex. In general, the antagonisms encountered involve competition with or inhibition of the positive physiological functioning of the vitamin in question. In contrast, the above experiments deal with the inhibition of vitamin destruction, a destruction which results from the action of a substance of biological origin. This substance, the fish principle, may be an important metabolic factor in the fish organism; however, with our present knowledge it can hardly be regarded as a positive agent engaged in promoting the physiological action of thiamine. It may even be suggested that similar destructive agents affecting other vitamins may occur in nature, in which case the search for specific inhibitor analogs should prove profitable.

Experimental

The fish principle used in these experiments was prepared from acetone desiccated powder of carp viscera[1] by four or five extractions with 10% sodium chloride in 0.2 *M* phosphate buffer of *p*H 7.4. The combined supernatants obtained by centrifuging were diluted with the same solvent so that 2 ml. contained the activity of 100 mg. of original powder and were adjusted to *p*H 7.4 before being used. In the inhibition tests 2 ml. of the extract plus the desired volume of inhibitor and water to make a total volume of 4 ml. were placed in test-tubes. One ml. of 25×10^{-4} *M* thiamine was added and the tubes were incubated for two hours at 37.5°. The reaction was stopped by the addition of 5 ml. of 20% trichloroacetic acid. After thirty minutes the flocculated protein was removed by centrifugation and 2 ml. was analyzed for thiamine,[4] comparison being made with an unincubated control to which the trichloroacetic acid had been added immediately following the thiamine. The per cent. inhibition was calculated by comparison with incubated tubes containing no inhibitor.

For the experiment involving the Lineweaver–Burk treatment 28 ml. of extract of the fish principle equivalent to 700 mg. of desiccated powder was placed in one flask and 28 ml. of extract and inhibitor in a second flask. After warming to 37.5°, 7 ml. of the proper concentration of thiamine also at 37.5°, was added to both flasks. Five ml. was removed at intervals for determination of the thiamine remaining, the reaction being stopped as described above. In all, five aliquots were removed from each flask, those from the two lower concentrations of thiamine at fifteen-minute and the others at twenty-minute intervals.

Summary

The destruction of thiamine by the Chastek-paralysis factor of fish tissues could be markedly decreased by the addition of cupric, zinc and ferric ions. Cyanide, fluoride, iodoacetate, sulfhydryl and sulfite were less effective. Other common enzyme inhibitors could not be tested since they interfered with the determination of thiamine by the diazotization method.

Compounds resembling the thiamine molecule in one or more features were also tested for inhibitory action. Among these, *o*-aminobenzyl- and *β*-aminoethyl-4-methylthiazolium chloride were found to be strongly inhibitory. Substitution of the amino group of these two by the nitro and phthalimido groups, respectively, abolished the inhibition in the case of the former and greatly reduced it in the case of the latter.

Other thiazoles and various 4-aminopyrimidines were either without effect or exhibited considerably lessened inhibition.

In the case of the aminobenzyl-methylthiazole, the extent of the inhibition proved to be dependent upon the ratio of its concentration to that of thiamine.

Use of the Lineweaver-Burk method showed that this compound specifically inhibited thiamine destruction by competing with the vitamin for the fish principle. The same method yielded a Michaelis constant of 0.831×10^{-4} mole per liter for thiamine and a similar constant of 0.0197×10^{-4} for the inhibitor.

The data presented show that the fish principle behaves with inhibitor substances as do many enzymes. This finding may be interpreted as additional evidence of the enzymatic nature of the fish principle.

ROCHESTER, N. Y. RECEIVED DECEMBER 30, 1943

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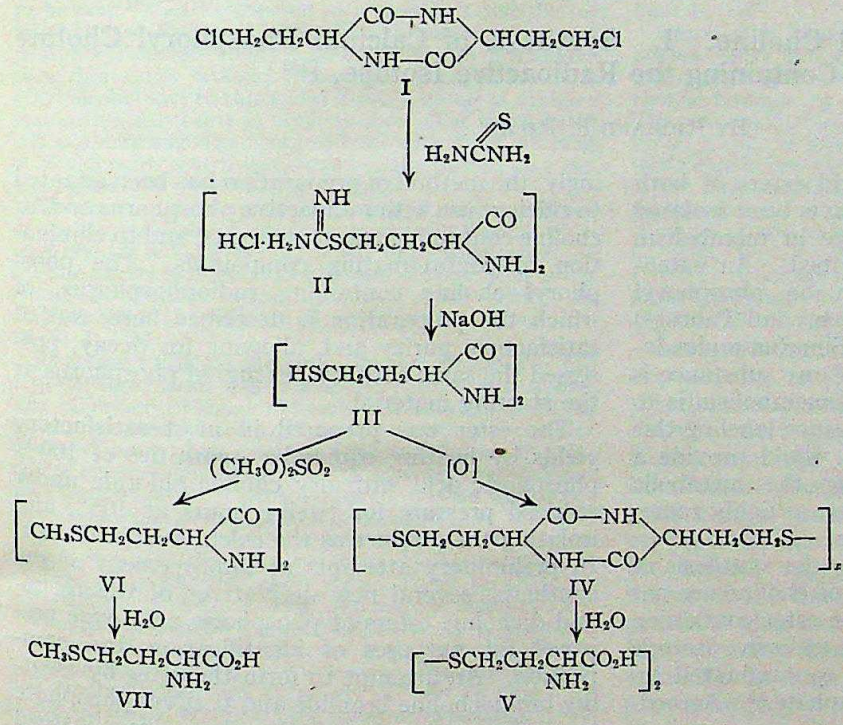
[CONTRIBUTION FROM THE NOYES LABORATORY OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

A New Synthesis of Homocystine and a Further Improvement in the Synthesis of Methionine

BY H. R. SNYDER AND GEORGE W. CANNON

In a study of the utilization of 3,6-bis-(β-chloroethyl)-2,5-diketopiperazine[1] (I) in the synthesis of amino acids it has been found that the substance (I) reacts with thiourea to give nearly quantitative yields of the bis-isothiouronium chloride (II). The ready availability of this salt is of interest because it should provide a convenient source of a number of important derivatives related to homocysteine, such as the diketopiperazine (III), homocystine (V), S-benzylhomocysteine and methionine (VII). Except for methionine,[1] these substances have been prepared most conveniently from benzyl β-chloroethyl sulfide through the malonic ester synthesis.[2,3,4]



Some of these possible transformations have been tested. Homocystine (V) was obtained in excellent yields by subjecting the isothiouronium salt to mild alkaline hydrolysis, followed by air oxidation in the presence of ferric chloride and finally by acid hydrolysis. Neither the diketopiperazine of homocysteine (III) nor the polymeric anhydride (IV) of homocystine was isolated.

Treatment of the isothiouronium salt with aqueous alkali followed by methyl sulfate gave poor yields of the anhydride of methionine (VI). However, when a mixture of the salt and methyl sulfate, suspended in ice-water, was decomposed by the gradual addition of aqueous sodium hydroxide, the diketopiperazine VI was produced in high yields. The crude product was of suitable quality for use in the preparation of *dl*-methionine. This method of converting the dichlorodiketopiperazine (I) to *dl*-methionine is more convenient than the earlier procedure,[1] in which the reaction of I with sodium methylmercaptide was employed.

Experimental

(a) **3,6-Bis-(β-isothiouroniumethyl)-2,5-diketopiperazine Chloride (II).**—A mixture of 47.8 g. (0.2 mole) of 3,6-bis-(β-chloroethyl)-2,5-diketopiperazine,[1] 33.5 g. (0.44 mole) of thiourea, and 500 cc. of absolute ethanol was heated under reflux for twenty-four hours. The reaction mixture was cooled in an ice-bath and the product collected by filtration; weight (air-dried) 77 g. (98%). It could be recrystallized from water to give a white solid which darkened at 250° and melted with decomposition at 255°.

Anal. Calcd. for $C_{10}H_{20}O_2N_6S_2Cl_2$: C, 30.69; H, 5.15. Found: C, 30.61; H, 5.29.

(b) **Homocystine (V).**—A solution of 8 g. (0.2 mole) of sodium hydroxide in 40 cc. of water was added dropwise to a stirred mixture of 19.5 g. (0.05 mole) of the isothiouronium salt and 100 cc. of water at room temperature. The stirring was continued for a total of one hour. Two crystals of ferric chloride were added to the mixture and air was bubbled through it for forty-eight hours. The mixture then was concentrated to dryness under diminished pressure. The residue was dissolved in 250 cc. of concentrated hydrochloric acid, and the solution was heated under reflux for three hours. It was then again concentrated to dryness under diminished pressure. The residue was extracted with several portions of boiling absolute ethanol. The combined alcoholic extracts were treated with Norite and then with an excess of pyridine. The solution was allowed to stand in a refrigerator over-night and the product was collected by filtration; it weighed 10 g. (74.5%). After several recrystallizations from water it darkened at 250° and decomposed without melting at 258–263° (lit.[5] 260–265°).

(c) **Methionine Anhydride (VI).**—A mixture of 19.5 g. (0.05 mole) of the diisothiouronium salt and 100 cc. of water was placed in a 500-cc. three-necked flask fitted with a reflux condenser, stirrer, and dropping funnel. The flask was immersed in an ice-bath and 15.1 g. (0.12 mole) of dimethyl sulfate was added at once to the reaction mix-

(1) Snyder, Andreen, Cannon and Peters, THIS JOURNAL, **64**, 2082 (1942).
(2) Patterson and du Vigneaud, *J. Biol. Chem.*, **111**, 393 (1935).
(3) Riegel and du Vigneaud, *ibid.*, **112**, 149 (1935–1936).
(4) Du Vigneaud, Patterson and Hunt, *ibid.*, **126**, 217 (1938).
(5) Butz and du Vigneaud, *J. Biol. Chem.*, **99**, 135 (1932–1933).

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ture. A solution of 11 g. (0.275 mole) of sodium hydroxide in 40 cc. of water was then added dropwise over a period of twenty minutes. The stirring was continued for a total of one hour, and the product was collected by filtration. The mother liquor was cooled overnight in a refrigerator and a small additional amount of product was obtained. The combined crops of the product weighed 13.5 g. (100%). After one recrystallization from ethanol, the methionine anhydride weighed 10.1 g. (75%) and melted at 226–227.5°. A mixed-melting point determination with an authentic sample of methionine anhydride was not depressed. It was of sufficient purity to give *dl*-methionine in 85–95% yields. Direct hydrolysis[1] of the crude product gave 10 g. (65%) of crude *dl*-methionine.

Summary

3,6-Bis-(β-chloroethyl)-2,5-diketopiperazine is converted quantitatively to the bis-isothiouronium salt by treatment with thiourea in boiling ethanol.

Treatment of the bis-isothiouronium salt with dilute alkali, followed by oxidation with air in the presence of ferric chloride and hydrolysis with acid, provides a convenient synthesis of homocystine.

Decomposition of the bis-isothiouronium salt with alkali in the presence of methyl sulfate produces *dl*-methionine. This method of converting the dichlorodiketopiperazine to *dl*-methionine is superior to that previously described.

URBANA, ILLINOIS RECEIVED JANUARY 17, 1944

[FROM THE DEPARTMENT OF BIOCHEMISTRY AND PHARMACOLOGY, THE UNIVERSITY OF ROCHESTER SCHOOL OF MEDICINE AND DENTISTRY]

Metabolism of Phosphoryl Choline. I. Synthesis of Calcium Phosphoryl Choline Chloride Containing the Radioactive Isotope, P^{32} [1]

BY RICHARD F. RILEY

Although monophosphoric acid esters of both choline[2] and ethanolamine[3,4] have been isolated from normal tissues, their place in metabolism has not been adequately described. An extension[5] of available information on phosphoryl choline (Smith,[6] Welch and Welch,[7] and Taurog[8]) therefore appeared of interest. Since an undue increase in tissue concentration of any substance is to be avoided where its normal metabolism is to be followed (ref. 9, p. 292) and since labeling this molecule with radiophosphorus would provide a convenient means of following the metabolic path of that portion of the ester, a highly radioactive preparation was desirable.

The published procedures for the synthesis of the monophosphoric acid ester of choline are not well suited to preparation of the ester containing radiophosphorus. They permit extensive isotope dilution[2,10,11] or yield products contaminated by the diester and inorganic phosphate.[12] Accordingly, the method of preparation has been adapted to efficient use with radioactive phosphorus and/or choline containing tracer elements, and to elimination of contaminating compounds. The phosphoryl choline containing radiophosphorus, of which the preparation is described here, was of satisfactory purity and, allowing for decay, possessed the same activity per mg. of phosphorus as the starting material.

The ester was prepared in most satisfactory yields by heating equimolar quantities of 100% phosphoric acid with dry choline chloride under reduced pressure for twelve hours at 165°, and isolating the product as the calcium chloride salt. In preliminary attempts at improvement of the synthesis, several new derivatives of the mono- and dicholine esters of phosphoric acid were prepared for purposes of identification and comparison. An attempt to form the ester by treating bromocholine bromide and trisilver phosphate or disilver monophenyl phosphate gave instead excellent yields of neurine. It was also found that choline hydroxide and phosphoric acid may be esterified in refluxing toluene to give a satisfactory product, although in rather low yield and with considerable decomposition.

Experimental

Calcium Phosphoryl Choline Chloride Containing P^{32}.—150 mg. of phosphoric acid containing P^{32} in 6 ml. of water was introduced into a pear-shaped flask of 35 ml. capacity. The flask was fitted with a standard taper 24 stopper and two outlets with glass stopcocks. The dilute acid was evaporated to 100% phosphoric acid by immersion in an oil-bath which was gradually raised to 180° as a stream of dry air was passed through the flask. Only 0.005% of the activity was lost by this evaporation. When complete, 214 mg. of pure dry choline chloride was well mixed with the phosphoric acid and about 1 g. of phosphorus pentoxide, mixed with asbestos contained in a Soxhlet thimble,

(1) The substance of this paper was presented in part before the American Chemical Society at Pittsburgh, September, 1943. This investigation was supported by a grant from the Nutrition Foundation, Inc., of New York City.

(2) F. Inukai and W. Nakahara, *Proc. Imp. Acad.* (*Tokyo*), **11**, 260 (1935).

(3) E. L. Outhouse, *Trans. Roy. Soc. Can.*, **29**, Sect. V, 77 (1935).

(4) S. P. Colowick and C. F. Cori, *Proc. Soc. Exp. Biol. and Med.*, **40**, 586 (1939).

(5) R. F. Riley, Abstracts, Pittsburgh Meeting, A. C. S., Sept., 1943, in press.

(6) M. I. Smith, *Nat. Inst. Health Bull.*, No. **165**, 11 (1936).

(7) A. DeM. Welch and M. S. Welch, *Proc. Soc. Exp. Biol. and Med.*, **39**, 7 (1938).

(8) Personal communication (1942).

(9) I. L. Chaikoff, *Physiol. Rev.*, **22**, 291 (1942).

(10) A. B. L. Beznak and E. Chain, *Quart. J. Exp. Physiol.*, **26**, 201 (1936–1937).

(11) R. H. A. Plimmer and W. J. N. Burch, *Biochem. J.*, **31**, 398 (1937).

(12) E. L. Jackson, THIS JOURNAL, **57**, 1903 (1935).

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supported over the reactants. The contents were maintained for twelve hours at 165° under vacuum. On cooling, the products were taken up in a few ml. of water, 100 mg. of calcium chloride added and the solution brought to the phenolphthalein end-point with saturated calcium hydroxide solution and worked up by the method of Plimmer and Burch[11]; yield 306 mg. or 63% of thin colorless rectangular plates. Unreacted phosphate, recovered as calcium phosphates during the isolation, was salvaged for further use by conversion to magnesium ammonium phosphate. The total recovery of radiophosphorus as the ester and magnesium ammonium phosphate was 96%. *Anal.* Calcd. for $C_5H_{13}O_4NPCaCl\cdot 4H_2O$: C, 18.2; H, 6.37; N, 4.25. Found: C, 18.11; H, 6.42; N, 4.19.

By isotope dilution, the product was found to contain 0.02% contaminating inorganic phosphorus and < 0.05% by colorimetric analysis. Calcium phosphoryl choline chloride prepared in this fashion contains negligible amounts of the diester, as indicated by analysis and the fact that measurable quantities of the insoluble diaurichloride could not be obtained from larger scale preparations utilizing non-isotopic phosphorus.

Phosphoryl Choline Reineckate.—3.37 g. of recrystallized phosphoryl choline aurichloride, prepared according to Jackson,[12] was decomposed with powdered silver by the procedure of Dudley.[13] The dilute aqueous solution of phosphoryl choline chloride so obtained was evaporated to a thin sirup, brought to incipient precipitation with ethyl alcohol and to this added a 100% excess of acidified ammonium reineckate in ethyl alcohol. The precipitated salt was centrifuged and washed twice with 20-ml. portions of alcohol with centrifugation and finally filtered on a sintered glass filter; yield 2.17 g. or 99%.

The compound does not precipitate well from an aqueous or acetone solution (*cf.* choline reineckate) although when once dried it redissolves only slowly in these solvents. It is quite insoluble in ethyl alcohol and dioxane after it has once been obtained in the dry state. *Anal.* Calcd. for $C_{14}H_{36}O_8N_8S_4P_2Cr$: N, 16.37; P, 9.05. Found: N, 16.28; P, 8.54.

Phosphoryl Choline Mercuric Chloride Complex.—0.75 g. of the aurichloride was decomposed with silver as above. The phosphoryl choline chloride, contained in 5 ml. of water, was precipitated as the mercuric chloride complex by the addition of an excess of a saturated alcoholic solution of mercuric chloride. The complex was recrystallized once from warm 80% alcohol, filtered, washed with absolute alcohol and dried; yield 1.08 g. or 76% as beautiful long white needles, singly and in clusters. It is more soluble in water than the mercuric chloride complex of choline; m. p. 180–184° cor. *Anal.* Calcd. for $C_5H_{16}O_4NP\cdot 3HgCl_2$: N, 1.40; P, 3.10. Found: N, 1.45; P, 3.26.

Phosphoryl Choline Phosphotungstate.—A preparation of characteristic composition was not obtained although phosphotungstic acid gave a water-insoluble microcrystalline product which was extremely difficult to filter. It contained 0.91% N; yield 71% based on N analysis.

Dicholine Phosphate Reineckate.—This was prepared by the same procedure given for the monoester: 0.35 g. of the diaurichloride gave 0.23 g. of reineckate; very slightly soluble in water, acetone, ether and chloroform; insoluble in ethyl alcohol. This salt probably is of variable composition. That obtained showed N, 19.70; P, 3.92; yield 79% based on P analysis.

Dicholine Phosphate Mercuric Chloride Complex.—This was prepared by the same procedure given for the monoester complex: 0.30 g. of the diaurichloride gave 0.13 g. of a fluffy crystalline powder on recrystallization of the crude product from hot water; m. p. 202–207°; N, 0.89; yield 13% based on N analysis.

Direct Esterification of Choline Hydroxide by Phosphoric Acid in Toluene.—Ten grams of choline chloride was dissolved in 50 ml. of water and stirred in the dark with a calculated excess of silver carbonate until the filtrate gave a negative test for halogen. It was filtered and the calculated quantity of barium hydroxide added. The solution was filtered from barium carbonate and the filtrate evaporated down under nitrogen with reduced pressure. The sirup obtained was distilled with toluene to remove further water, 3.83 ml. of 100% phosphoric acid added slowly and distillation continued until no more water came over with the toluene, further toluene being added as required. On cooling the toluene was decanted from the residue which was washed with two small portions of absolute alcohol and dried in the air. The residue was taken up in 10 ml. of water, filtered and precipitated by addition of 10 volumes of absolute alcohol. The precipitated sirup was taken up in water, 8.0 g. of calcium chloride added and the solution neutralized to phenolphthalein with saturated calcium hydroxide solution. The filtrate[14] from this solution was evaporated under reduced pressure on the steam-bath to a thin sirup and precipitated by the addition of 200 ml. of absolute alcohol. The crystalline product on drying in air following a second precipitation weighed 3.2 g. or 24%. The product was obtained as thin fragile rectangular plates or needles depending on the rate of crystallization. Analysis showed this to be the calcium chloride salt of Plimmer and Burch.[11] *Anal.* Calcd. for $C_5H_{13}O_4NPCaCl\cdot 4H_2O$: P, 9.46; N, 4.25; H_2O, 21.86. Found: P, 9.2; N, 4.10; H_2O, 21.4; ionic P, 0.07.

Reaction of Bromocholine Bromide and Silver Phosphates.—Five grams of trisilver phosphate suspended in 300 ml. of absolute alcohol reacted with 2.95 g. of bromocholine bromide by refluxing for six hours in the dark. The reaction mixture was cooled, filtered to separate silver bromide and the filtrate, after decolorization with Norite, worked up in two parts to give the picrate and aurichloride of the main reaction product; yield 65%. The neurine picrate melted at 270° and the aurichloride at 243°. *Analysis* of the picrate showed: calcd. for $C_{11}H_{14}O_7N_4$: C, 42.05; H, 4.49; P, 0.00. Found: C, 42.17; H, 4.36; P, 0.00. A similar experiment employing disilver monophenyl phosphate in place of the trisilver phosphate gave an 89% yield of neurine isolated as the picrate.[15]

Acknowledgments.—The author takes this opportunity to thank Dr. Harold C. Hodge of this department for his help and advice throughout the development of this work. Dr. Donald Ketchum of the Eastman Kodak Company and Mr. Robert Bauman of the University of Rochester kindly carried out the combustion analyses reported here. We also wish to acknowledge the helpful suggestions of Dr. Arnold Weissberger of the Eastman Kodak Company and express our thanks to Dr. Robley D. Evans of the Massachusetts Institute of Technology, who made available the high activity sample of radiophosphorus employed.

Summary

1. An economical method for the preparation of phosphoryl choline containing isotopic elements has been developed and applied to the synthesis of the ester containing highly active radiophosphorus.

2. Several new derivatives of the mono- and dicholine phosphoric acid esters have been described.

ROCHESTER, N. Y. RECEIVED DECEMBER 31, 1943

(13) H. W. Dudley, *Biochem. J.*, 23, 1164 (1929).

(14) Filtration of these solutions containing calcium phosphates may be difficult due to the gelatinous nature of the suspended material. However, use of filter aids is not recommended as it was found that the desired compound is strongly adsorbed by such preparations.

(15) Disilver monophenyl phosphate was prepared from the acid kindly supplied by the Victor Chemical Company.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

A New Method for the Measurement of Tyrosinase Catecholase Activity. II. Catecholase Activity Based on the Initial Reaction Velocity

BY WILBUR H. MILLER,[1] M. FRANK MALLETTE, LLOYD J. ROTH AND CHARLES R. DAWSON

In a previous publication[2] a new technique for the determination of the catecholase activity of the phenol oxidizing enzyme, tyrosinase, was described. This technique was referred to as the chronometric method since it involves the measurement of the time necessary for a given quantity of the enzyme to produce *o*-benzoquinone in the catechol–enzyme system just in excess of that necessary to oxidize a small amount of ascorbic acid also present in the system. The end-point time, time of appearance of excess *o*-benzoquinone, is indicated by a blue coloration at the point where the reaction mixture is continuously sampled dropwise into an acidified starch–iodide indicator solution.

Because it seemed advisable for purposes of comparison to continue the activity data in a form previously used in this and other laboratories, the chronometric method was calibrated against the direct manometric method of measuring the catecholase activity. That is, the end-point times obtained using various amounts of the enzyme with a prescribed amount of ascorbic acid in the system were correlated with the activity of the enzyme as based on oxygen uptake measurements made during the enzymatic oxidation of catechol in the absence of ascorbic acid. A simple equation was thus given for the calculation of the activity from the end-point time, based on the calibration value of 34 catecholase units for an end-point of sixty seconds using a 250-cc. reaction volume. This value (34 units) was obtained after a statistical treatment of a large number of one minute reading experiments using an appropriate dilution of the enzyme in the direct manometric method.[3] It was pointed out that such activity measurements made by the chronometric method were much more reproducible than those obtained using the manometric method and could be obtained with considerably less effort.

A difficulty in obtaining a reliable measure of the catecholase activity of tyrosinase with the usual Warburg manometer technique rests on the fact that during the enzymatic oxidation of catechol the enzyme frequently is very rapidly inactivated. In such a case the course of the oxygen uptake is at no time linear in form, and rate measurements are therefore difficult to obtain. This difficulty generally becomes more and more evident as the purity of the enzyme, or freedom from extraneous inactive protein material, is increased. The limitations of the respirometer method are such that accurate readings of oxygen uptake are not possible during the initial phases of the reaction, hence rate measurements during the first two to three minutes of the reaction are subject to an experimental error estimated by Parkinson and Nelson[4] to be about 20–30%. On the other hand, end-point times by the chronometric method can be obtained with good precision at any time within the interval of twenty to one hundred and fifty seconds after initiating the enzymatic oxidation of catechol.

An application of the chronometric method to a study of this inactivation of the enzyme occurring during the initial phases of the enzymatic oxidation of catechol reveals that the different types of tyrosinase preparations[5] differ markedly in the degree of inactivation of the enzyme that occurs during the first sixty seconds of the reaction.[8] This of course means that catecholase activities based on rate measurements made after the reaction has progressed for a short time are influenced by the degree of enzyme inactivation that has occurred up to that time. In other words, a measurement of the rate of oxidation (activity) made at sixty seconds using a preparation that does not inactivate during this time will give a true value of the original activity of the enzyme. However, the measurement made at sixty seconds for a preparation that has undergone serious inactivation during the first minute of the reaction will, of course, yield an activity value lower than the true activity of the original enzyme preparation.

It is apparent that to compare on a common basis the catecholase activities of tyrosinase preparations differing in the degree of enzyme inactivation that occurs during the initial phases of the enzymatic oxidation of catechol, the activities must be based on the initial reaction velocity. In terms of oxygen uptake, or in terms of *o*-benzo-

(1) Present address: Stamford Research Laboratories, American Cyanamid Company, Stamford, Conn.

(2) W. H. Miller and C. R. Dawson, THIS JOURNAL, **63**, 3375 (1941).

(3) D. C. Gregg and J. M. Nelson, *ibid.*, **60**, 2501 (1938).

(4) G. G. Parkinson and J. M. Nelson, *ibid.*, **62**, 1693 (1940).

(5) Preparations of tyrosinase from the common mushroom *Psalliota campestris* vary in their ratio of catecholase to cresolase activity depending on the method of isolation and purification employed. Those which are relatively much more active with catechol than with *p*-cresol have been termed high catecholase preparations to distinguish them from the so-called high cresolase preparations in which the two activities are more nearly comparable. These preparations have properties that are quite different[3,4,6,7] and the question of whether or not they are mixtures of two enzymes, or result because of modification of one enzyme protein during processing, etc., has not yet been definitely settled.

(6) W. H. Miller and C. R. Dawson, THIS JOURNAL, **63**, 3368 (1941).

(7) W. H. Miller and C. R. Dawson, *ibid.*, **64**, 2344 (1942).

(8) To be published.

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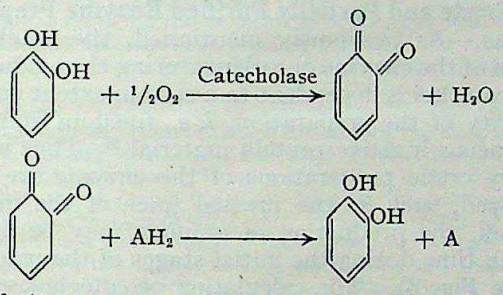
quinone production, the initial reaction velocity is dO_2/dt or dQ/dt where $t \cong 0$. The lack of precision inherent in the manometric method makes the determination of dO_2/dt at $t \cong 0$ impracticable, but a slight modification of the chronometric technique as previously described yields the value of dQ/dt at $t \cong 0$ with good precision. It is the purpose of this communication, therefore, to describe how the true catecholase activity of the enzyme, based on the initial reaction velocity and hence not influenced by the inactivation characteristics of the preparation, may be obtained using the chronometric method.

The Initial Reaction Course.—As previously indicated, when catechol is enzymatically oxidized in the presence of ascorbic acid,[9] no detectable amount of *o*-benzoquinone exists in the solution, and the reaction mixture remains perfectly colorless until the moment the ascorbic acid (AH_2) has all been converted to dehydroascorbic acid (A)



If the experiment is set up a number of times using different amounts of ascorbic acid with a given amount of enzyme and catechol, a series of end-point times (time of appearance of *o*-benzoquinone in system) is obtained. In this way the production of *o*-benzoquinone (or its equivalent—the disappearance of ascorbic acid) can be measured as a function of time for a given amount of the enzyme. The method is, therefore, nothing more than an indirect titration of the *o*-benzoquinone, performed in such a manner that the quinone is never present in the reaction mixture until the instant of its detection. This eliminates from consideration the many complex side reactions which make the direct titration of *o*-benzoquinone unsuitable for measuring the enzyme activity.[11] By using small amounts of ascorbic acid in the system the *o*-benzoquinone production can be followed during the very early stages of the reaction with good precision.

The data given in the form of Curves I, II and III in Fig. 1 show, in terms of quinone production, the initial reaction course during the enzymatic oxidation of catechol as catalyzed by three

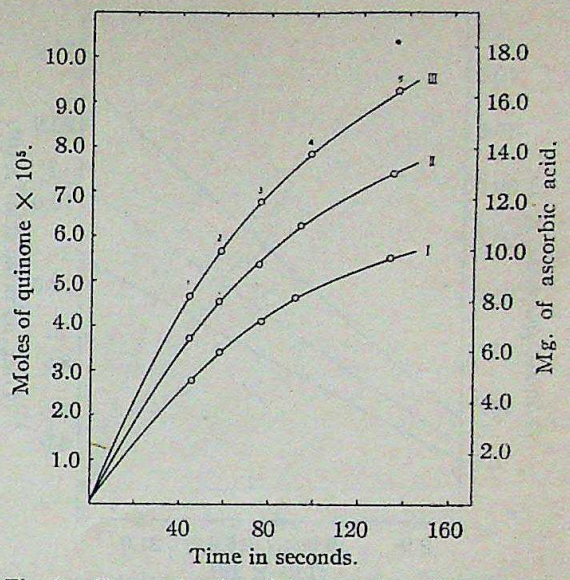


Fig. 1.—Curves showing the production of *o*-benzoquinone during the initial phase of the enzymatic oxidation of catechol. Aerobic oxidation catalyzed by three different amounts of a purified high catecholase preparation of tyrosinase.[12] Each experimental point obtained and checked (see experimental section) using a 250-cc. reaction volume containing 50 mg. of catechol (optimum) and ascorbic acid as shown; *p*H 5.5; temp., 25°. Enzyme employed was tyrosinase preparation C143F1, diluted 1:10 and then this sub-dilution further diluted 1:100 just before using; total dilution 1:1000. Curve I, 6 cc.; Curve II, 8 cc.; Curve III, 10 cc. The undiluted enzyme had a dry wt. of 5.9 mg./cc.,[13] contained 0.07% Cu,[14] 475 cresolase units/cc.,[3] and was stable for a long period when stored at refrigerator temperature. In the 1:10 dilution it was stable for several days at low temperature. See experimental section for method of obtaining data.

different amounts of a purified, typical, high catecholase preparation of tyrosinase.[5] Besides enzyme and ascorbic acid, as shown, the original reaction mixtures for each experimental point contained catechol in optimum concentration for this type enzyme preparation, *i. e.*, 50 mg. in a 250-cc. reaction volume, added at zero time to the buffered enzyme–ascorbic acid mixture (*p*H 5.5) to initiate the reaction. The oxidations were carried out at 25°. Other experimental details are given in the legend of the figure and the experimental section.

Because the catechol concentration remains constant during the reaction and is present in large excess in comparison to the amount of *o*-benzoquinone formed, the drop in rate of production of quinone that is evident in each case can only be attributed to serious inactivation of the enzyme in the early stages of the reaction.

(9) The ascorbic acid functions only as a reducing agent and does not significantly inhibit or accelerate the enzyme action. Its oxidation is not catalyzed by the enzyme under these conditions, nor does it affect the inactivation of the enzyme.[2,10]

(10) B. J. Ludwig and J. M. Nelson, THIS JOURNAL, **61**, 2601 (1939).

(11) C. R. Dawson and J. M. Nelson, THIS JOURNAL, **60**, 245 (1938).

(12) Prepared from the common mushroom, *Psalliota campestris*, by a modification (to be published later) of the method described by Ludwig and Nelson.[10]

(13) J. B. Lutz and J. M. Nelson, *J. Biol. Chem.*, **107**, 169 (1934).

(14) Determined by H. A. Krebs, *Biochem. Z.*, **190**, 134 (1927).

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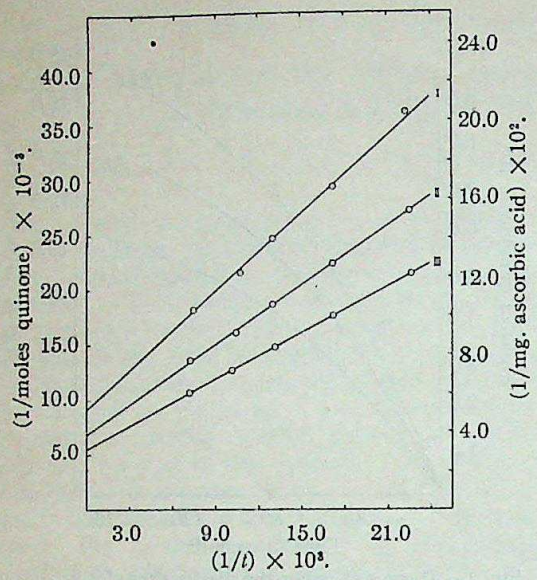

Fig. 2.—Reciprocal plot of data in Fig. 1. The linear curves (I, II and III) are expressed by Equation 2 and therefore verify that the initial reaction course during the enzymatic oxidation of catechol follows Equation 1. The most probable curve was established in each case by the method of residuals[15] using large-scale plots.

The Initial Reaction Velocity.—When the reciprocal of the quinone is plotted against the reciprocal of the time, linear curves are obtained as shown in Fig. 2. This fact indicates that during the initial stages of the enzymatic oxidation of catechol by a purified high catecholase preparation of tyrosinase the *o*-benzoquinone is produced in accordance with the following equation

$$Q = at/(b + t) \qquad (1)$$

since the linear curves are expressed by the reciprocal equation

$$1/Q = b/a(1/t) + 1/a \qquad (2)$$

where Q is the *o*-benzoquinone, and a and b are constants which may be evaluated by determining the slope and intercept of the linear curves of Eq. 2.

Differentiation of Eq. 1 in respect to t gives equation 3.

$$\frac{dQ}{dt} = \frac{ab}{(b + t)^2} \qquad (3)$$

and it follows that when $t \cong 0$

$$\frac{dQ}{dt_{(t \cong 0)}} = a/b \qquad (4)$$

Thus the initial reaction velocity (a/b) is the reciprocal of the slope of the linear curves shown in Fig. 2 (see Eq. 2) and may be determined from the experimental data.

The Unit of Catecholase Activity.—In all previous publications from this and certain other laboratories concerning the enzyme tyrosinase, one unit of enzyme activity has been defined as that amount of enzyme that, when catalyzing the oxidation of the phenolic substrate under specified conditions, causes an oxygen uptake of 10 cu. mm. per minute. This rate of oxygen uptake is equivalent to 8.93×10^{-7} mole of quinone per minute or 1.49×10^{-8} mole of quinone per second. Thus in terms of the initial reaction velocity (Eq. 4), which may be expressed as moles of quinone per second, the catecholase activity is calculated from

$$\text{Catecholase Units} = (a/b)/1.49 \times 10^{-8} \qquad (5)$$

and one unit of catecholase becomes that amount of enzyme which produces *o*-benzoquinone at an initial rate of 1.49×10^{-8} mole of quinone per second. The original definition of a catecholase unit has not been changed, but the portion of the reaction from which the unit is calculated has been shifted.

Crude and Partially Purified Enzyme Preparations.—As previously mentioned, the inactivation of the enzyme occurring during the oxidation of catechol is dependent to a certain extent on the purity of the preparation, *i. e.*, freedom from extraneous inactive protein material.[16] Thus when very crude preparations of the enzyme are employed, such as the pressed juice of the mushroom, the production of quinone may be linear with time during the initial stages of the reaction (see Fig. 3). The calculation of catecholase activity in these cases is, of course, simplified since the slope of the reaction curve is constant and gives directly the initial reaction velocity in moles of quinone per second.

It can be seen that a linear reaction course is nothing more than a special case of the expression as given in Eq. 1. For as the constants a and b become very large, *i. e.*, approach infinity, b becomes very large in respect to t and Eq. 1 approaches the expression for a straight line through the origin, *i. e.*

$$Q = at/b = kt \qquad (6)$$

As the purification of a high catecholase type preparation of tyrosinase is increased, *i. e.*, the activity per mg. dry weight is increased, the inactivation of the enzyme during the initial stages of the oxidation of catechol soon becomes evident. That is, the reaction course generally departs from a linear form after two or three steps in the purification process. It has been our experience in following through a large number of such preparations that the reaction course always follows the expression given by Eq. 1, *i. e.*, the reciprocal plot

(15) H. M. Goodwin, "Elements of the Precision of Measurements and Graphical Methods," McGraw-Hill Book Co., New York, N. Y., 1920.

(16) It should be pointed out that the inactivation characteristics of a tyrosinase preparation during the oxidation of catechol appear also to be dependent on the ratio of the catecholase to cresolase activity of the enzyme.[5] Preparations relatively high in cresolase activity generally are more stable than high catecholase preparations during the oxidation, and several purified high cresolase preparations have been obtained that show no inactivation during the initial stages of the oxidation of catechol.[5]

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of quinone versus time yields linear curves of the type expressed by Eq. 2 and shown in Fig. 2. The values of a and b decrease to constant values that are characteristic of the high catecholase type preparation, and further purification has little or no effect on the curvature of the reaction course. In other words, after a certain stage in the purification is reached, further purification has little or no effect on the inactivation characteristics of the high catecholase type preparation. The application of Eq. 1 to a study of the inactivation of the catecholase activity of tyrosinase is to be published later.

The Activity Determination: Experimental.—The chronometric method as originally described made use of a 250-cc. reaction volume. Experience in this Laboratory has shown that the reaction system can be reduced to a 100-cc. volume with advantage if all of the reagents of the system are reduced proportionately, *i. e.*, to 2/5 scale. Much less enzyme, catechol, ascorbic acid and buffer are used up, therefore, per end-point determination; an important factor when a large number of determinations are made per day. The precision of the measurements and working range of enzyme concentration do not appear to be significantly different in the smaller volume. The method as described below is, therefore, for the 100-cc. volume system.

A 300-cc. round-bottom three-neck flask[17] is clamped in position in a 25° thermostat. One neck of the flask is to hold a capillary siphon tube for carrying the reaction mixture dropwise (about 2 drops per second) over into the acidified starch iodide indicator solution. Another neck allows for the introduction of a medium stream of air bubbles which serve to agitate the contents of the flask and also to start the siphon flowing when the third (center) neck is momentarily closed. The center neck of the flask is used for introducing the reagents which are previously maintained at 25° in the thermostat.[18]

In the flask are placed 10 cc. of 0.2 M citric acid—0.4 M secondary sodium phosphate buffer (pH 5.1) and enough water to make the total volume 100 cc. when the other reagents have been added. Just previous to starting the reaction the ascorbic acid and enzyme are added. Usually for the first end-point an accurately known quantity of ascorbic acid (about 3 mg.) is introduced in the form of a 0.1% solution which is also 0.1% in metaphosphoric acid (the latter stabilizes the ascorbic acid to autoxidation but has no effect on the enzymatic reaction). The ascorbic acid and enzyme are rinsed in with a measured quantity of water, and the siphon tube is then adjusted in position. The air bubbler is inserted, and the reaction is initiated about ten to fifteen seconds afterwards by rapidly introducing an aqueous solution of catechol from a small erlenmeyer flask or cylinder. The pH of this final reaction is 5.5. At any convenient time thereafter (usually 5 to 10 seconds) the siphon is started, and the end-point time, the time at which o-quinone is existent in the reaction mixture due to complete removal of reducing agent, is indicated by the appearance of a blue color at the point where the reaction mixture drops into the acidified starch–iodide indicator solution. The indicator solution is a mixture of 5 cc. of 1% starch solution, 25 cc. of 10% potassium iodide solution, and 25 cc. of 2 N sulfuric acid containing 1% pyrogallol. To greatly facilitate the observation of the end-point it is advantageous to use the indicator solution in a small crystallizing dish illuminated from below through white opal glass.. The indicator solution should be stirred slowly at a constant rate during the determination. The effect on the end-point time caused by certain variations in experimental conditions has been discussed elsewhere.[2]

(17) A 500-cc. flask works equally well.

(18) The diluted enzyme is kept at 0–5° at all times. Experience has shown that many tyrosinase preparations, particularly when purified, tend to lose catecholase activity very rapidly when allowed to stand in highly dilute solution at room temperature. Concentrated preparations (in excess of 1 mg. of enzyme protein per cc.) are generally quite stable. To dilute the stock enzyme for activity determination cold water should be used, and the analysis made within a few minutes of the dilution. Several determinations generally can be made on the same dilution if it is kept in an ice-bath at 0–5°.

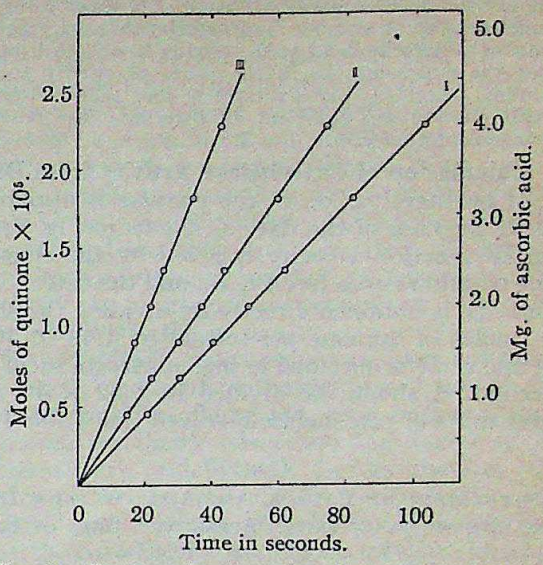

Fig. 3.—Curves showing the linear production of o-benzoquinone during the initial phase of the enzymatic oxidation of catechol when catalyzed by three different amounts of crude extract preparation[19] of tyrosinase from the common mushroom, *Psalliota campestris*. Each experimental point was obtained and checked using 100 mg. of catechol (optimum) in a 100-cc. reaction volume buffered to pH 5.5 as described in the experimental section. Curve I, 1 cc. of a 2:17 dilution of the extract; Curve II, 1 cc. of a 3:18 dilution; Curve III, 1 cc. of a 5:17 dilution. See Table I for calculation of catecholase activities. The undiluted crude extract had a dry wt. of about 6 mg./cc. and contained 23 cresolase units/cc.

To determine the catecholase activity of tyrosinase by this method it is first necessary to establish the optimum concentration of substrate (catechol) to be used, since the rate of oxidation varies with the catechol concentration for different tyrosinase preparations.[2] This is best accomplished by diluting the enzyme so that when 50 mg. of catechol and 3 mg. of ascorbic acid are used an end-point is obtained in the region of forty to sixty seconds. Then using the same amount of enzyme and ascorbic acid the end-point determination is repeated three or four times while varying the original catechol concentration until the quantity giving the shortest end-point time has been determined. Purified high catecholase preparations usually have an optimum catechol concentration in the vicinity of 20 mg. per 100 cc. reaction volume, whereas crude preparations and high cresolase preparations generally show maximum activity and little variation between 100–200 mg. of catechol.

With the optimum catechol concentration established the initial reaction course is then determined by repeating

(19) 1 lb. of mushrooms was passed through a meat grinder into two volumes of cold acetone (chilled with dry-ice) to wash out natural substrates and coloring matter. After filtering immediately, the pulp was frozen with dry-ice for two hours and then broken up and suspended in 600 cc. of water containing a drop of concentrated ammonia solution. After standing overnight at refrigerator temperature the extract and pulp were separated by pressing through

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the end-point determination a number of times using the same amount of enzyme and catechol but varying the amount of ascorbic acid used—usually from 1 to 4 mg. so that the end-points lie in the range of twenty to one hundred seconds. Usually three or four such end-points (with checks) are sufficient to determine the reaction course as plotted in Fig. 1 or 3.

Calculation of Catecholase Activity from Data.—If no inactivation of the enzyme is apparent, as in the case of the data as shown in Fig. 3, the initial reaction velocity is given by the slope of the reaction curve (see Eq. 6), and the catecholase activity is obtained directly by dividing the slope in moles of quinone per second by 1.49×10^{-8}. If the slope is obtained in mg. of ascorbic acid per second, it should be divided by 2.62×10^{-3} to give units of catecholase involved (see Table I).

TABLE I

CALCULATION OF CATECHOLASE ACTIVITY FROM DATA. NO ENZYME INACTIVATION APPARENT. DATA OF FIG. 3

Curve	Enzyme diln. factor	Slope, mg. AH_2 per sec.	Units in reaction, slope/ 2.62×10^{-3}	Units/cc., undiluted
I	8.5	0.0388	14.8	126
II	6.0	.0540	20.6	124
III	3.4	.0933	35.6	121
			Average ± a.d.	124 ± 2

If inactivation of the enzyme is apparent, as in the case of the curves in Fig. 1, the best value of the catecholase activity is obtained from the reciprocal plot of the data as shown in Fig. 2. If care is taken to establish the best linear curve through the experimental points (see legend Fig. 2) the reciprocal of the slope of this curve (the initial reaction velocity) is directly proportional to the amount of enzyme taken when the conditions specified above are employed. This proportionality is shown by the data as arranged in Table II.

TABLE II

CATECHOLASE ACTIVITY FROM THE RECIPROCAL PLOT DATA (FIG. 2). ENZYME INACTIVATION APPARENT

Curve	Enzyme, cc.	Slope (b/a), sec. per mole Q	Initial vel. (a/b) moles Q per sec.	Catecholase units $(a/b)/1.49 \times 10^{-8}$	Units/cc.
I	6.0	11.8×10^5	8.48×10^{-7}	56.8	9.47
II	8.0	8.94×10^5	11.2×10^{-7}	75.2	9.40
III	10.0	7.03×10^5	14.2×10^{-7}	95.4	9.54
			Average ± a.d.		9.47 ± 0.05

If only the activity of the enzyme is desired and not the values of a and b of Equation 1 or 2, it is not necessary to plot the reciprocal curve (Fig. 2). The initial reaction velocity can be obtained directly from the original data by inserting the values of two experimental points into the following equation

$$a/b = \frac{(Q_1C_2)(t_2 - t_1)}{(t_1t_2)(Q_2 - Q_1)} \qquad (7)$$

where Q_1 is the moles of quinone formed in t_1 seconds, and Q_2 the moles formed in a longer time t_2. It is generally more convenient to use Eq. 7 in terms of mg. of ascorbic acid rather than moles of quinone, since the data are obtained directly in terms of ascorbic acid. The initial reaction velocity is then converted into catecholase activity in the manner described previously and illustrated in Table I. This method of calculating the activity directly from the original data is much less time-consuming than the method involving the reciprocal plot. However, the results obtained are less reliable since they are based on only two experimental points. For example, using this method for three different pairs of points (1 and 3, 2 and 4, 3 and 5) for each of the three curves of Fig. 1 yields an average value of 9.37 ± 0.33 (3.5%) units per cc. as the activity of the diluted enzyme (compare with Table II).

Discussion

It seems advisable to compare the catecholase activity of tyrosinase as determined by the method described above with that obtained by other methods of determination. Two other methods that are in use are (I) the direct monometric method on catechol,[3,20] and (II) the manometric method using a mixture of hydroquinone and catechol as proposed by Adams and Nelson.[21] Each of these methods (I and II) depends on a rate measurement made at some time after the enzymatic oxidation of catechol has been initiated, and the activity results are, therefore, influenced by what has happened to the enzyme during the reaction previous to that rate measurement. It follows, therefore, that only in the case of an enzyme which shows no inactivation during the initial stages of the reaction can these methods yield results that are comparable to the results obtained with the chronometric method as described above. In the usual case, where inactivation of the enzyme is evident, the chronometric method based on the initial reaction velocity will give considerably higher values of catecholase activity. It follows that no conversion factor is possible to convert catecholase activity as determined by any of these methods into activity as based on the initial reaction velocity unless the nature and degree of inactivation in the early stages of the reaction are also known.

In the direct manometric method on catechol, as used by Gregg and Nelson,[3] the inert protein material gelatin is placed in the reaction system to "protect" the enzyme to some extent against inactivation. More reproducible results are obtained in the presence of gelatin than when gelatin is absent from the system, and the reaction course is somewhat more linear in form during the first two minutes of the reaction when gelatin is employed.[6] The diluted enzyme stands in the buffered reaction system (containing gelatin) during a ten to twenty minute temperature equilibra-

(20) D. Keilin and T. Mann, *Proc. Roy. Soc.* (London), **125B**, 187 (1938).

(21) M. H. Adams and J. M. Nelson, THIS JOURNAL, **60**, 2474 (1938).

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tion period (25°), and then the reaction is initiated by the addition of catechol. Readings of oxygen uptake are taken every minute.

If the activity of a purified high catecholase preparation of tyrosinase is determined by this method and then by the chronometric method as based on the initial reaction velocity, about twice as much catecholase activity will be indicated in the latter case. A good share of this discrepancy between the two methods is due to the considerable inactivation of the enzyme that occurs during the first minute of the reaction, and the rest can undoubtedly be ascribed to the difference in the experimental conditions. The main experimental difference between the two systems lies in the fact that in the chronometric system no gelatin is employed, and the diluted enzyme is not subjected to a long temperature equilibration period prior to the measurement. Both of these factors have been shown to lower the activity of the enzyme, particularly when the activity is based on the first minute reading of oxygen uptake.[6]

The Adams and Nelson manometric method of measuring the catecholase activity of tyrosinase[21] is based on the rate of oxygen absorption while the enzyme catalyzes the oxidation of a small amount of catechol in the presence of a relatively large amount of hydroquinone. Gelatin is also employed in the system. At the time it was proposed, it was believed that the hydroquinone functioned only as a reductant of the *o*-benzoquinone, thereby maintaining a constant concentration of catechol during the measurement. The presence of hydroquinone in the catechol–enzyme system markedly stabilizes the enzyme against inactivation during the oxidation, and the reaction course as followed by oxygen uptake tends to be linear for an appreciable time.[10] Because of the linear reaction course, reproducible rate measurements of the enzymatic oxidation of catechol became possible with the introduction of this substrate mixture, and the method met with favor. It did much to stimulate studies of the catecholase activity of tyrosinase, and made possible the comparison of this activity with the monophenolase activity of the enzyme.

However, these studies have shown that hydroquinone does not act merely as a reductant for the *o*-benzoquinone. Under certain conditions it is oxidized by the enzyme,[22] and previous publications[4,6] have emphasized the fact that the stabilizing effect of hydroquinone against the inactivation of the enzyme varies with the nature of the enzyme preparation. In all cases when hydroquinone is in the system the initial rate of enzymatic oxidation is less than when catechol is oxidized alone, *i. e.*, catecholase activity obtained by this method is always less than that obtained in the direct manometric method on catechol. Apparently the hydroquinone behaves as a competitive inhibitor in the system.

If these effects of hydroquinone were constant, no serious criticism to the continued use of the method could be offered but, as a matter of fact, both the stabilizing effect and the degree of inhibition vary widely with factors such as the purity of the enzyme and the ratio of the catecholase and cresolase activities. It is obvious that the catechol–hydroquinone method does not give a true measure of the catecholase content of any tyrosinase preparation, and the continued use of the method is, therefore, open to serious criticism.

Summary

1. A chronometric method based on the indirect titration of *o*-benzoquinone is described for following the initial reaction course during the enzymatic oxidation of catechol.

2. The precision is such that the initial reaction velocity (dQ/dt at $t \equiv 0$) may be determined and used for calculation of the catecholase activity of the enzyme tyrosinase.

3. The value of catecholase activities based on the initial reaction velocity, particularly when comparing enzymes having different inactivation characteristics, has been discussed.

4. Two other methods now in use for the measurement of tyrosinase catecholase activity have been discussed in comparison with the chronometric method.

5. It is felt that the chronometric method of measuring the catecholase activity of tyrosinase is superior to other methods now in use.

NEW YORK, N. Y. RECEIVED JANUARY 5, 1944

(22) D. C. Gregg and J. M. Nelson, THIS JOURNAL, **62**, 2510 (1940).

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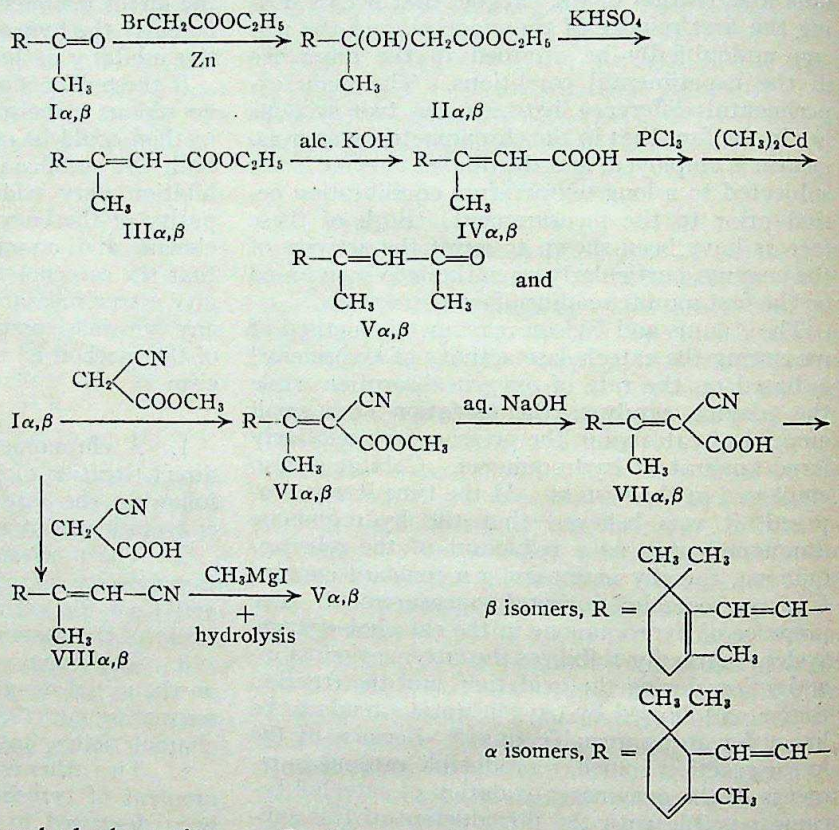
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Polyenes. I. The Synthesis and Absorption Spectra of the Ionylideneacetones and Related Compounds[1,2]

BY WILLIAM G. YOUNG, LAWRENCE J. ANDREWS AND STANLEY J. CRISTOL

In a study of synthetic methods for increasing the polyene chain of β-ionone, β-ionylideneacetone has been prepared by two different procedures. Because the absorption maximum of this ketone was found to lie at 285 mμ instead of in the expected range of 300–320 mμ, it seemed possible that during some stage in the preparation of the sixteen carbon ketone the double bond in the β-ionone ring had rearranged to the position which it occupies in α-ionone. Consequently, the preparation of α-ionylideneacetone from α-ionone by the same methods used to prepare the β isomer was undertaken. A comparison of the absorption spectra of α- and β-ionylideneacetone and of the intermediates involved in their syntheses coupled with a critical investigation of the structure of these ketones by hydrogenation, ozonization and hypochlorite oxidation seems to indicate that no isomerization of the ring structure occurred during the synthesis of either sixteen-carbon ketone.

The Preparation of the Ionylideneacetones.—The β-ionone used in these syntheses had absorption maxima at 296 mμ, ε 8600 and 222 mμ, ε 7640; the α-ionone had maxima at 227 mμ, ε 12850 and 296 mu, ε 1950.[3] The reaction paths involved are as follows



Contrary to the report of Karrer and co-workers,[4] the crude product of the Reformatsky

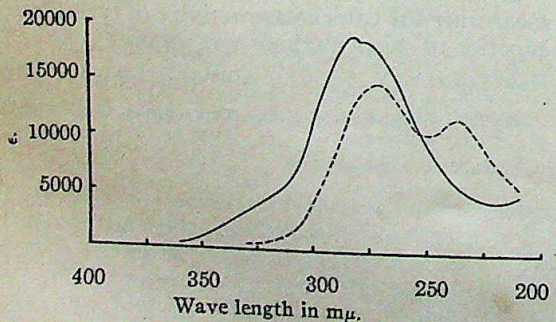


Fig. 1.—Spectra of the ethyl ionylideneacetates: ——, β; - - -, α.

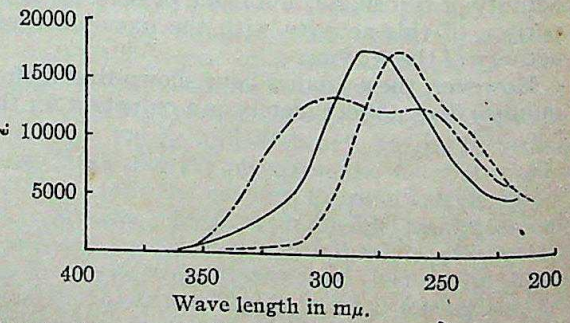


Fig. 2.—Spectra of the ionylideneacetic acids: ——·——, β (solid); ——, β (liquid); - - -, α.

(1) This paper was presented before the Division of Organic Chemistry of the American Chemical Society, Pittsburgh, Pa., September, 1943.

(2) This work was made possible by a research grant from Sharp and Dohme, Inc.

(3) The purities of these ionones were estimated at 80–85% based on a highly purified sample prepared by a method the details of which are in the process of publication.

(4) Karrer, Salomon, Morf and Walker, *Helv. Chim. Acta*, 15, 878 (1932).

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reaction on β-ionone did not dehydrate on distillation. It was always found necessary to heat the hydroxy esters (IIα,β) with potassium bisulfate to obtain the ethyl ionylideneacetates (IIIα,β). The esters were saponified to the corresponding acids (IVα,β). Figure 1 gives the spectra of these esters (IIIα,β). The β compound showed a maximum farther toward the visible than that of the α isomer.[5] Figure 2 gives the spectra of α-ionylideneacetic acid and of liquid and crystalline β-ionylideneacetic acid. The crystalline β acid shows two maxima at 294 mμ, ε 13700 and at 260 mμ, ε 12900 (Karrer[4] reports a flat maximum from 270–310 mμ, ε *ca.* 11200). The cyclocitrylideneacetic acids, prepared for comparison purposes by hypochlorite oxidation of the ionones, show a much larger difference in the positions of their maxima (α isomer, <212.5 mμ, β isomer, 277 mμ) than do the corresponding ionylideneacetic acids.

The ionylideneacetones (Vα,β) were prepared by the action of dimethylcadmium[6] on the acid chlorides of IVα,β.[7] They were also prepared by the reaction of the ionylideneacetonitriles (VIIIα,β) with methylmagnesium iodide.

The transformations of the ionones to the ionylideneacetonitriles were carried out by condensation with cyanoacetic acid[8] using a mixture of ammonium acetate and acetamide as catalysts and removing water formed, by co-distillation with the solvent as the reaction proceeded.[9] The structure of the β-nitrile was proved by conversion of the nitrile to β-ionylideneacetic acid.[4,8] The nitriles

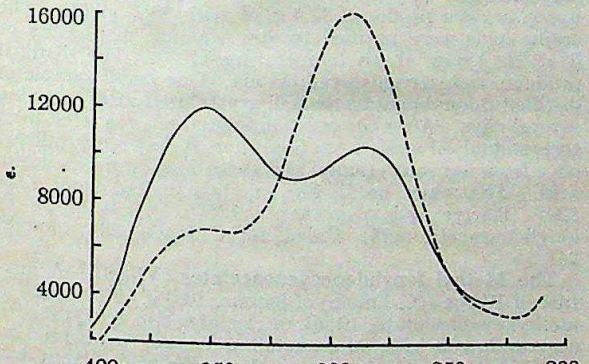

Fig. 3.—Spectra of the methyl ionylidenecyanoacetates: – – –, α; ———, β.

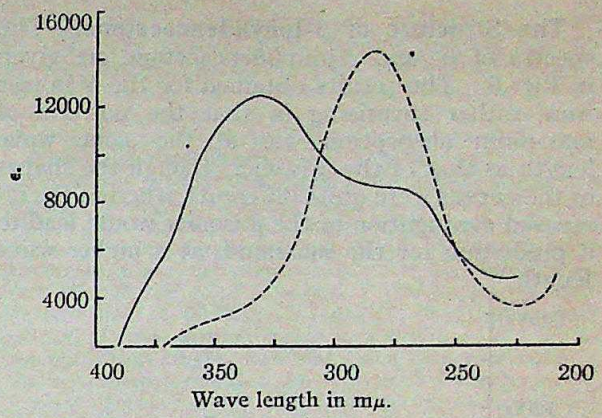

Fig. 4.—Spectra of the ionylidenecyanoacetic acids: – – –, α; ———, β.

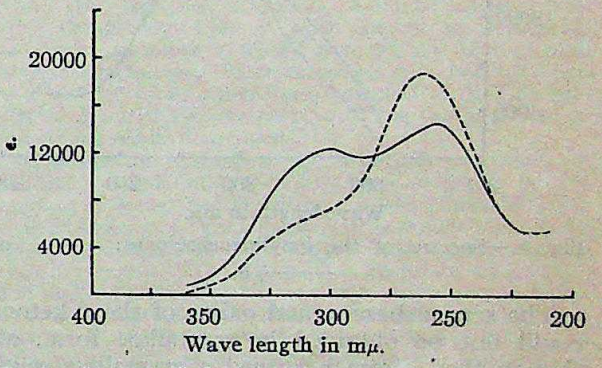

Fig. 5.—Spectra of the ionylideneacetonitriles: – – –, α; ———, β.

were also prepared by decarboxylation of the ionylidenecyanoacetic acids (VIIα,β) which were obtained by saponification of the methyl esters (VIα,β) produced by condensation of the ionones with methyl cyanoacetate. The spectra of VI, VII, VIII α and β are given in Figs. 3–5. These spectra do not suggest that any of the compounds prepared from β-ionone had isomerized to the α form.

The absorption maxima and extinction coefficients of the polyenes derived from the ionones are given in Table I.

TABLE I

THE ABSORPTION MAXIMA AND EXTINCTION COEFFICIENTS OF THE POLYENES DERIVED FROM THE IONONES

Compound[a]	$\lambda_{max.}$, mμ	$\epsilon_{max.}$[b]
Ethyl β-ionylideneacetate	283	18950
Ethyl α-ionylideneacetate	272, 236	14700, 11800
β-Ionylideneacetic acid (solid)[c]	283	17700
(liquid)	294, 260	13700, 12900
α-Ionylideneacetic acid	267	17650
β-Ionylideneacetone	285	11600
α-Ionylideneacetone	285	14500
Methyl β-ionylidenecyanoacetate	353, 286	12000, 10300
Methyl α-ionylidenecyanoacetate	292.5	16100
β-Ionylidenecyanoacetic acid	332, 275	12500, 8700
α-Ionylidenecyanoacetic acid	286	14300
β-Ionylideneacetonitrile	300, 256	12500, 14500
α-Ionylideneacetonitrile	262.5	18900
β-Cyclocitrylideneacetic acid	277	9240
α-Cyclocitrylideneacetic acid	<212.5	>10100

[a] These compounds were prepared from the commercial ionones. [b] The solvent was 95% ethanol. [c] M. p. 124°.

(5) After this paper was submitted for publication the article of Sobotka, Bloch and Glick, THIS JOURNAL, **65**, 1961 (1943), appeared. These authors found that the barium salt of β-ionylideneacetic acid cleaves to give α-ionone on dry distillation. Their suggestion that the ring double bond isomerization takes place during the Reformatsky reaction on β-ionone does not seem in accord with our findings. There is a much larger difference in the refractive indices of the α- and β-ionylideneacetates prepared in the present work than in those found by Sobotka and co-workers.

(6) Gilman and Nelson, *Rec. trav. chim.*, **55**, 518 (1936).

(7) Karrer and Morf, *Helv. Chim. Acta*, **17**, 3 (1934), have prepared β-ionylideneacetone by treatment of β-ionylideneacetyl chloride with methylzinc iodide.

(8) Wittig and Hartmann, *Ber.*, **72B**, 1387 (1939).

(9) Cope, THIS JOURNAL, **59**, 2327 (1937).

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The Structure of β-Ionylideneacetone.—The spectra of α- and β-ionylideneacetone are given in Fig. 6. The results obtained for the β isomer were rather surprising in that the position of maximum absorption was at the same wave length as that of the α isomer (though the shapes of the curves were quite different), whereas the increased conjugation of the β isomer would lead to a prediction for the maximum at a higher wave length.[10]

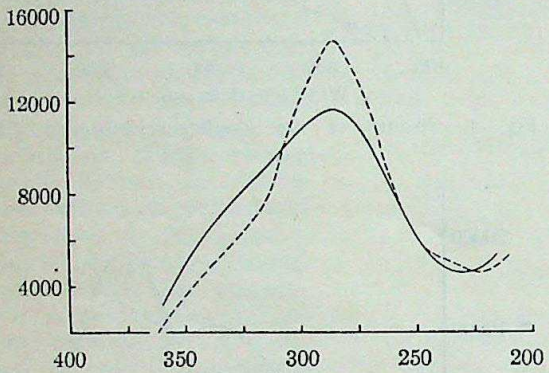

Fig. 6.—Spectra of the ionylideneacetones: – – –, α; ———, β.

The semicarbazone and oxime of the β ketone could not be obtained in crystalline form, although the α isomer formed a crystalline semicarbazone. The presence of the ketone group in the β isomer was shown by reaction with Girard's reagent T[11] and subsequent recovery of the ketone by acid hydrolysis.

On hydrogenation over a platinum oxide catalyst the β ketone, which should have three carbon—carbon double bonds, absorbed 3.06 moles of hydrogen. Under the same conditions, β-ionone absorbed 2.05 moles of hydrogen. Ozonolysis of the ketone according to the method of Karrer and co-workers[12] gave geronic acid (isolated as the semicarbazone) in the same yield as that obtained from β-ionone, indicating that the compound had the β ring structure. No isogeronic acid semicarbazone (arising from an α ring) was isolated, although specific attempts were made to isolate this substance by virtue of its limited solubility in hot ethyl acetate.[12,13] Under the same conditions, ozonolysis of α-ionone or of α-ionylideneacetone gave similar yields of isogeronic acid. Hypochlorite oxidation[14] of β-ionylideneacetone produced a liquid acid which solidified after molecular distillation. This proved to be β-ionylideneacetic acid. These data serve to establish the structure of the β-ionylideneacetone.

(10) This anomalous spectral behavior in a β-ionone derivative has been noted in one other case by Burawoy, *J. Chem. Soc.*, 20 (1941). He compared the spectra of a large number of semicarbazones of unsaturated aldehydes and ketones with those of the parent carbonyl compounds. In general the semicarbazones have absorption maxima farther toward the visible than those of the parent compounds. β-Ionone furnished the sole exception to this rule; it ($\lambda_{max.}$ at 293 mμ) gave a semicarbazone with $\lambda_{max.}$ at 277 mμ.

(11) Girard and Sandulesco, *Helv. Chim. Acta*, **19**, 1095 (1936).

(12) Karrer, Helfenstein, Wehrli and Wettstein, *ibid.*, **13**, 1096 (1930).

(13) Karrer, Morf and Walker, *ibid.*, **16**, 975 (1933).

(14) Bogert and Davidson, THIS JOURNAL, **54**, 334 (1932).

Experimental Part

Ethyl α- and β-Ionylideneacetates (IIIα,β).—These esters were prepared from 100 g. of ionones by a modification of the method of Karrer[4] for the preparation of the β ester. The petroleum ether–benzene solution of the product from the Reformatsky reaction was distilled from a water-bath to remove the lower boiling solvent. To the residue was added 20 g. of fused and powdered potassium bisulfate after which the removal of the solvent was continued on an oil-bath. Dehydration began when the bath temperature was 150°. After two hours at this temperature the residue was cooled and taken up in ether. The ether solution was washed first with sodium bicarbonate solution then with water and dried over magnesium sulfate. After removal of the ether the ester was distilled under reduced pressure (yield approximately 50%). The properties of the esters were as follows: for ethyl β-ionylideneacetate, b. p. 162.5–164.5° (6 mm.); $n^{20.5}D$ 1.5310. *Anal.* Calcd. for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99; sapon. eq., 262.4. Found: C, 77.42; H, 10.13; sapon. eq., 260.2. For ethyl α-ionylideneacetate, b. p. 162.5° (5–7 mm.), $n^{23.2}D$ 1.5140. *Anal.* Found: C, 77.65; H, 10.31; sapon. eq., 264.8.

In one preparation of ethyl β-ionylideneacetate the dehydration with potassium bisulfate was omitted. Distillation of the crude reaction product gave the hydrated ester (IIβ), b. p. 153.5–155.5° (2–3 mm.); $n^{22.5}D$ 1.4880; sapon. eq. calcd., 280.4; found, 281.5. This material reacted vigorously with acetyl chloride. Dehydration with potassium bisulfate in a manner similar to that previously described gave ethyl β-ionylideneacetate.

α- and β-Ionylideneacetic Acids (IVα,β).—These were prepared from the ionylideneacetates according to the saponification procedure previously described.[4] Forty-five g. of ester produced 37.4 g. of acid (95% yield). The crude acids were purified by low vacuum distillation at 3×10^{-3} mm. (bath temperature 110°). The distilled products were greenish-yellow oils. One small sample of distilled β-ionylideneacetic acid crystallized after standing several days. After the crystalline product was freed from the residual oil using a suction filter, it was recrystallized once from aqueous ethanol and twice from aqueous acetic acid. The white needle-like crystals melted from 122–124° (Karrer and co-workers,[4] 125°). *Neut eq.* of β-ionylideneacetic acid. Calcd. for $C_{15}H_{22}O_2$, 234; found, 241.

The Methyl Ionylidenecyanoacetates (VIα,β).—A mixture of 19.2 g. (0.10 mole) of ionone, 10.0 g. (0.10 mole) of methyl cyanoacetate, 40 ml. of glacial acetic acid, 1.0 g. of acetamide and 1.0 g. of ammonium acetate was heated on an oil-bath at such a rate that the acetic acid solvent and the water formed in the reaction were removed over a period of four hours. The residue was dissolved in ether and the resulting solution was washed with water and dilute aqueous sodium carbonate and dried over magnesium sulfate. The ether was removed and the products were distilled at reduced pressure. Methyl β-ionylidenecyanoacetate was a viscous orange oil boiling at 165–168° (2 mm.), $n^{20}D$ 1.5795 (Wittig and Hartmann[8] give b. p. 171–172° (0.38 mm.)). *Anal.* Calcd. for $C_{17}H_{23}NO_2$: C, 74.69; H, 8.48. Found: C, 74.63; H, 8.64. The α isomer was a viscous yellow oil which boiled at 154.5–157.5° (1.5 mm.), $n^{20}D$ 1.5628. *Anal.* Found: C, 74.57; H, 8.71. The yield of ester was about 50%.

The Ionylidenecyanoacetic Acids (VIIα,β).—Two grams (0.0073 mole) of each ester (VIα,β) was heated on a steam-bath with 18 ml. of 1 *N* sodium hydroxide solution with intermittent shaking until the second phase disappeared. The alkaline solution was extracted with ether and acidified with dilute phosphoric acid. The liberated acid was extracted with ether. After removal of the ether, the β

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acid crystallized slowly. It was recrystallized from ligroin and benzene giving a yellow solid, m. p. 160–163° with decomposition. *Anal.* Calcd. for $C_{16}H_{21}NO_2$: C, 74.10; H, 8.16. Found: C, 73.87; H, 8.24. Wittig and Hartmann[8] report this acid as an oil. The α acid did not crystallize even after long standing. The recovery of the acids from the esters was about 90%.

The Ionylideneacetonitriles (VIIIα,β).—The nitriles were prepared by the condensation of the ionones with cyanoacetic acid as described above for the reaction of the ionones with methyl cyanoacetate. β-Ionylideneacetonitrile was a yellow oil, b. p. 138–140° (3 mm.), $n^{20}D$ 1.5566. *Anal.* Calcd. for $C_{15}H_{21}N$: C, 83.67; H, 9.83; N, 6.50. Found: C, 82.88; H, 9.97; N, 6.30. The α isomer was a yellow oil, b. p. 147.5–150° (3 mm.), $n^{20}D$ 1.5486. *Anal.* Found: C, 83.14; H, 9.91. The yield of crude nitrile was 69%.

β-Ionylideneacetonitrile was prepared by the decarboxylation of β-ionylidenecyanoacetic acid,[8] and the product was comparable to that prepared directly from cyanoacetic acid and β-ionone.

β-Ionylideneacetic Acid from β-Ionylideneacetonitrile.—β-Ionylideneacetic acid was obtained by hydrolysis of the β nitrile with alcoholic potassium hydroxide according to the directions of Wittig and Hartmann.[8] After three recrystallizations from dilute acetic acid the white solid, m. p. 122–125°, gave no melting point depression with the acid prepared from ethyl β-ionylideneacetate.

The Ionylideneacetones (Vα,β).—The preparation of α-ionylideneacetone was carried out as follows: dimethylcadmium was prepared by the method of Gilman and Nelson[6] by treatment of a solution of 0.20 mole of methylmagnesium iodide in 100 ml. of ether with 18.4 g. (0.10 mole) of anhydrous cadmium chloride. To the well-stirred mixture was added over a one-hour period a solution of 32.3 g. (0.128 mole) of α-ionylideneacetyl chloride[7] in 130 ml. of ether. The reaction mixture was refluxed and stirred on a water-bath for three hours and poured onto a mixture of cracked ice and aqueous ammonium chloride. The ether layer was washed with two 50-ml. portions of water and dried over magnesium sulfate. After removal of the ether the product was distilled under reduced pressure. The main portion (7.0 g.) distilled from 135.5–138° (2.5 mm.), $n^{26.3}D$ 1.5298. *Anal.* Calcd. for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 81.05; H, 10.35.

Similarly 1.0 g. of β-ionylideneacetone was prepared from 6.4 g. of β-ionylideneacetic acid. This ketone distilled from 131–132° (2.5 mm.), $n^{18.0}D$ 1.5412. *Anal.* Found: C, 81.86; H, 10.33. Karrer and Morf[7] reported that β-ionylideneacetone prepared by the reaction of β-ionylideneacetyl chloride and methylzinc iodide distills from 105–106° (0.1 mm.), $n^{17.5}D$ 1.5430.

The ionylideneacetones were also prepared as follows: a solution of 35.0 g. (0.16 mole) of β-ionylideneacetonitrile in 40 ml. of ether was added dropwise with stirring to 0.5 mole of methylmagnesium iodide in 200 ml. of ether. Then the solution was heated at gentle reflux for three days and decomposed in the usual manner with aqueous ammonium chloride. The ether layer was washed repeatedly with water, filtered and shaken for several days with 360 ml. of 2 *N* sulfuric acid. It was separated and washed with water and sodium bicarbonate solution and dried over sodium sulfate. After removal of the ether, the product was distilled under reduced pressure. Redistillation gave 9.0 g. of β-ionylideneacetone, b. p. 130.5–133.5° (2 mm.), $n^{20}D$ 1.5452. *Anal.* Calcd. for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.07; H, 10.58.

Similar experiments with methyllithium gave products with the same properties and with no improvement in yield.

α-Ionylideneacetonitrile and methylmagnesium iodide gave the same yield of α-ionylideneacetone, b. p. 134.5–135° (3 mm.), $n^{20}D$ 1.5433. *Anal.* Found: C, 82.09; H, 10.40.

Attempts were made to prepare a solid semicarbazone or oxime of β-ionylideneacetone, but the products obtained were invariably low melting oils. α-Ionylideneacetone gave a crystalline semicarbazone, m. p. 162.5–164° (after recrystallization from aqueous alcohol). *Anal.* Calcd. for $C_{17}H_{27}N_3O$: C, 70.55; H, 9.40. Found: C, 70.27; H, 9.77. The presence of the carbonyl group in β-ionylideneacetone was demonstrated by reaction with Girard's reagent T according to the procedure of Girard and Sandulesco.[11] The ketone was recovered unchanged from the reagent after hydrolysis with aqueous oxalic acid.[11]

Ozonolysis Experiments.—The ozonolyses were carried out in dilute carbon tetrachloride and glacial acetic acid solution according to Karrer and co-workers.[12,13] The geronic (or isogeronic) acid was recovered as the semicarbazone. One g. of β-ionone gave about 150 mg. of crude geronic acid semicarbazone which, after recrystallization from ethanol, melted at 161.5–163.5° (softened at 151.5°). Karrer[12] gives m. p. 162°. α-Ionone (1.18 g.) gave about 250 mg. of crude isogeronic acid semicarbazone which was insoluble in hot ethyl acetate and which upon recrystallization from alcohol melted at 191–195° (with decomposition). Strain[15] reports m. p. 193–195° for isogeronic acid semicarbazone. One gram of β-ionylideneacetone gave about 200 mg. of crude geronic acid semicarbazone, soluble in ethyl acetate. After recrystallization from ethanol it melted at 161.5–163° (softened at 150°). A mixed melting point with the product from β-ionone showed no depression. α-Ionylideneacetone (1.06 g.) gave 93 mg. of isogeronic acid semicarbazone. After extraction with hot ethyl acetate and recrystallization from ethanol, it melted at 191–194°. A mixed melting point with the product from α-ionone showed no depression.

Hypochlorite Oxidation of β-Ionylideneacetone.—A solution of sodium hypochlorite was prepared by the method of Bogert and Davidson.[14] To a sample of 1.5 g. (0.0065 mole) of β-ionylideneacetone was added slowly 7.8 ml. (0.0195 mole) of the freshly prepared sodium hypochlorite reagent. The ketone was cooled in an ice-bath and shaken during the addition which took twenty minutes. Ten ml. of methanol was added. The odor of chloroform was noted. After the reaction mixture had stood for one hour in the ice-bath and one hour at room temperature, the solvents were removed at reduced pressure. Dilute phosphoric acid was added to acidify the residue, and the oil was extracted with 40 ml. of ether. The acid was extracted from the ether solution with two 20-ml. portions of 5% aqueous sodium hydroxide solution. The residue in the ether solution was recovered. It had an absorption spectrum and refractive index similar to those of the original ketone. The basic extract was acidified with dilute phosphoric acid, and the liberated acid was extracted with two 10-ml. portions of ether. Removal of the ether under reduced pressure left 0.9 g. of crude tan-colored acid. A portion of this acid was submitted to molecular distillation. The fraction distilling at an air-bath temperature of 140° (2.5×10^{-3} mm.) was an extremely viscous oil which crystallized slowly. Two recrystallizations from aqueous acetic acid gave a white solid, m. p. 122–124°. A mixed melting point with a sample of β-ionylideneacetic acid prepared from β-ionylideneacetonitrile showed no depression.

Quantitative Hydrogenation of β-Ionone and β-Ionylideneacetone.—Quantitative hydrogenations of approximately 0.25-g. samples of β-ionone and of β-ionylideneacetone were carried out using 60 ml. of ethanol and 0.1 g. of platinum oxide.[16] The hydrogenations went nearly to completion within an hour but were usually allowed to run for several hours to insure complete reduction of the olefin bonds.

α- and β-Cyclocitrylideneacetic Acids.—These were prepared by hypochlorite oxidation of the ionones by a procedure similar to that described for the oxidation of β-ionylideneacetone. The crude acid from 2.0 g. of β-ionone was a yellow solid weighing 1.53 g. It was obtained as white needle-like crystals after one recrystallization from aqueous ethanol and two recrystallizations from aqueous acetic acid. The properties of β-cyclocitrylideneacetic acid were as follows: m. p. 106–108°; *Anal.* Calcd. for $C_{12}H_{18}O_2$: C, 74.20; H, 9.34; neut. eq., 194. Found: C, 73.83; H, 9.39; neut. eq., 192. On quantitative hydrogenation

(15) Strain, *J. Biol. Chem.*, **102**, 146 (1933).

(16) Adams, Voorhees and Shriner, *Org. Syntheses*, **VIII**, 92 (1928).

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over Adams catalyst the acid absorbed 1.96 moles of hydrogen (theoretical value 2.00 moles).

From 4.0 g. of α-ionone was obtained 0.34 g. of a yellow oily acid which would not solidify. No investigation of its physical properties other than its absorption spectrum was made. Considerable unreacted α-ionone (2.57 g.) was recovered in this experiment.

Absorption Spectrum Measurements.—Determinations of the ultraviolet absorption spectra of the polyenes were made on the Beckman Spectrophotometer.

The authors are indebted to Dr. R. O. Clinton and to Mr. J. W. Ralls for the combustion analyses reported in this paper.

Summary

The α- and β-ionylideneacetones have been prepared from both the ethyl ionylideneacetates and the ionylideneacetonitriles, each of which may be prepared conveniently from the ionones. β-Ionylideneacetone shows an absorption maximum farther toward the ultraviolet than might be expected. A study of the spectra of all the intermediates in the preparation of the ionylideneacetones has been made. The structures of the ionylideneacetones have been established by the application of quantitative hydrogenation, ozonization and hypochlorite oxidation procedures.

Los Angeles, California Received September 7, 1943

[Contribution from the Hayden Laboratories of Northeastern University]

Generalized Acid-Base Catalysis. I. Condensation of *o*-Benzoylbenzoic Acid in Sulfuric Acid

By W. F. Luder and Saverio Zuffanti

Many of the catalytic effects observed in organic reactions can be explained readily as instances of simple acid-base catalysis if one adopts the conception of acids and bases proposed by G. N. Lewis.[1,2,3] One example is the condensation of *o*-benzoylbenzoic acid to anthraquinone, which has been studied by several authors[4,5,6] without arriving at a completely satisfactory explanation of the effects observed.

Deane and Huffman[6] have extended rate measurements of the *o*-benzoylbenzoic acid condensation into oleum of concentrations up to 29% SO_3 at 75 and 85°. They found that the velocity constant increased steadily up to their maximum sulfur trioxide percentage. In some work under way in this Laboratory on the acidity curve of oleum (to be reported in a later paper of this series), our preliminary measurements indicate the same steady increase at 40° up to 65% SO_3, the maximum concentration so far investigated.

This increase in reaction rate with increased concentration of sulfur trioxide in sulfuric acid is readily understood when considered from the Lewis viewpoint. It is merely due to increased over-all acidity. Sulfur trioxide is a stronger acid than sulfuric acid. Lewis and Bigeleisen[7] have shown that the acidity of sulfuric acid solutions increases with concentration of sulfur trioxide. Close correlation is evident in comparing the Lewis and Bigeleisen plot of Hammett's acidity function[8] with the plot of variation in reaction rate with concentration of sulfur trioxide given by Deane and Huffman.[6] This would indicate that the condensation of *o*-benzoylbenzoic acid is an acid-catalyzed reaction, and that the reaction rate does not depend upon a particular species, but rather upon the acid strength. Probably SO_3, H_2SO_4, and H_3O^{+1} are the three principal species involved, but the question of the exact proportion is unimportant since the over-all acidity can be measured experimentally. Of course it is obvious that in 65% oleum the ratio of SO_3 to H_3O^{+1} is very great.

According to this viewpoint the inhibiting effect of the product anthraquinone and of other substances can readily be explained. Anthraquinone is weakly basic. The oxygen atoms each can donate a share in a pair of electrons to a sufficiently strong acid. The presence of the anthraquinone in such a highly acidic medium simply decreases its acidity and therefore its effectiveness as a catalyst. A similar explanation applies to the other inhibitors tested by Deane and Huffman. This is especially interesting since several of these substances such as $AlCl_3$, HCl, and $CuCl_2$ are typical generalized acid catalysts. Even these acids, strong enough to catalyze Friedel–Crafts and similar reactions, are forced to behave as weak bases by the stronger mixture of sulfur trioxide and sulfuric acid.[3]

In view of this very great acidity of fuming sulfuric acid,[7] the statement of Deane and Huffman[6] that, "The effect of definite added amounts of concentrated hydrofluoric acid will more fully indicate the status of this reaction as a case of acid-base catalysis," is not likely to be upheld. They themselves had already tried a stronger acid than HF[3], namely, $AlCl_3$, and found that it did

(1) Lewis, *J. Franklin Inst.*, **226**, 293 (1938).

(2) Luder, *Chem. Rev.*, **27**, 547 (1940).

(3) Luder and Zuffanti, "Catalysis from the Viewpoint of the Electronic Theory of Acids and Bases" presented as a part of the Symposium on Molecular Addition Compounds before the Division of Physical and Inorganic Chemistry of the American Chemical Society, 106th meeting, Pittsburgh, Penna., September 6, 1943, and to be published shortly in *Chemical Reviews*.

(4) Gleason and Dougherty, This Journal, **51**, 310 (1929).

(5) Newman, *ibid.*, **64**, 2324 (1942).

(6) Deane and Huffman, *Ind. Eng. Chem.*, **35**, 684 (1943).

(7) Lewis and Bigeleisen, This Journal, **65**, 1144 (1943).

(8) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940.

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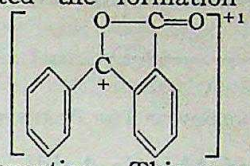
not increase the reaction rate in fuming sulfuric acid, but actually decreased it.

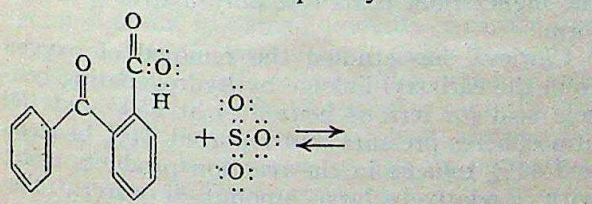
Newman[5] has postulated the formation of the cyclic carbonium ion  as the first step in the condensation. This suggestion is based on the formation of a quantity of pseudo-ester when methyl alcohol was present. The cyclic ion is considered as formed by the reaction of sulfuric acid on the *o*-benzoylbenzoic acid with H_3O^{+1} and $2HSO_4^{-1}$ as the other products. This explanation conforms to the Brönsted theory of acids and bases, but obviously the Brönsted theory cannot explain the large increase in velocity constant as the amount of sulfur trioxide is increased. On the other hand, the observed behavior is exactly what is expected on the basis of the electronic theory of acids and bases. Sulfur trioxide is a much stronger acid[7] (*i. e.*, has a greater tendency to appropriate lone electron-pairs) than H_2SO_4 or H_3O^{+1}.

However, this does not mean that the hypothesis of a cyclic ion is incorrect. The cyclic ion could be formed just as well by sulfur trioxide as by sulfuric acid

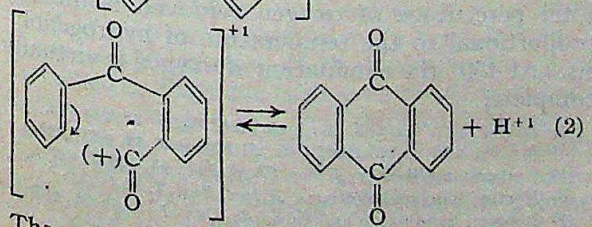
o-Benzoylbenzoic acid + $SO_3 \rightleftharpoons$ (cyclic ion)$^{+1}$ + HSO_4^{-1}

So whether the cyclic ion or some other explanation is adopted, the ability of the Lewis theory to explain the observed catalytic effects is not affected.

An alternative mechanism which we prefer for reasons discussed subsequently is as follows



(1)



(2)

The use of H_2SO_4, H_3O^{+1}, or any other acid species present, in place of the sulfur trioxide in the above equations would serve equally as well since according to the Lewis theory acids coördinate with lone electron-pairs. In equation (1) the sulfur trioxide behaves as a typical acid[2] by coördinating with the oxygen electron-pair to split off the OH^{-1} group thus leaving the carbon atom electron-deficient. This makes the carbon atom acidic since it now has a great tendency to appropriate a lone electron-pair to complete its octet again. The two possibilities are: the formation of the cyclic ion and the formation of anthraquinone according to equation (2) above. Both reactions undoubtedly take place since Newman seems to have demonstrated conclusively the existence of a large proportion of the cyclic ion at low temperatures. But since the reaction under discussion is the formation of anthraquinone, it seems unnecessary to involve the cyclic ion. We prefer to regard its formation as a side reaction to, rather than the first step in, the production of anthraquinone.

The reasons for this preference are: (1) it fits the experimental facts equally as well as Newman's explanation; (2) it is simpler and more direct; (3) it is in accord with the newer explanation of the mechanism of acylations[3,9]; (4) when the structural formulas of all three species are considered there seems to be no way of getting a cyclic ion from *o*-benzoylbenzoic acid except through the open-chain ion as an intermediate step.

However, whichever choice of mechanism is made, the interpretation of the experimental data by means of the electronic theory of acids and bases is still applicable. Both mechanisms involve a cyclic ion and both can be catalyzed by SO_3 as well as by H_2SO_4 or H_3O^{+1}. Both agree that the immediate percursor of anthraquinone is the open-chain ion.

Gleason and Dougherty[4] showed that the condensation is actually first order and not merely an apparent first order reaction because of an excess of sulfuric acid. No explanation of this has been offered nor of the rapid and large evolution of heat observed when oleum is added to the *o*-benzoylbenzoic acid. We have observed that this rapid evolution of heat on mixing is many times greater at high sulfur trioxide concentrations, corresponding roughly to the much greater velocity constant. A logical explanation of these two facts in keeping with the other aspects of the Lewis interpretation is that the carbonium ion is formed rapidly according to equation (1) upon mixing. The rate-determining step would then be equation (2), which is obviously first order. The difference in rate with increasing amounts of SO_3 is due to the shifting of the equilibrium in equation (1) so that the initial concentration of carbonium ion is greater as the acidity of the solution is increased.

Summary

An explanation of some effects in the catalyzed condensation of *o*-benzoylbenzoic acid to anthra-

(9) Price, *Chem. Rev.*, **29**, 37 (1941).

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quinone is given according to the electronic theory of acids and bases.

An alternative mechanism is proposed, but it is shown that the application of the Lewis theory is equally valid for both mechanisms considered.

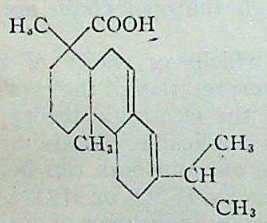
BOSTON, MASSACHUSETTS RECEIVED SEPTEMBER 29, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF FUEL TECHNOLOGY OF THE PENNSYLVANIA STATE COLLEGE]

The Hydrogenolysis of Abietic Acid[1]

BY H. B. CHARMBURY AND C. C. WRIGHT

Although many investigations on the hydrogenolysis of coal are reported in the literature, interpretation of the results has been hindered because of the lack of information concerning the mechanism of the reaction. One method of attack upon this problem has been through hydrogenolysis of pure organic compounds, several of which, such as benzene, indene, naphthalene, naphthols, phenol, cresols and carboxylic acids[2] have already been studied. The complexity of the compounds has been gradually increased with the ultimate goal of hydrogenating polynuclear structures as closely related to the so-called "coal molecule" as possible. The present work is concerned with the hydrogenolysis of abietic acid, I,



I

the structure of which is such that information may be secured concerning oxygen removal from the carboxyl group, alkyl severance of the two different alkyl groups, alicyclic decomposition due to the breakdown of the hydrophenanthrene structure and hydrogen consumption due to saturation of the double bonds and to hydrogenation cracking reactions.

Hydrogenolyses were conducted for two hours at temperatures ranging from 325 to 450°, with initial hydrogen pressures of 1900 to 1975 P. s. i. (133.6–138.9 kg./sq. cm.). Because the results of these experiments indicated that 400° is the critical temperature for oxygen removal, alkyl severance and hydrogen consumption, experiments were also conducted at this temperature, using the same initial hydrogen pressure, for 1, 2 and 3 one-hour periods. The reaction gases were removed and the retort charged with fresh hydrogen at the end of each one-hour period.

(1) From the thesis of H. B. Charmbury presented to the faculty of The Pennsylvania State College in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) The hydrogenolysis of these compounds has been studied by the British Fuel Research Board and their results will be found in the Board reports from 1931 to 1938 inclusive.

Oxygen Removal.—Using temperatures and pressures in the range of 300–500° and 1000–3000 P. s. i. several investigators[3,4,5,6] have shown that much of the oxygen present in coal is removed rapidly and in the early stages of hydrogenation and that the remaining oxygen is removed at a slow but rather constant rate. Boomer[7] has suggested a theory that coals contain at least two types of oxygen: oxygen as carboxyl which is removed rapidly, and oxygen as hydroxyl which is more resistant. Fisher[8] also supports this theory and shows that using a Pittsburgh coal 60% of the oxygen is eliminated much more rapidly than the remaining 40% and that most of the oxygen which is removed in the early stages appears in the products as water. Storch[9] has studied the oxygen removal of the anthraxylon fraction of various coals and found that the oxygen is removed as carbon dioxide and water in the early stages and that the oxygen removal increases with decreasing rank of the coal. An extended study by Storch[10] revealed that upon hydrogenation the low rank coals high in oxygen lose 10–20% of their oxygen as carbon dioxide whereas the higher rank coals lose only 3 to 6% in this form.

Cawley[11] has studied the removal of oxygen from the carboxyl linkage by hydrogenating benzoic acid (or ferrous benzoate) at 450° and 100 atmospheres pressure and reported 24% benzene and 41% toluene in the reaction products along with a relatively large amount of water. The presence of toluene and water indicates a removal of oxygen by a reduction of the carboxyl group.

The data of Fig. 1 show, however, that the removal of oxygen from abietic acid takes place for the most part as a straight decarboxylation with the formation of carbon dioxide, and that the total percentage of oxygen removed is directly proportional to the temperature of hydrogenolysis. At 450° the elimination of oxygen is virtually complete.

(3) Bakes, *Dept. Sci. Ind. Research Tech. Paper*, **37**, 214 (1933).
(4) Boomer and Saddington, *Can. J. Research*, **12**, 825 (1935).
(5) Graham and Skinner, *J. Soc. Chem. Ind.*, **48**, 129T (1929).
(6) Horton, King and Williams, *J. Inst. Fuel*, **7**, 85 (1933).
(7) Boomer, Saddington and Edwards, *Can. J. Research*, **13B**, 11 (1935).
(8) Fisher and Eisner, *Ind. Eng. Chem.*, **29**, 1371 (1937).
(9) Storch, *et al.*, *Fuel*, **19**, 13 (1940).
(10) Storch, *et al.*, *ibid.*, **20**, 5 (1941).
(11) Cawley, *ibid.*, **12**, 167 (1933).

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The data of Table I for intermittent operation substantiate the results obtained for two hour hydrogenolyses with respect to the formation of carbon dioxide and indicate relatively rapid oxygen removal as carbon dioxide. This supports Boomer's[7] interpretation of coal hydrogenation data.

TABLE I

REMOVAL OF OXYGEN AS CARBON DIOXIDE, CARBON MONOXIDE AND WATER FOR INTERMITTENT HYDROGENOLYSES

	% Oxygen removed as				
During	CO_2	CO	$CO_2 + CO$	H_2O	$CO_2 + CO + H_2O$
1st hr.	61.1	12.0	73.1	5.8	78.9
2nd hr.	0.0	3.0	3.0	4.9	7.9
3rd hr.	.0	0.0[a]	0.0[a]	0.3[a]	0.3[a]

[a] These values are corrected for the amount of CO and H_2O formed as a result of the decomposition of 0.22 g. of CO_2 present as impurities in the original hydrogen gas, assuming the decomposition takes place as $CO_2 + H_2 \rightarrow CO + H_2O$.

The carbon monoxide obtained in both the continuous and intermittent hydrogenolyses may result from the partial reduction of the carboxyl group to form the aldehyde followed by its decomposition, or from the reduction of carbon dioxide. Since the presence of aldehydes and alcohols was not detected in the reaction products and since the amount of carbon dioxide decreases above 400° with an increase in the amount of carbon monoxide, it appears that the carbon monoxide results from the reduction of the carbon dioxide. This is further substantiated by the fact that during the third hour of intermittent operation not all of the carbon dioxide present as an impurity in the original hydrogen gas could be accounted for, but small amounts of carbon monoxide and water were found. This can only be explained by a reduction of the carbon dioxide at this temperature and pressure to form the other gases. Such a reduction has been suggested by Storch[12] to take place in the gaseous products resulting from coal hydrogenation.

The water formation may result from the reduction of the oxides of carbon, from the reduction of the carboxyl group, or as LaLande[13] suggests from the pyrolysis of abietic acid by the formation of the anhydride.

It is believed that the same type of reduction of the carboxyl linkage does not occur with abietic acid as Cawley[11] observed with benzoic acid because of the presence of the stable methyl group attached to the same carbon as the carboxyl and/or because of the fact that the carboxyl group is attached to a tertiary alicylic carbon atom and not an aromatic structure. The present work as well as that of Cawley[11] substantiates Boomer's theory[7] in regard to carboxyl oxygen removal and both may be used to explain Storch's[10] results, since it

(12) Storch, *et al.*, U. S. Bur. Mines, Reports Investigations, 3498.

(13) LaLande, *Ind. Eng. Chem.*, 26, 673 (1934).

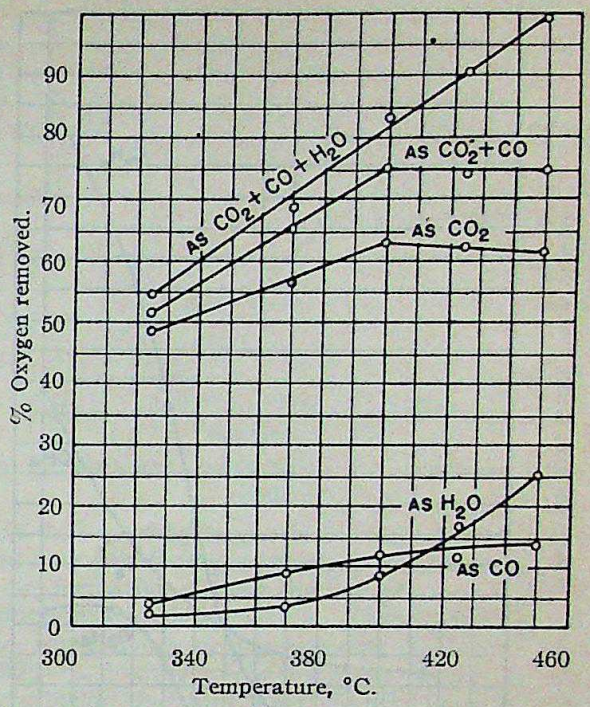

Fig. 1.—Oxygen removal for two-hour hydrogenolyses.

is generally known[14] that the aromaticity of coals increases with increasing rank.

Alkyl Severance.—The British Fuel Research Board[15] has carried out the destructive hydrogenation of such compounds as 1- and 2-methyl- and 2,6-dimethylnaphthalene and found that the methyl groups are stable up to rather high temperatures. For example, at 450° these compounds are only demethylated to the extent of about 3%, but at 500° almost complete demethylation takes place. The 2,6-dimethyl compound is demethylated in stages yielding methylnaphthalene as an intermediate product.

At the present time, the authors do not know of any literature concerning the higher hydrocarbon gases which are obtained as a result of coal hydrogenation because all the data presented in the technical literature are in terms of Orsat analyses and thus the saturated gases are reported only as methane and ethane.

Some idea concerning the amount of alkyl severance which occurs during the hydrogenolysis of abietic acid may be obtained by examining Fig. 2. This figure shows the grams of methane, ethane and propane formed from 100 g. of the acid as a function of the hydrogenolysis temperature. From the amount of propane formed it may be seen that depropylation does not occur to any appreciable extent up to a temperature of about 380°, but that above this temperature it increases rather rapidly. The theoretical yield of propane from 100 g. of abietic acid by the removal of the isopropyl group alone is 14.6 g. and if the ethane

(14) Bone and Himus, "Coal, Its Constitution and Uses," Longmans, Green and Co., New York, N. Y., 1936.

(15) British Fuel Research Board Report P-75 (1934).

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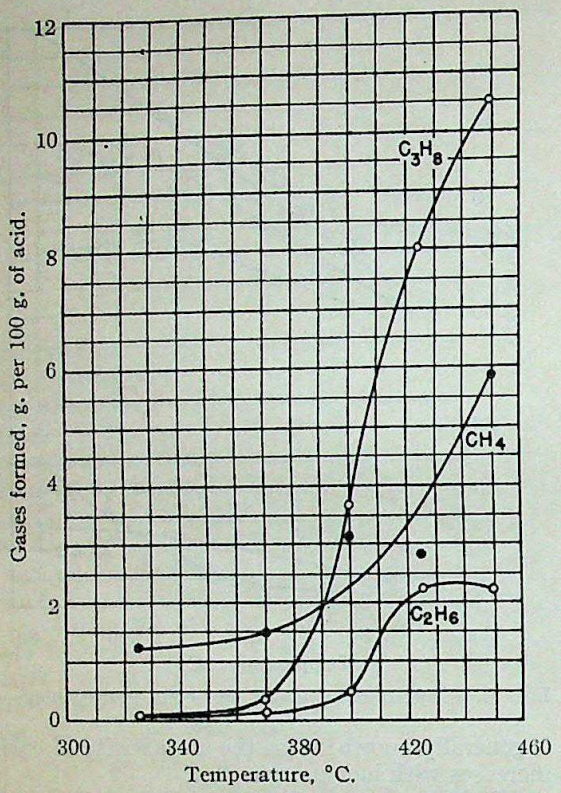

Fig. 2.—Alkyl severance for two-hour hydrogenolyses.

present is considered as resulting from the cracking of propane the total amount formed at 450° is 13.6 g.

The amount of propane formed on one hour of hydrogenolysis was only 0.98 g. as compared with 3.12 g. for two hours of continuous operation. During the second and third hours of operation only 0.53 g. and 0.37 g. were formed. Thus, after three hours of intermittent operation the total amount of propane was only 1.88 g. These data indicate that the amount of depropylation is a function of hydrogen concentration or partial pressure. Although the exact partial pressure of hydrogen cannot be calculated because of the unknown vapor pressure of the various liquid products at reaction conditions, it is, nevertheless, possible to obtain a general idea of the relative values by considering the concentration of hydrogen in the non-condensable gases at the completion of the reaction. These values are respectively 90.39% after two hours continuous operation and 92.59, 97.25 and 97.53% after the first, second and third hour of intermittent operation.

Further evidence of depropylation may be found in the liquid products resulting from the second and third hours of hydrogenolyses. Although these products were not definitely identified, the ultimate analyses definitely indicate a removal of the isopropyl group. Table IV lists the ultimate analyses of these compounds and the possibilities are 1,12-dimethyl- and 1-methyldodecahydrophenanthrene.

Because no ethane was detected in the gaseous products from the intermittent operations as compared to 0.47 g. from the two hour continuous hydrogenolysis, the experiments establish definitely that the ethane results from the cracking of propane during the second hour of continuous treatment. This again can be attributed to the lower partial pressure of hydrogen.

The mechanism of methane formation is more complex for it may result from demethylation, from the reduction of carbon monoxide, from the cracking of higher hydrocarbon gases and from alicyclic decomposition. The relatively large amount of methane at the low temperatures appears to be due to demethylation, probably of the methyl group in the number 12 position since all of the dehydrogenation experiments[16,17,18] show this group to be far less stable than the group in the number 1 position. This may occur as a straight dealkylation or as the severance of the methyl group with an adjacent hydrogen. At the higher temperatures methane is believed to result from all four possible methods.

The hydrogenolysis of the abietic acid for one, two and three hours resulted in the formation of approximately 2 g. of methane during the first hour, 1 g. during the second and 1 g. during the third. This compares with 3.69 g. for two hours of continuous operation and indicates that the methane formation is a function of time as well as hydrogen concentration. It is believed that at 400° for different lengths of time practically all the methane formation results from demethylation since there is very little evidence of alicyclic decomposition and only a small amount of carbon monoxide available for reduction.

Alicyclic Decomposition.—The present data concerning alicyclic decomposition are rather limited due to the fact that none of the hydronaphthalenes or the two-ring intermediate compounds have been definitely identified even though data are available on the three-ring structures, as well as on the final single-ring products of this type of decomposition. At 370° there is evidence of hydrogen addition either as a saturation of one of the two double bonds or as a 1,4 addition to the conjugated system. At the higher temperatures, however, dehydrogenation takes place as indicated by the presence of two and three double bonds in the liquid products. Since this type of dehydrogenation occurs, there is less tendency for alicyclic decomposition.

From the two hour hydrogenolyses the amounts of the two-ring intermediate products have been estimated in terms of the total products from the distillation curves to be about 3, 17, 20 and 25% at temperatures of 370, 400, 425 and 450°, respectively, and 10, 2 and 1% during the first, second

(16) Diels and Karstens, *Ber.*, **60**, 2323 (1927).

(17) Ruzicka and Waldmann, *Helv. Chim. Acta*, **16**, 842 (1933).

(18) Fieser, "Chemistry of Natural Products Related to Phenanthrene," A. C. S. Monograph No. 70, Reinhold Publishing Corp., New York, N. Y., 1936.

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and third hour of intermittent hydrogenolysis. Thus, even after three hours, the amount was appreciably less than that obtained for two hours of continuous operation. These data indicate that at 400° the extent of alicyclic decomposition is a function of the hydrogen concentration and emphasizes the fact that very misleading conclusions may be obtained from coal hydrogenolysis experiments when the hydrogen concentration is not considered in interpreting the results.

The specific dispersion, refractive index and boiling point data show that these intermediate compounds are related to the alkyl hydronaphthalenes although no particular compound has been definitely identified. This would indicate splitting of one of the three rings with the formation of a hydronaphthalene ring structure and an alkyl side chain. Biggs[19] has shown that the oils resulting from the hydrogenation of Pittsburgh coal are chiefly polyhydroaromatic hydrocarbons and LeClaire[20] has found the same results for other coals. LeClaire's data indicate that the distillation fractions of such oils have refractive indices ranging from 1.4823 to 1.5710, densities ranging from 0.888 to 1.038, and specific dispersions ranging from 97.9 to 174.4.

The final products of alicyclic decomposition did not amount to more than approximately 10% of the total products even at the highest temperature of hydrogenolysis. However, the physical properties of some of the fractions of the products indicated that the following compounds were present: *trans*-1,2-dimethylcyclohexane, methylcyclohexane, 1,3-dimethylcyclopentane, ethylcyclohexane and 3,5-dimethylcyclohexene-1. Since there were no five-numbered rings in the original material, the presence of 1,3-dimethylcyclopentane indicates that isomerization must have taken place. Such an isomerization was described by independent workers[21,22] who hydrogenated benzene and cyclohexane under similar conditions and identified methylcyclopentane in the products. The presence of methyl and ethyl cyclohexane indicate agreement with the theory of Hall[23] concerning the alicyclic decomposition of hydronaphthalene.

Hydrogen Consumption.—Figure 3 shows the grams of hydrogen consumed as a function of hydrogenolysis temperature. The rather low hydrogen consumption at the lower temperatures is due principally to the saturation of one of the double bonds, to demethylation and to depropylation. The higher consumption of hydrogen at the higher temperatures is due to the alkyl and alicyclic decomposition and also to the reduction of the oxides of carbon.

The intermittent hydrogenolyses show that

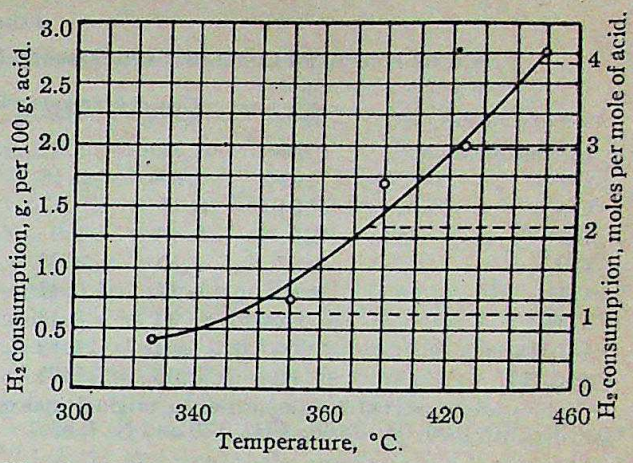

Fig. 3.—Hydrogen consumption for two-hour hydrogenolyses.

only 0.48 g. of hydrogen is consumed during the first hour and 0.44 g. of this can be accounted for in the formation of methane and propane and the reduction of carbon dioxide. During the second and third hours of intermittent operation virtually no hydrogen consumption occurred. In fact, during the third hour, slightly more hydrogen was recovered than was available at the beginning of the third hour of treatment. These data compare with a hydrogen consumption of 1.67 g. during the two-hour continuous hydrogenolysis at the same temperature. Despite the relatively low consumption of hydrogen the carbon and hydrogen analyses of the products isolated indicate that one of the two possible ethylenic linkages had been saturated and thus show the probable dehydrogenation of some of the unidentified products.

The foregoing data may be interpreted as evidence that hydrogen consumption under the conditions investigated is primarily due to cracking reactions and that little, if any, hydrogen is consumed in the saturation of ethylenic linkages. Storch,[9,10,24,25] on the other hand, has shown that after the first hour the hydrogen consumption upon hydrogenolysis of a Pittsburgh seam coal at 1000 p. s. i. and 400° is a straight line function of the reaction time up to fifteen hours of treatment, and that the straight line relationship is likewise true, irrespective of the rank or oxygen content of the coals studied. From 20 to 25% of the hydrogen consumed in this manner may have been utilized in the removal of non-carboxyl oxygen according to data for oxygen removal, but the marked difference between the results for coal and abietic acid requires further explanation. In part, the difference may be due to the more aromatic structure and greater ease of saturation of ethylenic linkages in coal, because of the presence of the hydrogen carrier, tetralin, and the 1% stannous sulfide, or as has been shown in previous sections

(19) Biggs, THIS JOURNAL, **58**, 1020 (1936); Biggs and Weiler, *ibid.*, **59**, 369 (1937).
(20) LeClaire, *ibid.*, **63**, 343 (1941).
(21) Ando, *J. Soc. Chem. Ind.* (Japan), **42**, 391 (1939); *C. A.*, **34**, 2339 (1940).
(22) British Fuel Research Board Report, pp. 172–181 (1938).
(23) Hall, *Fuel*, **12**, 76 (1933).
(24) Storch, Fisher, Eisner and Clarke, *Ind. Eng. Chem.*, **32**, 346 (1940).
(25) Storch, Hawk and O'Neill, THIS JOURNAL, **64**, 230–236 (1942).

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TABLE II

WT. OF HYDROGEN CONSUMED AND GASEOUS PRODUCTS FORMED G./100 G. OF ABIETIC ACID

	Time of hydrogenolysis, 2 hours					Temperature of hydrogenolysis, 400°		
Products[a] formed	325°	370°	400°	425°	450°	During 1st hr.	During 2nd hr.	During 3rd hr.
H_2 consumed[b]	0.40	0.73	1.67	1.99	2.76	0.48	0.00	−0.02
CO	.65	1.66	2.18	2.09	2.47	2.22	.56	.19
CO_2	7.04	8.17	9.17	9.10	8.91	8.90	.03	− .22
H_2O	0.3	0.4	1.0	2.0	3.0	0.81	.63	.14
CH_4	1.27	1.50	3.69	2.82	5.83	2.20	1.03	1.03
C_2H_6	0.00	0.17	0.47	2.24	2.17	0.00	0.00	0.00
C_3H_8	.02	.30	3.12	8.02	10.50	.98	.53	.37
i-C_4H_{10}	.00	.00	1.69	2.55	6.82	1.37	1.38	.32
n-C_4H_{10}	.00	.00	0.73	0.61	1.09			

[a] Values are corrected for impurities in original hydrogen. [b] Percentage composition of original gas: CO_2, 0.15; O_2, 0.35; CO, 0.00; H_2, 98.40; CH_4, 0.30 and N_2, 0.80.

of the paper due to cracking reactions which appear to be favored at lower partial pressure of hydrogen.

Experimental

Procedure and Apparatus.—The acid used in the experiments was obtained by recrystallization of commercial abietic acid using LaLande's[13] modification of Steele's[26] method. At least three recrystallizations were used for each batch of crystals after which they were dried at reduced pressure over anhydrous calcium chloride at 65° for a period of three hours, weighed and placed immediately into the hydrogenation retort under an atmosphere of hydrogen. The melting point of the acid was 158° and did not vary more than ±1° for the various batches. The analyses of the various batches of acid varied within 0.1% of the theoretical values for C and H.

The hydrogenations were conducted in an alloy steel rotary type retort previously described.[27] One hundred grams of the recrystallized acid was placed in the retort together with the alloy steel stirrer, the retort flushed several times with hydrogen, and hydrogen introduced to a pressure of 1900 to 1975 p. s. i. (133.6–138.9 kg./sq. cm.). After checking the retort for leaks, it was placed in the hot furnace and heated to the reaction temperature in eighty to one hundred and thirty minutes, depending upon the temperature desired. Hydrogenolyses were conducted for one hundred and twenty minutes at 325, 370, 400, 425 and 450° and also at 400° for one, two and three sixty-minute periods with the reaction gases being removed and the retort charged with fresh hydrogen after each hour. After each of the reaction periods the retort was cooled rapidly to 150° and the gaseous products removed at this temperature.

The reaction gases were passed through a series of traps to separate and isolate the various components. The first trap was immersed in ice water, the second in a dry ice–acetone mixture, the third trap was a tube packed with ascarite and anhydrone, and the fourth trap was immersed in liquid air. The non-condensable gases then passed through a sampling bottle and a Sargent wet test meter.

The non-condensable gases were analyzed using the U. S. Steel Chemist Procedure with a Burrell Delux Model H apparatus. The gaseous products trapped in liquid air were identified by their boiling points as determined on a low temperature Podbielniak fractional distillation apparatus, Standard Precision Model J. The higher boiling gases collected in the first two traps as well as the Podbielniak residue were separated using a Penn State semi-micro distillation column and where a sufficient quantity of any one component was available it was identified by its physical constants.

After removal of the gaseous products the retort was cooled to room temperature and the remaining products removed by solution in ether and separated into basic, acidic and neutral fractions by extraction with 5% hydrochloric acid and 5% sodium hydroxide. The neutral fractions were separated by distillation at reduced pressure, and where a sufficient quantity of any one fraction was available it was purified by semi-micro distillation at reduced pressure and the probable structure determined by interpretation of the physical constants according to Thorpe and Larson,[28] and the quantitative elementary analysis.

Experimental Results.—The results for the hydrogen consumed and the gaseous products formed are listed in Table II.

The residues from the Podbielniak distillations of products resulting from the two-hour hydrogenolyses at 400, 425 and 450° were of sufficient amounts to warrant further investigation. Each individual residue was separated by semi-micro distillation. The refractive index, $n^{20}D$, of the various fractions from the 400° hydrogenolysis varied from 1.3980 to 1.4492. From this distillation there was about 0.5 g. which had a n of 1.4275, a boiling point of 119° at 732 mm., and a density of 0.773 at 20°/4°. These values agree with those for *trans*-1,2-dimethylcyclohexane.[29] The residue from the hydrogenolysis at 425° had a n ranging from 1.3691 to 1.4155 and a boiling point ranging from 40 to 92° but did not yield enough of any one fraction to be identified. The n range of the distilled residue from the hydrogenolysis at 450° varied from 1.3690 to 1.4426, the main portion of which had a n of 1.4240, a boiling point at 732 mm. of 97°, and a density at 20°/4° of 0.768. These values agree with those of Egloff[30] for methylcyclohexane.

The weight of condensable material obtained in traps 1 and 2 from the two-hour hydrogenolyses at 325, 370 and 400° was not sufficient to warrant further investigation. However, in each case there was obtained two immiscible layers in trap 1, the bottom layer of which was identified as

(26) L. L. Steele, THIS JOURNAL, **44**, 1333 (1922).

(27) C. C. Wright and A. W. Gauger, The Pennsylvania State College, Mineral Industries Experiment Station Technical Paper No. 31.

(28) R. E. Thorpe and R. G. Larson, *Ind. Eng. Chem.*, **34**, 853 (1942).

(29) A. P. I. Hydrocarbon Research Project at Ohio State Univ., 1941.

(30) Egloff, "Physical Constants of Hydrocarbons," Reinhold Publishing Corp., New York, N. Y., 1940.

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TABLE III

LIQUID PRODUCTS OF HYDROGENOLYSIS G./100 G. ABIETIC ACID

	Time of hydrogenolysis 2 hours					Temperature of hydrogenolysis, 400°		
	325°	370°	400°	425°	450°	During 1st hr.	During 2nd hr.	During 3rd hr.
Ether insoluble	5.1	None	None	None	None	None	None	None
Extract by acid	3.2	1.1	0.1	0.4	Trace	0.3	Trace	Trace
by alkali	17.5	14.1	2.7	1.6	0.8	3.4	0.8	0.8
Neutral material	62.8	67.6	68.9	59.4	47.7	80.4	76.6	75.3

water. The top layer, as well as the material in trap 2, could be identified only as a hydrocarbon. There was also obtained in trap 1 in each case a very small amount of red brown solid material which was identified as iron oxide. This resulted from the decomposition of an iron salt of abietic acid which will be described later.

After removal of the water layer the combined condensable material obtained in traps 1 and 2 from the two hour hydrogenolyses at 425 and 450° was dried and fractionated by semi-micro distillation. The n of the various fractions from the hydrogenolysis at 425° ranged from 1.4113 to 1.4520. Of these fractions it was possible to identify two different constituents. The first had a n of 1.4113, a boiling point of 90 to 91° at 729 mm. and a density at 20°/4° of 0.743. These values agree with those presented by Evans[31] for 1,3-dimethylcyclopentane. The second constituent had a n of 1.4356, a boiling point of 128° at 731 mm. and a density of 20°/4° of 0.783. These values agree with those of Levina[32] for ethylcyclohexane. The n of the fractions from hydrogenolysis at 450° ranged from 1.4110 to 1.4630. The main portion had a boiling point of 128° at 732 mm., a density at 20°/4° of 0.792 and a n of 1.4430. These values agree with those presented by Knoevenagel[33] for 3,5-dimethylcyclohexene-1.

The products obtained in traps 1 and 2 minus the water, from any one run of the intermittent hydrogenolyses were insufficient for further investigation. They were all combined, however, and distilled using the semi-micro column. The refractive indices and distillation temperatures of the various fractions ranged from 1.3781 to 1.4490 and from 38 to 124°, but there was not enough of any one fraction to be definitely identified.

The results of separating the products remaining in the retort into acid soluble, alkali soluble and neutral fractions are shown in Table III.

Examination of the products of hydrogenolysis at 325° which remained in the retort after the gaseous products had been removed, showed one which appeared to be ether insoluble but which upon closer examination was found to be very slightly soluble in ether. It was a light gray amorphous solid with a characteristic odor and a decomposition range of 230 to 232°. On ignition it decomposed into a black solid which burst into a bright flame and left a dark red residue. The amorphous solid was identified as an iron salt of abietic acid by tests with KCNS and $K_4Fe(CN)_6$ and by mixed melting point determinations on the recrystallized alkali soluble portion of the compound with freshly prepared abietic acid.

When the acid extracted material shown in Table III was made alkaline with 5% sodium hydroxide, ferric hydroxide precipitated. This indicated the presence of an iron salt of abietic acid in the ether soluble fraction.

The alkali extracts were acidified with 5% hydrochloric acid and extracted with ether. The ether solutions were dried over anhydrous sodium sulfate and stripped of ether over a steam-bath. On standing overnight a white crystalline material separated from the liquid fractions obtained from the hydrogenolyses at the three lowest temperatures. These crystals, representing approximately 90% of the total amount present, were identified by mixed melting points as unreacted abietic acid. The identity of the remaining liquid acidic material was not definitely established but it had a n of 1.524 and an ultimate analysis of 80.65 to 80.76% C, 10.53 to 10.80% H, and 8.55 to 8.71% O. These liquid acids also gave a negative test for unsaturation which indicated that they may be the tetrahydroabietic acid about which the existing literature is rather confusing.

Distillation of the neutral products from the hydrogenolysis at 325° under reduced pressure yielded water as a distillate and left a wax-like residue. A portion of this residue was soluble in hot acetone and crystallized from the acetone upon cooling. The crystals were separated by filtration but upon exposure to air they turned into a wet amorphous mass. Filtration of the crystals in a desiccator over phosphoric anhydride was successful, but in attempting to determine the melting point the same type of transformation again occurred. The residue from the acetone extraction was identified as a sodium salt of abietic acid.

The neutral products from each hydrogenolysis were distilled under reduced pressure and in each case, small fractions collected and their refractive indices measured at 15°. Where various fractions showed the same refractive index they were combined and redistilled using the semi-micro column. On redistillation only the middle 60% of the fraction was used for obtaining the physical constants. Table IV shows the probable products from the hydrogenolyses based on their elementary analyses, and specific dispersions. Since, to

(31) Evans, *J. Inst. Petroleum Tech.*, **24**, 321 (1938).
(32) Levina, *J. Gen. Chem.* (U. S. S. R.), **8**, 1776 (1938).
(33) Knoevenagel, *Ann.*, **297**, 113 (1897).

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TABLE IV

PROBABLE PRODUCTS OF HYDROGENOLYSIS OF ABIETIC ACID

Temp. of hydrogenolysis, °C.	Time of hydrogenolysis, hr.	% of neutral prdts.	B. p. °C.	B. p. Mm.	n_D^{20}	d^{20}_4	Probable product	Analyses, %[a] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Sp. disp. Calcd.	Sp. disp. Found
370	2 contin.	48	139–142	4	1.5165	0.943	12-Me-Δ9,14-dodecahydroretene[b]	87.61	87.71	12.39	12.13	107.9	107.1
400	2 contin.	18	122–125	4	1.5312	.946	1,12-DiMe-Δ9,14; 7,8 decahydrophenanthrene[b]	88.81	88.68	11.19	11.14	144.6	144.0
400	2 contin.	27	143–146	5.5	1.5252	.943	12-Me-decahydroretene[c]	88.29	88.16	11.71	11.76	137.4[e]	137.4
400	1st	21	122–128	4	1.5242	.942	2 Structural isomers of decahydroretene	88.44	88.31	11.56	11.42	142.7 118.7	129.9
400	1st	24	127–130	3	1.5191	.938	1,12-DiMe-dodecahydrophenanthrene	87.99	87.92	12.01	12.05	109.8	128.8
400	2nd	15	127–131	2	1.5222	.943	1-Me-dodecahydrophenanthrene	88.15	88.00	11.84	11.75	110.4	124.4
400	3rd	25	146–155	5	1.5238	.942	1-Me-dodecahydrophenanthrene	88.15	87.98	11.84	11.80	110.4	134.0
425	2 contin.	30	118–120	3	1.5329	.946	1-Me-Δ7,8; 9,14 decahydrophenanthrene[d]	89.03	88.93	10.97	10.91	147.8	148.2
450	2 contin.	10	112–116	4	1.5476	.951	1-Me-octahydrophenanthrene	89.92	89.69	10.08	10.09	[f]	179.9

[a] Data given are the mean of duplicate analyses agreeing within 0.1%. [b] Colorless liquid with a characteristic odor. Gave positive unsaturation tests with Br_2 and $KMnO_4$. [c] Green liquid with a characteristic odor. Unsaturation test with $KMnO_4$ required heat. [d] Colorless liquid with a kerosene-like odor. Unsaturation tests positive. [e] Assuming double bonds to be in conjugated position but not in the 7, 8 position, the latter giving a sp. disp. of 140.5. [f] Various calculated figures for sp. disp. depending on location of double bonds are: Δ9, 14; 5, 13; 7,8: 172.8; Δ9, 14; 7, 8; 12, 13: 185.3; Δ9, 14; 7, 8; 10, 11: 185.3; Δ9, 14; 10, 11; 12, 13:149.9.

the authors' knowledge, the physical constants of these products are not presented in the technical literature no comparison could be made.

Summary

The hydrogenolysis of abietic acid for two hours at temperatures ranging from 325 to 450° and initial hydrogen pressure of 1900 to 1975 P. s. i. and also at 400° for one, two and three hours at the same pressure has shown that:

1. The amount of unconverted acidic material is quite appreciable at 325° but decreases to practically zero as the temperature is increased to 450°.
2. The removal of oxygen takes place, for the most part, as a straight decarboxylation with the formation of carbon dioxide in the early stages of hydrogenolysis.
3. The total percentage of oxygen removed is directly proportional to the temperature of hydrogenolysis and is virtually complete at 450°.
4. The formation of carbon monoxide results at least in part from the reduction of the carbon dioxide.
5. Depropylation does not occur to any appreciable extent up to a temperature of about 380°, but increases rapidly above this temperature.
6. Depropylation is also a function of hydrogen concentration or partial pressure of hydrogen.
7. Part of the ethane results from the cracking of propane.
8. Severance of one of the methyl groups occurs to an appreciable extent even at the lower temperatures of hydrogenolysis and is also a function of time and hydrogen concentration.
9. Alicyclic decomposition does not occur to any appreciable extent up to a temperature of 425°, but increases rapidly above this temperature and is a function of hydrogen concentration.
10. The hydrogen consumption at the lower temperatures is due principally to the partial saturation of the ethylenic linkages and at the higher temperatures to the alkyl and alicyclic decomposition as well as to the reduction of the oxides of carbon.

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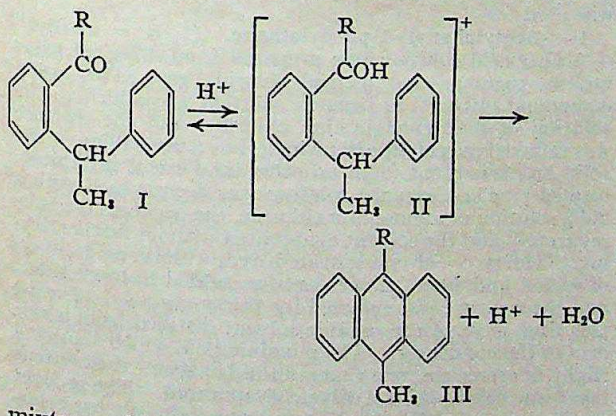
The Influence of *n*-Alkyl Groups on the Rate of a Cyclization Reaction

BY ERNST BERLINER

A general inductive effect, which is described as manifesting itself in a feeble electron-release character, is attributed to alkyl groups.[1] This effect is considered to increase with the amount of branching in the order: methyl, ethyl, *i*-propyl, *t*-butyl, and with increasing length of a normal alkyl chain from methyl to about *n*-propyl or *n*-butyl, where a maximum is reached beyond which the effect is usually not transmitted. The nature and order of the effect are not very well defined or understood as yet, but it seems increasingly probable that in some cases (where the order appears reversed) no-bond resonance or hyperconjugation[2] (the Baker–Nathan effect[3]) may play an important, if not decisive, part. In addition, steric considerations cannot be neglected.[4]

Even though still imperfectly defined, the concept of an inductive effect has been used frequently and successfully to account for certain regularities in changes of physical constants (dipole moments, acid dissociation constants) and reaction rates, and considerable kinetic data derived from measurements in homologous series have been interpreted on this basis.[5]

In the present investigation measurements have been made of the rate of cyclization of ketones of the type I to the 9,10-disubstituted anthracenes (III), a reaction first described by Bradsher.[6] The reaction was carried out in a



mixture of boiling acetic and hydrobromic acid, and the group R was varied from methyl to *n*-hexyl. The first step in the cyclization reaction involves the addition of a proton to the carbonyl group with the rapid establishment of a mobile equilibrium between the ketone and the conjugate acid II.[7] The latter exists as a resonance hybrid that attacks the *ortho* position of the opposite benzene ring in a normal aromatic substitution reaction.[8,9] As expected, the rate was found to be first order with respect to the ketone and is determined presumably by the attack of the carbonium ion on the benzene ring. The first order rate constants for the reactions of the different ketones as well as the half-life time of the cyclization reactions are listed in Table I.

TABLE I

Ketone R	K (min.$^{-1}$) $\times 10^{-2}$	$t_{1/2}$, min.
Methyl	4.6	15
Ethyl	1.8	38.4
n-Propyl	0.99	70
n-Butyl	.35	198
n-Pentyl	.36	192
n-Hexyl	.36	192
Phenyl	.16	433[a]
Benzyl	.91	76[a]

[a] The results obtained with the phenyl and benzyl ketones are not strictly comparable to those of the other ketones since some of the material remained undissolved when the reaction started. The values may, however, be taken as fair approximation.

The rate was found to decrease steadily from methyl to *n*-butyl and then to remain constant within the limits of the experimental error. The rate is also dependent upon the acid concentration; when the concentration of acid was lowered to three-fourths of the original, the observed rate constant for the methyl ketone was 0.76×10^{-2}.[10]

The decrease in rate with increasing length of the alkyl chain can be explained in terms of the inductive effect: an increase of electron density on the positive central carbon atom, caused by the electron release of the alkyl groups, results in a decrease of the effective positive character. Due to an increase in the energy of activation of the substitution reaction, the attack on the benzene ring becomes more difficult, and a decrease in rate results. This decrease reaches a limit with the limit of the inductive effect.

Although the electronic interpretation seems more attractive at the present time and fits well into the general picture of reaction mechanisms,

(1) (a) Watson, "Modern Theories of Organic Chemistry," Oxford, 1941, pages 92 ff.; (b) Ingold, *Chem. Rev.*, **15**, 238 (1934).
(2) Mulliken, Rieke and Brown, THIS JOURNAL, **63**, 41 (1941); Hughes, Ingold and Taher, *J. Chem. Soc.*, 949 (1941).
(3) Baker and Nathan, *ibid.*, 1844 (1935).
(4) Bartlett and Rosen, THIS JOURNAL, **65**, 543 (1943).
(5) Ref. 1a, pages 92 ff. and 135 ff.
(6) Bradsher, THIS JOURNAL, **62**, 486, 1077 (1940).
(7) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 237.
(8) Berliner, THIS JOURNAL, **64**, 2894 (1942).
(9) Bradsher and Smith, *ibid.*, **65**, 854 (1943).
(10) The lack of exact relationship between the rate and acid concentration may be due to the possibility that the actual concentration of acid in the refluxing mixture of acetic acid, hydrobromic acid, and water was not exactly three-fourths of the original. Because of this fact and a possible loss of solvent the rate constants presumably do not constitute absolute values. The stress is laid on the difference in rate of the different ketones.

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it should be emphasized that equally plausible explanations possibly might be obtained from purely stereochemical considerations. The slow reaction of the phenyl ketone can be ascribed to steric effects as well as to additional resonance of the conjugate acid with the benzene ring, which distributes the charge over two nuclei and makes it less available for the attack. This additional effect is not present with the benzyl group, which has a rate comparable to that of the *n*-propyl group, but on the other hand has steric requirements quite different from those of the phenyl group.

The results obtained do not confirm the statement of Bradsher and Smith[9] that the rate of cyclization is roughly independent of the nature of the group R.

Acknowledgment.—I wish to express my sincere thanks to Professor L. F. Fieser, Harvard University, for his help and kind interest in the work.

Experimental

Rate Measurements.—All determinations were carried out under the same conditions: approximately 0.002 mole of the ketone (about 500 mg.) was dissolved in 10 cc. of glacial acetic acid in a 50-cc. round-bottomed flask equipped with a ground glass reflux condenser. Four cc. of hydrobromic acid (48%) and one cc. of water were added, and the flask was immersed in a Wood's metal-bath which was preheated to 133–134° and maintained at this temperature. The first three ketones were soluble in the cold mixture, while the other three dissolved in the boiling mixture. The hydrocarbons resulting from the cyclization separated from the boiling solution. After a given time the flask was removed from the bath and cooled in an ice-bath. A crystal of the pure hydrocarbon was added if crystallization was slow. The solid material was filtered and washed with two 25-cc. portions of distilled water. It was dried in a vacuum oven overnight and weighed. The amount of hydrocarbon left in the mother liquor was negligible and never exceeded a few mg. In a typical case the following results were obtained

R = methyl

Ketone, g.	Hydrocarbon, g.	Time, min.	K (min.$^{-1}$) $\times 10^{-2}$
0.4464	0.1877	13	4.70
.4470	.2492	20	4.66
.4412	.3103	30	4.82
.4471	.3451	40	4.57
.4485	.3612	50	4.17
			Av. 4.58

Preparation of Materials.[11]—The preparation of the intermediate ketones was similar to the procedure used by Bradsher.[6]

***o*-Chlorobenzophenone.**—This compound has been prepared previously but no exact procedure is given.[12] The acid chloride was prepared from *o*-chlorobenzoic acid (147 g.) and phosphorus pentachloride (100 g.). The phosphorus oxychloride was removed *in vacuo* and the acid chloride dissolved in 300 cc. of dry benzene. This solution was dropped on a suspension of 170 g. of aluminum chloride and 400 cc. of benzene in a three-necked flask equipped with a reflux condenser, a dropping funnel, and a hydrogen chloride trap. The addition took two hours, after which time the mixture was allowed to stand at room temperature for five hours. The reaction was completed by refluxing the mixture gently for thirty minutes. Hydrochloric acid and small pieces of ice were added carefully; the layers were separated, and the aqueous layer extracted with some fresh benzene. The combined layers were dried, the solvent evaporated, and the product distilled. It distilled at 181° at 18–19 mm. (redistilled at 178–180° (14–15 mm.)) and solidified to small crystals melting at 43–44°.[13] The yield was 175 g. (85.7%).

1-(*o*-Chlorophenyl)-1-phenylethylene was prepared according to Bergmann and Bondi[14] from magnesium (8 g.), methyl chloride gas, and *o*-chlorobenzophenone (39 g.). The mixture was refluxed overnight and decomposed with ice-cold 30% sulfuric acid. The yield was 29.7 g. (77%) of a colorless oil that distilled at 164–166° (17 mm.). Bergmann and Bondi report the value of 162–163° (18 mm.). The same compound could also be prepared from *o*-chloroacetophenone and phenylmagnesium bromide, but the yield was not higher than 50%.

1-(*o*-Chlorophenyl)-1-phenylethane.—Twelve grams of the above olefin was dissolved in 20 cc. of absolute alcohol and hydrogenated in the presence of Raney nickel catalyst at atmospheric pressure. The product distilled at 156–157° (12 mm.) as a colorless oil with a pleasant, fruit-like odor. The yield was almost quantitative. A sample redistilled at 158° (12 mm.) had the following composition:

Anal.[15] Calcd. for $C_{14}H_{13}Cl$: C, 77.59; H, 6.05. Found: C, 77.10; H, 6.03.

1-(*o*-Cyanophenyl)-1-phenylethane.—A mixture of the above chloro compound (27.5 g.), 14 g. of cuprous cyanide (dried at 100° for ten hours before use), and 12.5 cc. of dry pyridine was refluxed for thirty-six hours in a Wood's metal-bath maintained at 250–260°. The product after isolation in the usual way distilled at 183–188° (16 mm.) as an amber colored oil.[16] The yield was 20 g. (75.7%). Material redistilled at 190–191° (17–18 mm.) showed the composition:

Anal. Calcd. for $C_{15}H_{13}N$: C, 86.92; H, 6.32. Found: C, 86.76; H, 6.11.

All the ketones and hydrocarbons were prepared in the same way. In a typical procedure the following method was used:

1-(*o*-Acetylphenyl)-1-phenylethane. (I, R = methyl).—A Grignard solution was prepared from 2.7 g. of magnesium turnings and methyl chloride gas. The cyano compound (10.3 g.) in benzene solution was added to the solution of methylmagnesium chloride, and the mixture was refluxed overnight after which time a crystalline, white solid had separated. (In no other case was a precipitate formed.) The Grignard solution was decomposed with a 20% solution of ammonium chloride, the organic layer was separated, and the solvent evaporated without further drying. Thirty cc. of concentrated hydrochloric acid, 40 cc. of water, and 40 cc. of acetone were added to the residue, and the mixture was refluxed for thirty minutes. During this time most of the organic solvent distilled from a side arm of the condenser. The remaining oil, which showed a slight fluorescence, was taken up in benzene; the benzene layer was dried, and the solvent evaporated. The product distilled at 184–186° (16–17 mm.) as a light, almost colorless oil. The yield was 8.4 g. (75.5%).

Anal. Calcd. for $C_{16}H_{16}O$: C, 85.67; H, 7.19. Found: C, 85.52; H, 6.81.

9,10-Dimethylanthracene.—A mixture of 1.2 g. of the above ketone, 15 cc. of glacial acetic acid, 10 cc. of hydrobromic acid, and 2 cc. of water was refluxed in an all-glass apparatus. After fifteen minutes a crystalline product

(11) All melting points are corrected.

(12) Overton, *Ber.*, **26**, 29 (1893); Graebe and Keller, *ibid.*, **32**, 1687 (1899).

(13) Auwers, *Ber.*, **58**, 50 (1925), reports a boiling point of 185–188° (13 mm.).

(14) Bergmann and Bondi, *ibid.*, **64**, 1473 (1931).

(15) Microanalyses by Miss E. Werble.

(16) Bergmann, *J. Org. Chem.*, **4**, 1 (1939), reports a boiling point of 166–168° (5 mm.) and 168–173° (3 mm.).

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separated from the boiling solution.[17] The flask was cooled after a total refluxing time of three hours and the hydrocarbon was filtered. Recrystallized from alcohol and little benzene, it forms yellow crystals, often described in the literature.[18] The melting point was 182.8–183.8°. The picrate forms dark brown needles of the melting point 179–180°. The physical constants of the other ketones and hydrocarbons are listed in Table II.

TABLE II

KETONE (I)

R	B. p. °C.	Mm.	Calcd., % C	Calcd., % H	Found, % C	Found, % H
Ethyl	189–190	16–17	85.67	7.61	85.24	7.32
n-Propyl	194–197	14–15	85.67	7.99	85.29	8.21
n-Butyl	205–206	17–18	85.67	8.33	85.34	8.04
n-Pentyl	209–212	15–16	85.67	8.63	85.46	8.31
n-Hexyl	217–219	14–15	85.66	8.9	85.31	8.61
Phenyl[23]	216–219	7–8	88.08	6.34	87.62	6.08
Benzyl	195–197	1–2	87.96	6.71	87.61	6.34

HYDROCARBON (III)

R	M. p., °C.	Solvent	Form
Ethyl	143.2–144	Alcohol	Yellow needles
n-Propyl	97.8–98.6	Alcohol	Orange plates
n-Butyl	78.2–78.8	Alcohol	Long yellow needles
n-Pentyl	71–71.8	Alcohol	Long yellow needles
n-Hexyl	65.8–66.5	Alcohol	Long yellow needles
Phenyl	113.5–114.5[19]	Benzene/ligr.	Yellow prisms
Benzyl	167.8–168.6	Alcohol/benz.	Long yellow needles

(17) The cyclization of the ketone which leads to 9-methylanthracene is reported to take place in four days (Bradsher, ref. 6a).

(18) Bachman and Chemerda, *J. Org. Chem.*, **4**, 583 (1939); Barnett and Matthews, *Ber.*, **59**, 1437 (1926); J. E. Jones, Thesis, Harvard University, 1941.

R	Calcd., % C	Calcd., % H	Found, % C	Found, % H	Picrates[20] M. p., °C.	Nitrogen, % Calcd.	Nitrogen, % Found
Ethyl	92.68	7.32	92.58	7.41	137.8–138.4	9.35	9.26
n-Propyl	92.11	8.04	92.26	7.74	125.5–126.2	9.06	8.57
n-Butyl	91.88	8.11	91.73	8.05	91.8–92.8	8.8	8.46
n-Pentyl	91.55	8.45	91.72	8.68	85.4–86.2	8.55	8.10
n-Hexyl	91.25	8.75	91.43	8.83	78.2–79.2[21]	5.38	5.13
Phenyl					125.2–126	8.64	8.46
Benzyl[22]	95.58	6.42	95.78	6.76			

Summary

The rate of the cyclization of different ketones to 9,10-disubstituted anthracenes has been measured and found to decrease as the number of carbon atoms on the alkyl groups increases. The decrease in rate can best be explained in terms of the inductive effect of alkyl groups. A number of 9-alkyl-10-methylanthracenes has been prepared and the physical constants are described.

(19) Barnett and Matthews, *Ber.*, **59**, 1437 (1926), report a melting point of 112°.

(20) All picrates form dark brown crystals and decompose when recrystallized from alcohol, benzene or ligroin. They are best recrystallized from methyl alcohol in the presence of some excess picric acid.

(21) 9-Hexyl-10-methylanthracene forms a picrate which contains two molecules of hydrocarbon. The same is reported for 9-butylanthracene (Stieglitz and Marx, *Ber.*, **56**, 1619 (1923)).

(22) This hydrocarbon did not form a picrate.

(23) This ketone solidified after long standing and had a crude melting point of 47–48°.

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[CONTRIBUTION FROM THE CENTRAL EXPERIMENT STATION, BUREAU OF MINES]

Hydrogenation of Anthracene by Tetralin[1]

BY MILTON ORCHIN[2]

Examination of some of the high-boiling liquid products obtained by hydrogenation of coal at the Bureau of Mines Central Experiment Station involved attempts at dehydrogenation. The physical properties of these oils indicated a large percentage of hydroaromatic compounds, yet catalytic liquid-phase dehydrogenation gave only small quantities of evolved hydrogen. To understand better the reactions that may occur when mixtures of aromatics and hydroaromatics such as are found in the products from the hydrogenation of coal are heated in the liquid phase in the presence of a catalyst, a study of the mixture anthracene and tetralin was undertaken.

The literature reveals that under the conditions necessary for liquid-phase dehydrogenation, the hydrogen is often utilized in what may be regarded as a sort of internal oxidation–reduction process. This transfer of hydrogen can be either intramolecular or intermolecular. Examples of the former are the conversion of methyl 2-(5,6,7,8-tetrahydro)-naphthyl ketone to 2-ethylnaphthalene[3]; and 1-hydroxy-1-allyl-1,2,3,4-tetrahydrophenanthrene to 1-*n*-propylphenanthrene.[4,5] Examples of the intermolecular transfer of hydrogen are the conversion of 2,3-naphthalic anhydride to 2,3-dimethylnaphthalene in small yield by means of *p*-cyclohexylphenol[6]; the disproportionation reactions in the terpene series[7]; the incomplete dehydrogenation of tetralin due to the equilibrium tetralin $\leftrightarrows$ naphthalene + $2H_2$[8]; and the work of Adkins and coworkers, who dehydrogenated many compounds by heating in a steel bomb with benzene as a hydrogen acceptor.[9]

(1) Published by permission of the Director, Bureau of Mines, U. S. Department of the Interior. Not copyrighted.

(2) Organic chemist, Central Experiment Station, Bureau of Mines, Pittsburgh, Pa.

(3) Newman and Zahm, THIS JOURNAL, **65**, 1097 (1943). Barbot, *Bull. soc. chim.*, [4] **47**, 1314 (1930), dehydrogenated the same ketone with sulfur at 220° and obtained a 71% yield of methyl 2-naphthyl ketone. Apparently, under these conditions the ketone group is not attacked.

(4) Bachmann and Wilds, THIS JOURNAL, **60**, 624 (1938).

(5) See also (a) Ruzicka, *Helv. Chim. Acta*, **19**, 419 (1936); (b) Fieser and Joshel, THIS JOURNAL, **61**, 2958 (1939); and (c) Mosettig and Duval, *ibid.*, **59**, 367 (1937); (d) for a recent complete review of the subject of dehydrogenation, see Plattner, *Die Chemie*, **55**, 131 (1942).

(6) Windaus and Thiele, *Ann.*, **521**, 163 (1935).

(7) Linstead, Michaelis and Thomas, *J. Chem. Soc.*, 1139 (1940).

(8) Linstead and Michaelis, *ibid.*, 1134 (1940).

(9) Adkins and Reid, THIS JOURNAL, **63**, 741 (1941), and Adkins, Richards and Davis, *ibid.*, **63**, 1320 (1941).

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When tetralin and anthracene were heated together at one atmosphere pressure in the presence of a palladium catalyst, some of the hydrogen was transferred from the tetralin to the anthracene with the formation of naphthalene and hydroanthracenes. The extent of the reaction was influenced by the temperature, as indicated by the table in the experimental part. When the temperature was such that about 24% of the theoretical quantity of hydrogen was evolved, a 30% yield of 1,2,3,4-tetrahydroanthracene was obtained.

When tetralin and anthracene were heated in a sealed tube, a 60% yield of 1,2,3,4-tetrahydroanthracene was obtained. In addition, small quantities of 9,10-dihydroanthracene and 1,2,3,-4,5,6,7,8-octahydroanthracene were formed. The reaction apparently resembles the catalytic hydrogenation of anthracene.[10]

In an extension of this method of hydrogenation, 2-cyclohexenone was used as a hydrogen donor in place of tetralin. 2-Cyclohexenone in its enolic form is a dihydrobenzene derivative, and its preparation by vapor-phase dehydration of 2-hydroxycyclohexanone gives considerable phenol.[11] The reaction between cyclohexenone and anthracene resulted in a 30% yield of 1,2,3,4-tetrahydroanthracene.

The reaction between tetralin and anthracene to give naphthalene, dihydroanthracene and tetrahydroanthracene may be represented stoichiometrically by the equations

$$(1)\quad C_{10}H_{12} + 2C_{14}H_{10} \rightleftharpoons C_{10}H_8 + 2C_{14}H_{12}$$

$$(2)\quad 2C_{14}H_{12} \rightleftharpoons C_{14}H_{10} + C_{14}H_{14}$$

Reaction (1) can proceed to a limited extent in the absence of a catalyst, as indicated by experiments 8 and 9. The disproportionation reaction (2) apparently requires a catalyst, as no 1,2,3,4-tetrahydroanthracene could be found in the same reactions. The isolation of some tetrahydroanthracene when dihydroanthracene was dehydrogenated is evidence for reaction (2).[12]

In one attempt to elucidate the steps of the reaction, 9,10-dihydroanthracene was refluxed in ethanol solution with Raney nickel. The reaction mixture gave a good yield of 1,2,3,4-tetrahydroanthracene. Anthracene was found to behave similarly. Apparently, the hydrogen adsorbed on the surface of Raney nickel can be utilized for the hydrogenation reactions, and this constitutes a novel method for the preparation of small quantities of tetrahydroanthracene.

When the tetralin–anthracene reaction is accompanied by the evolution of hydrogen, the origin of the hydrogen, of course, is tetralin. As the temperature is increased, the hydrogen may also result from dehydrogenation of the hydroanthracenes. Undoubtedly other equilibria are present in the system at different times, but the mechanism of the reaction remains speculative.

The results support the theory that one of the steps in the hydrogenation of coal is the transfer of hydrogen from a reactive hydrogen donor to a molecule that can act as a hydrogen acceptor.[13] The ease of transfer of hydrogen also suggests that considerable discretion must be exercised in determining "primary" products of the hydrogenation of coal.

Experimental[14]

The apparatus used in the open-tube experiments consisted simply of a test-tube containing the reactants connected to a reflux condenser by either a rubber stopper or a ground-glass joint. A piece of rubber tubing led from the top of the condenser to an inverted cylinder of water standing in a water-bath. The catalyst used in each experiment (except 8 and 9) was a mixture of palladium and charcoal containing approximately 30% palladium.[15]

Materials

Tetralin.—A good grade of commercial tetralin, obtained by the hydrogenation of naphthalene, was distilled twice from sodium and the middle cut of the second distillation used.

Anthracene.—Commercial anthracene was purified by two distillations with ethylene glycol[16] and twice recrystallized from benzene, melting point 215.2–217.2°. For purposes of comparison, samples of 9,10-dihydroanthracene, 1,2,3,4-tetrahydroanthracene and 1,2,3,4,5,6,7,8-octahydroanthracene were prepared.

9,10-Dihydroanthracene.[17]—Sodium reduction of an amyl alcohol solution of anthracene gave 84% of 9,10-dihydroanthracene, m. p. 108.0–109.8°.

1,2,3,4-Tetrahydroanthracene prepared from the reaction between anthracene and tetralin was purified through the picrate,[18] and after two recrystallizations from alcohol, the hydrocarbon was obtained as colorless plates, m. p. 100.5–101.5°. The trinitrobenzene complex also was prepared, yellow needles, m. p. 133.2–133.8°, from alcohol. *Anal.*[19] Calcd. for $C_{20}H_{17}N_3O_6$: N, 10.63. Found: N, 10.43.

Subsequently, tetrahydroanthracene was prepared from 9,10-dihydroanthracene and from anthracene. To 0.5449 g. of 9,10-dihydroanthracene in 25 ml. of ethanol there was added about 8 g. of Raney nickel.[20] After the mixture was refluxed for two and one-half hours in a nitrogen atmosphere, it was filtered, and the filtrate was concentrated. On cooling, 0.3326 g. of 1,2,3,4-tetrahydroanthracene, m. p. 98.0–100.2°, was obtained. The mother liquor was treated with 0.3 g. of *s*-trinitrobenzene and 0.245 g. of the 1,2,3,4-tetrahydroanthracene trinitrobenzene complex, m. p. 132.8–133.4°, was obtained, making a total yield of 81%. When 0.3377 g. of anthracene in 50 ml. of ethanol was treated with about 10 g. of Raney nickel, a 71% yield of 1,2,3,4-tetrahydroanthracene was obtained.

1,2,3,4,5,6,7,8-Octahydroanthracene.—β-2-(5,6,7,8-Tetrahydronaphthoyl)-propionic acid was prepared in 70% yield by the Friedel–Crafts reaction between tetralin and succinic anhydride in nitrobenzene at 0°. Benzene also

(10) Fries and Schilling, *Ber.*, **65**, 1494 (1932).

(11) Bartlett and Woods, THIS JOURNAL, **62**, 2933 (1940).

(12) In this connection, it is interesting to note that Fries and Schilling (ref. 10) obtained some anthracene when they hydrogenated dihydroanthracene at room conditions. Wieland, *Ber.*, **45**, 485 (1912), also obtained anthracene from dihydroanthracene by shaking a benzene solution of the latter with a special palladium black catalyst.

(13) Storch, *Chem. Rev.*, **29**, 483 (1941).

(14) All melting points corrected.

(15) Zelinsky and Turowa-Pollak, *Ber.*, **58**, 1295 (1925).

(16) Fieser, "Experiments in Organic Chemistry," 2d ed., D. C. Heath Co., Boston, Mass.

(17) Bamberger, *Ber.*, **20**, 3075 (1887).

(18) Schroeter, *ibid.*, **57**, 2014 (1924).

(19) Dr. T. S. Ma, University of Chicago.

(20) Prepared by Mary E. Montague and E. H. Kaplan, of this laboratory. Cf. Adkins, "Organic Syntheses," **21**, 15 (1941).

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TABLE I

REACTIONS BETWEEN TETRALIN AND ANTHRACENE

Reactions 1 to 4, inclusive, were open-tube reactions; all others were sealed-tube reactions.

Expt.	Starting materials, g. $C_{10}H_{12}$[b]	$C_{14}H_{10}$[c]	Pd-C	Bath temp., °C.	Time, hours	% H_2 evolved[d]	Per cent. products[a] $C_{10}H_{12}$[b]	$C_{10}H_8$[e]	$C_{14}H_{10}$[c]	$C_{14}H_{12}$[f]	$C_{14}H_{14}$[g]	$C_{14}H_{18}$[h]
1	0.462	None	0.137	225–230	7	83	+[i]	+	−[j]	−	−	−
2	0.458	1.001	0.131	225–230	7	0	+	+	93	+	+	−
3	0.59	0.531	0.100	270–290[k]	7	65	−	+	79	−	+	−
4	1.01	0.75	0.100	220–260[l]	6.5	24	42	44	44	1	30	−
5	1.98	5.00	0.100	300–315	5	−	+	+	83	−	−	−
6	4.98	3.56	0.100	300–330	6	−	16	54	+	+	41	−
7	5.4	6.20	0.500	340	7	−	14.8	69.3	9.0	3.5	61.3	0.8
8	1.98	2.686	None	290 350	8 6	−	+	−	87	4	0	−
9	1.98	2.607	None	390–420	1	−	+	−	88	5	0	−

[a] The percentage figures are yields based upon starting tetralin (in the case of naphthalene) and anthracene (in the case of hydroanthracenes). The figures represent the minimum amount present. [b] Tetralin. [c] Anthracene. [d] These figures are based upon the theoretical yield of 44.8 ml. hydrogen per millimole of tetralin. [e] Naphthalene. [f] 9,10-Dihydroanthracene. [g] 1,2,3,4-Tetrahydroanthracene. [h] 1,2,3,4,5,6,7,8-Octahydroanthracene. [i] + means isolated and identified but not determined quantitatively. [j] − means not isolated; may or may not be present. [k] Inside temperature 230–250°. [l] Inside temperature 230–235°.

can be used as the solvent.[3,21a] Clemmensen reduction of the keto acid gave γ-2-(5,6,7,8-tetrahydronaphthyl)-butyric acid in 94% yield.[3] The acid was converted to the acid chloride at room temperature with thionyl chloride. In the hope of minimizing the formation of 4-keto-1,2,3,4,-5,6,7,8-octahydrophenanthrene, the acid chloride was cyclized in carbon disulfide at 0° with stannic chloride. However, cyclization took place in both directions.[21b] The mixture of ketones (11.7 g. from 15.0 g. of the tetralylbutyric acid) was reduced by the Clemmensen procedure[16] and gave 4.72 g. of 1,2,3,4,5,6,7,8-octahydroanthracene, m. p. 71–72°, recrystallized from alcohol, melting point 72.0–73.0°.

2-Cyclohexenone.—After several unsuccessful attempts to prepare this ketone by selenium dioxide oxidation of cyclohexene (mole for mole in ethanol solution), it was prepared in poor yield (10%) by the chromic oxide oxidation of cyclohexene,[22] $n^{24}D$ 1.483; compound with 2,4-dinitrophenylhydrazine, m. p. 171.5°, after sintering at 163°.[22a] *Anal.*[19] Calcd. for $C_{12}H_{12}N_4O_4$: N, 20.28. Found: N, 20.02.

Reactions between Tetralin and Anthracene.—The conditions and results of the various experiments are summarized in the table. In working up the mixtures resulting from the reactions between anthracene and tetralin the problem in the most extreme case was one of separating and identifying tetralin, naphthalene, anthracene, 9,10-dihydroanthracene, 1,2,3,4-tetrahydroanthracene, and 1,2,3,4,5,6,7,8-octahydroanthracene. The reaction mixtures were not worked up in the same fashion each time, but characteristic differences in properties of these six substances were utilized to advantage. These differences may be summarized briefly. Tetralin and naphthalene sublime and steam-distil more readily than the other substances and, of these, only naphthalene forms a picrate. Anthracene alone of all these substances forms an adduct with maleic anhydride.[23] The adsorption of the anthracenes on a column of activated alumina in increasing strength of adsorption is octahydroanthracene, 1,2,3,4-tetrahydroanthracene, 9,10-dihydroanthracene, and anthracene (see below). 1,2,3,4-Tetrahydroanthracene forms a picrate, whereas 9,10-dihydroanthracene does not. The former also readily forms a complex with *s*-trinitrobenzene.[24]

Experiment 7 will be described in detail, as it illustrates all the techniques used in separating and identifying products.

Experiment 7.—A mixture of 6.2 g. of powdered anthracene, 0.5 g. of palladium-charcoal, and 5.5 cc. of tetralin was heated in a sealed tube in a nitrogen atmosphere at 340° for seven hours. The tube was cooled and opened (no pressure), the contents were dissolved in benzene, filtered, and distilled at the vacuum of the water pump. A high-boiling fraction of 4.6 g. was collected at a bath temperature of 170° and a residue (A) was retained in the flask.

The distillate consisted of naphthalene and tetralin, separated by precipitation of naphthalene as the picrate and estimation of the tetralin content of the oily hydrocarbon residue by comparison of its refractive index with that of a synthetic mixture of known composition.

Residue A yielded anthracene in the form of its maleic anhydride adduct. The filtrate from that afforded 1,2,3,4-tetrahydroanthracene, crystallizing from alcohol. Trinitrobenzene was now added to the solution, precipitating a mixture of the complexes of naphthalene and tetrahydroanthracene. The hydrocarbons were regenerated by passage of the complexes through alumina and separated by steam-distillation.

The material in the mother liquor from the complex precipitation was recovered, dissolved in benzene–petroleum ether and separated into 9,10-dihydro- and 1,2,3,4,-5,6,7,8-octahydro-anthracene by chromatographic adsorption on a column of alumina.

The isolated products were identified by their melting points and mixed melting points. The yields of purified products obtained are recorded in the table.

Chromatographic Separation of 9,10-Dihydroanthracene and 1,2,3,4-Tetrahydroanthracene.—A solution of 100 mg. of 9,10-dihydroanthracene and 100 mg. of 1,2,3,4-tetrahydroanthracene in 100 ml. of petroleum ether (b. p. 60–68°) was passed through a 9-inch column containing 65 g. of activated alumina. Following the 100 ml. of solution, an additional 125 ml. of petroleum ether, then 100 ml. of 20% benzene in petroleum ether, were passed through the column by gravity. The receivers were changed after

(21)(a) Krollpfeiffer and Schafer, *Ber.*, **56**, 620 (1923).

(21)(b) These authors cyclized γ-2-tetralylbutyric acid by heating it with concentrated sulfuric acid and obtained a 75% yield of the ketoanthracene. No keto phenanthrene was isolated.

(22) Whitmore and Pedlow, THIS JOURNAL, **63**, 758 (1941).

(22)(a) Whitmore and Pedlow give the melting point of cyclohexenone 2,4-dinitrophenylhydrazone as 117°, while Bartlett and Woods (ref. 11) give the melting point as 163°. Although these discrepancies are not readily explained, it should be noted that the hydrazone can theoretically exist in stereoisomeric forms, and there is the additional possibility that the cyclohexene portion may undergo spontaneous aromatization.

(23) Bachmann and Kloetzel, *ibid.*, **60**, 481 (1938).

(24) Although 9,10-dihydroanthracene can also form a complex with trinitrobenzene (Sudborough, *J. Chem. Soc.*, 1339 (1916)), the complex dissociates readily and is difficult to obtain.

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about every 50 ml. of solution had been collected. Six fractions were thus collected. Evaporation of fractions 1, 2, 3 and 6 gave no residue. The fourth fraction gave a mixture with m. p. 75–88°. The fifth fraction gave crystals, m. p. 104.5–108.5°, and after recrystallization there was obtained 25 mg., m. p. 108.0–109.8°, identical with 9,10-dihydroanthracene.

Dehydrogenation of 9,10-Dihydroanthracene.—In a test-tube connected to a reflux condenser were placed 1.00 g. of 9,10-dihydroanthracene and 100 mg. of palladium–charcoal catalyst. The tube was placed in a bath at 200° for a few minutes, during which time 6 ml. of gas was collected (blank). The temperature was raised to 300° and kept at 300–340° for three hours, during which time an additional 118 ml. of gas was collected (83%). The reaction mixture was cooled, dissolved in benzene, filtered, and the anthracene removed by means of maleic anhydride. There was obtained 1.24 g. of adduct equivalent to 0.8 g. of anthracene (80%). After the excess maleic anhydride had been removed, the remaining material was treated with trinitrobenzene; whereupon 70 mg. of the 1,2,3,4-tetrahydroanthracene complex, m. p. 128–131°, was obtained, mixed melting point, no depression.

Reaction between 2-Cyclohexenone and Anthracene.—In a preliminary experiment, cyclohexenone was refluxed with palladium–charcoal, but no hydrogen was evolved.[25] A mixture of 2.95 g. anthracene, 3.84 g. cyclohexenone, and 300 mg. of palladium–charcoal was heated in a sealed tube for seven and one-half hours at 295–325°. The tube was cooled in dry-ice, opened (pressure), and the contents dissolved in benzene and filtered. The benzene solution was extracted with 5% sodium hydroxide solution and the alkaline extract made to 500 ml. A 20-ml. aliquot was titrated with potassium bromate–potassium bromide solution.[26] The titration indicated 1.74 g. of phenol present in the total reaction mixture. The tribromophenol formed in the titration was filtered and recrystallized from ethanol, m. p. 91–92° (literature reports 95°). The benzene solution remaining after the alkaline extraction was treated with maleic anhydride and 1.64 g. endoanthracene maleic anhydride was precipitated and filtered. The excess maleic anhydride was extracted from the filtrate, the benzene was evaporated, and the residue was distilled. The distillate (2.45 g.) was dissolved in 20 ml. of ethanol and treated with 2 g. of picric acid. There was obtained 1.52 g. of orange-yellow crystals, m. p. 110–113°, identical with the picrate of 1,2,3,4-tetrahydroanthracene. The mother liquor was passed through a column of activated alumina. The first fraction gave 50 mg. of 1,2,3,4-tetrahydroanthracene. The second fraction contained some tetrahydroanthracene, some dihydroanthracene, and some other material that may have resulted from the polymerization of cyclohexenone. After removal of about 135 mg. of 9,10-dihydroanthracene, m. p. 107–109°, mixed melting point, no depression, the remaining material was treated with trinitrobenzene. There separated 0.386 g. of 1,2,3,4-tetrahydroanthracene trinitrobenzene complex, m. p. 128–130.5°, mixed melting point, no depression. The mother liquor was not investigated further.

(25) Compare Ruzicka, ref. 5a, who by heating 3-methylcyclohexene-2-one for two days with selenium at 260° obtained only a 15% yield of *m*-cresol.

(26) United States Pharmacopeia, X.

Acknowledgment.—The author wishes to express his appreciation to Dr. H. H. Storch for his interest and suggestions throughout this work and to Dr. M. S. Newman for suggestions regarding the manuscript.

Summary

When anthracene and tetralin are heated together at 1 atmosphere pressure in the presence of a palladium catalyst, a 30% yield of 1,2,3,4-tetrahydroanthracene can be obtained.

When anthracene and tetralin are heated together in a sealed tube in the presence of a palladium catalyst, the reaction resembles a catalytic hydrogenation of anthracene and a 61% yield of 1,2,3,4-tetrahydroanthracene along with small amounts of 9,10-dihydroanthracene, and 1,2,3,4,5,6,7,8-octahydroanthracene are obtained. This type of hydrogenation of anthracene can also be achieved with 2-cyclohexenone.

The dehydrogenation of 9,10-dihydroanthracene in the liquid phase results in expulsion of less than the theoretical quantity of hydrogen and formation of some 1,2,3,4-tetrahydroanthracene.

1,2,3,4-Tetrahydroanthracene can be conveniently prepared in good yield by refluxing an ethanol solution of anthracene or 9,10-dihydroanthracene with Raney nickel.

PITTSBURGH, PA. RECEIVED DECEMBER 10, 1943

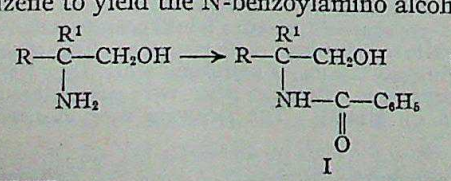
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF INDIANA UNIVERSITY]

Amino Acids. III. α-Amino-*n*-butyric Acid and α-Amino-isobutyric Acid

BY JOHN H. BILLMAN AND EARL E. PARKER

The method used for the synthesis of alanine[1] from 2-amino-*n*-propanol has now been extended to the preparation of α-amino-*n*-butyric acid and α-amino-isobutyric acid from 2-amino-*n*-butanol and 2-amino-2-methyl-*n*-propanol.

The amino alcohols were benzoylated with benzoyl chloride and anhydrous sodium carbonate in benzene to yield the N-benzoylamino alcohol I.

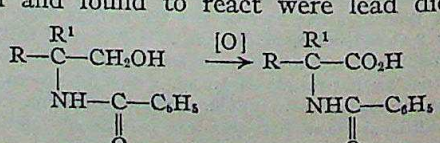


(1)

I

The yield of crude 2-benzoylamino-*n*-butanol was 89–91% while the yield of pure 2-benzoylamino-2-methyl-*n*-propanol was 78–79%.

A number of oxidizing agents were tried in order to ascertain whether any of them possessed advantages over alkaline permanganate for the oxidation of the benzoylated amino alcohols to the corresponding amino acids II. Among those examined and found to react were lead dioxide,



II

(1) Billman and Parker, THIS JOURNAL, 65, 2455 (1943).

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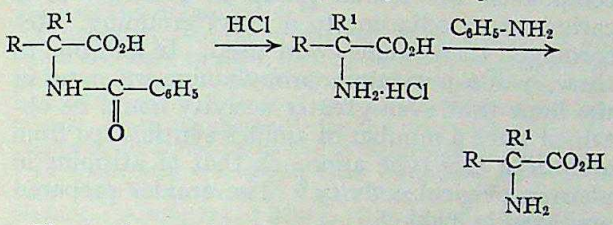
sodium dichromate and sulfuric acid, chromic acid, ammonium persulfate, and nitric acid. None of them were as good as alkaline permanganate.

The yields of α-benzoylamino-*n*-butyric acid and α-benzoylamino-isobutyric acid, containing very small amounts of benzoic acid as impurity, were 67–72% and 91–93%, respectively.

The benzoylated amino acids were hydrolyzed to yield approximately the theoretical amounts of the amino acid hydrochlorides. The yields of pure α-amino-*n*-butyric acid and α-aminoisobutyric acid obtained upon liberation from their hydrochlorides were 72 and 86%, respectively.



The authors wish to thank Eli Lilly and Company for assistance in this work.

Experimental

2-Benzoylamino-*n*-butanol.—In a liter 3-necked flask equipped with a dropping funnel, a thermometer, and an efficient stirrer were placed 500 cc. of benzene, 25 g. of anhydrous sodium carbonate and 18.3 g. of pure 2-amino-*n*-butanol. The mixture was vigorously stirred and cooled to 10°. A solution containing 28.1 g. of benzoyl chloride and 100 cc. of benzene was then added drop by drop at such a rate that the temperature did not exceed 10°. After forty-five minutes, a second 25 g. of sodium carbonate was added. The mixture was stirred for four hours, then the bath was removed and stirring continued for four additional hours.

The dropping funnel was then replaced by a condenser and the reaction refluxed until no odor of benzoyl chloride could be detected. The hot mixture was filtered to remove the inorganic material. This residue was extracted with two 100-cc. portions of hot benzene. The combined filtrates were reduced to 400 cc. and chilled in the refrigerator. The crystals of 2-benzoylamino-*n*-butanol were filtered off and washed with cold benzene. A small second crop was obtained by evaporating the filtrate to 150 cc. The product weighed 34–35 g. (89–91%) and melted at 97–98°.

Recrystallization from toluene yielded a product melting at 98–99°. Calcd.: N, 7.25. Found: N, 6.98.

α-Benzoylamino-*n*-butyric Acid.—In 400 cc. of water containing 2 g. of sodium hydroxide was suspended 32.5 g. of crude 2-benzoylamino-*n*-butanol. To this vigorously stirred mixture was added 36 g. of potassium permanganate at such a rate that the temperature did not exceed 40°. Stirring was continued until most of the permanganate had been consumed and the temperature had fallen to room temperature. The manganese dioxide was filtered off and the excess of permanganate reduced with saturated sodium bisulfite solution. The mixture was again filtered, acidified with concentrated hydrochloric acid, and chilled in the refrigerator. The benzoylamino-*n*-butyric acid weighed 23.7–25.1 g. and melted at 139–40°. This was a 67–72% yield of crude material.

α-Amino-*n*-butyric Acid Hydrochloride.—In a typical experiment 25.1 g. of crude α-benzoylamino-*n*-butyric acid was suspended in 200 cc. of 18% hydrochloric acid and refluxed eight hours. The mixture was cooled to room temperature and the benzoic acid filtered off. The filtrate was then evaporated to dryness under reduced pressure. A small portion of water was added and the process repeated. The operation was repeated again with water and three more times with absolute alcohol. A theoretical yield of 17 g. of α-amino-*n*-butyric acid hydrochloride was obtained. Calcd.: N, 10.05. Found: N, 10.04.

α-Amino-*n*-butyric Acid.—The α-amino-*n*-butyric acid hydrochloride (17 g.) was dissolved by warming it with 100 cc. of 95% alcohol. The mixture was filtered and treated with 20 cc. of pure aniline. It was then chilled in the refrigerator for several hours. The product was filtered off and washed with absolute alcohol to free it of aniline. The yield of halogen free α-amino-*n*-butyric acid was 9 g. or 72% of the theoretical. *Anal.* Calcd.: N, 13.6. Found: (Van Slyke) N, 13.8.

2-Benzoylamino-2-methyl-*n*-propanol.—In a liter 3-necked flask equipped with a dropping funnel, a thermometer, and an efficient stirrer were placed 400 cc. of benzene, 50 g. of anhydrous sodium carbonate and 18.3 g. of pure 2-amino-2-methyl-*n*-propanol. The mixture was vigorously stirred and cooled to 10° with an ice-bath. A solution containing 28.1 g. of benzoyl chloride and 100 cc. of benzene was then added at such a rate that the temperature did not exceed 10°. After the mixture had been stirred for four hours, the bath was removed and stirring continued for two more hours.

The dropping funnel was then replaced by a condenser and the mixture refluxed until all of the benzoyl chloride had reacted. The hot mixture was then filtered to remove the inorganic material. This residue was extracted with two 100-cc. portions of hot benzene. The combined filtrates were reduced to 400 cc. and the solution chilled. The crystals of 2-benzoylamino-2-methyl-*n*-propanol were filtered off and washed with two small portions of cold benzene. This filtrate was reduced to 100 cc. and 200 cc. of petroleum ether added. The gummy solid that was obtained was recrystallized from benzene and yielded a small amount of crystals of the same purity as the original batch. The total yield was 30.2–30.5 g. (78–79%) of material melting 88–89°. *Anal.* 7.10% nitrogen. A sample that was recrystallized three times from benzene melted 89–90°. *Anal.* Calcd.: N, 7.25. Found: N, 7.24.

α-Benzoylamino-isobutyric Acid.—In 400 cc. of water containing 4 g. of sodium hydroxide was suspended 38.6 g. of 2-benzoylamino-2-methyl-*n*-propanol. To this vigorously stirred mixture was added 42.1 g. of potassium permanganate at such a rate that the temperature did not exceed 40°. Stirring was continued until most of the permanganate had been consumed and the temperature had fallen to that of the room. The manganese dioxide was filtered off and the excess of permanganate reduced with methyl alcohol. The mixture was again filtered and acidified with concentrated hydrochloric acid and chilled. The α-benzoylamino-isobutyric acid was filtered off and the filtrate neutralized with bicarbonate and evaporated to 150 cc. under reduced pressure. The solution was acidified and yielded from 1 to 4 g. of product. The total yield was 37.6–38.6 g. (91–93%) of material melting over a one or two degree range between 193 and 198°.

α-Amino-isobutyric Acid Hydrochloride.—In a typical experiment 37.8 g. of α-benzoylamino-isobutyric acid was suspended in 300 cc. of 18% hydrochloric acid and refluxed for eight hours. The mixture was worked up by the same procedure as for isolating α-amino-*n*-butyric acid hydrochloride; yield 25.4 g. (99%).

α-Aminoisobutyric Acid.—The aminoisobutyric acid hydrochloride (24.8 g.) was dissolved in 150 cc. of hot 95% alcohol, treated with 24 cc. of pure aniline, and chilled in the refrigerator. The product was filtered off and washed with absolute alcohol to free it of aniline. The yield of α-aminoisobutyric acid was 15.7 g. or 86% of the theoretical. *Anal.* Calcd.: N, 13.59. Found: (Van Slyke) N, 13.48.

Summary

A new method has been developed for the synthesis of α-amino-*n*-butyric acid and α-amino-isobutyric acid from the corresponding amino alcohols.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF INDIANA UNIVERSITY]

Amides of Nicotinic Acid and Related Acids. II

BY JOHN H. BILLMAN AND JOHN L. RENDALL[1,2,3]

In the first[4] of a series of articles on the preparation of compounds possessing antispasmodic and anticonvulsant activity, it was found that certain amides showed promise as antispasmodics and anticonvulsants. Further investigation of amides of various acids disclosed the fact that the benzyl amide of nicotinic acid possessed rather pronounced antispasmodic activity. However, the activities of other amides of nicotinic acid differ markedly. For example, nicotinamide[5] is relatively inert in regard to spasmodic or convulsant action while diethyl nicotinamide (Nikethamide)[6] possesses convulsant activity. It seemed, therefore, to be of interest to prepare other amides of nicotinic acid and related acids such as α-picolinic, γ-picolinic, quinoline-3-carboxylic, pyrazine monocarboxylic and pyrazine 2,3-dicarboxylic acids in order to compare their pharmacological activity. The amides were prepared by interaction of the appropriate amine either with the heterocyclic ester or the free acid.

It was thought that the activity of the benzyl amide might be due to the basicity and/or the solubility of the amine used in making the amide. Therefore, amines were selected which resemble benzylamine in structure or solubility. An amine which should have about the same solubility as benzylamine is *n*-amylamine, since a *n*-butyl group is considered approximately equivalent to a phenyl group in estimating solubility. An amine which should possess about the same basicity as benzylamine is allylamine, for in both compounds the amino group is attached to a carbon atom adjacent to a vinyl grouping. Accordingly, these amines were used. In addition to these, γ-di-*n*-butylaminopropylamine was used in the hope that even greater activity could be obtained since a number of amides synthesized from amines of this type approach that of atropine in pharmacological activity.[7] The amides prepared are listed in Table I.

TABLE I

Amides	M. p., °C.	B. p. °C.	B. p. Mm.	Yield	% Nitrogen Calcd.	% Nitrogen Found
Benzyl nicotinamide	72–73			93.0	13.20	13.08
n-Amyl nicotinamide		170–171	1	49.4	14.58	14.67
Allyl nicotinamide[a]		158–161	1	50.0	17.29	17.20
Dibutylaminopropyl nicotinamide		226–230	2	60.1	14.42	14.12
				98.0[b]		
Benzyl γ-picolinamide	84.5–85.0			54.0[c]	13.20	12.95
n-Amyl γ-picolinamide		178–182	2	70.5	14.58	14.70
Allyl γ-picolinamide		158–159	2	51.8	17.29	17.22
Dibutylaminopropyl γ-picolinamide		236–240	2	78.2	14.42	14.13
				51.7[b]		
Benzyl α-picolinamide	87.0–87.5			73.3[c]	13.20	13.00
n-Amyl α-picolinamide		135–138	2	83.3	14.58	14.65
Allyl α-picolinamide		166–170	1	94.4	17.29	17.16
Dibutylaminopropyl α-picolinamide		209–212	1	92.1	14.42	14.22
Benzyl pyrazine monocarboxamide	116.0			31.0	19.72	19.64
N,N′-Dibenzyl pyrazine-2,3-dicarboxamide	171–171.5			78.2	16.18	16.29
N,N′-Diamyl pyrazine-2,3-dicarboxamide	145.5–146.0			20.0	18.30	18.14
Benzyl quinoline-3-carboxamide	139–139.5			47.8	10.77	10.91

[a] Pictet and Sussdorff, *Arch. Sci. phys. nat. Genève.*, [4] **5**, 122; *Chem. Zentr.*, 69, 677 (1898). [b] Prepared according to Method "A." [c] Prepared according to Method "B."

Experimental

Two procedures were used in the preparation of the amides:

Method "A."—A xylene solution of the amine and acid was refluxed and the water evolved during the reaction collected in a calibrated water trap. Since the water could be measured, it was found possible to gage the speed and extent of completion of the reaction.

Obviously method "A" could not be used conveniently in the preparation of the amyl and allyl amides because of the low boiling points of the amines. It is interesting to note, however, that even when the *n*-amylamine salt of nicotinic acid was isolated and heated in refluxing xylene, dehydration could not be effected. Heating the salt to 180° in a vacuum of 2 mm. caused decomposition to the acid and amine.

Method "B."—The various amines were treated with the ethyl esters of nicotinic, α-picolinic, γ-picolinic and quinoline-3-carboxylic acids to yield the corresponding amides.

(1) Submitted to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree, Doctor of Philosophy, in the Department of Chemistry, Indiana University.

(2) Eli Lilly Fellow for the years 1941–1943.

(3) Present address, B. F. Goodrich and Co., Akron, Ohio.

(4) Billman and Hidy, THIS JOURNAL, **65**, 760 (1943).

(5) Supniewski, Hano and Taschner, *Bull. inter. acad. polon. sci., Classe med.*, 85–97 (1936); *Ber. ges. Physiol. exptl. Pharmakol.*, **99**, 674 (1937); *C. A.*, **32**, 9280[2] (1938).

(6) Myers. *J. Hyg.*, **40**, 474 (1940).

(7) U. S. Patent 2,009,144, July 23, 1935.

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α- and γ-Picolinic Acid Hydrochlorides.—Oxidation of the corresponding picolines yielded the acids which were then isolated as the hydrochlorides.[8]

Ethyl Esters.—The ethyl esters of nicotinic, α-picolinic and γ-picolinic acids were prepared in yields ranging from 78–85% according to a procedure described by LaForge[9] for the preparation of ethyl nicotinate.

Ethyl quinoline-3-carboxylate was prepared by a series of reactions consisting of the bromination of quinoline hydrobromide,[10] formation of the nitrile with cuprous cyanide,[11] subsequent hydrolysis with 70% sulfuric acid[10] and esterification according to the method used by LaForge.[9] A 55% yield of the ethyl ester based on 3-bromoquinoline was obtained.

Pyrazine-2,3-dicarboxylic Acid.—The acid was prepared by the oxidation of quinoxaline according to directions given by Gabriel and Sonn.[12]

Quinoxaline.—In the preparation of quinoxaline, it was found necessary to use a dilute solution of *o*-phenylenediamine and glyoxal bisulfite; otherwise, polymeric substances formed and little if any of the product was obtained. Since the method[12] for the preparation of quinoxaline is vague, we are including the procedure we used.

In a one-liter erlenmeyer flask containing 400 ml. of water at 70°, was placed 27.0 g. (0.25 mole) of *o*-phenylenediamine. A solution of 68.8 g. (0.26 mole) of glyoxal bisulfite in 300 ml. of water heated to 70° was then added with shaking. The shaking was continued for five minutes after completion of the mixing. The solution was allowed to cool to approximately 40° and 100 g. of potassium carbonate added. The quinoxaline separated and was extracted with 100 ml. and three 50-ml. portions of ether. The ether extracts were combined, dried over anhydrous sodium sulfate and distilled. Yields from 29.6 to 30.5 g. of product (90.8–93.5% of theoretical) boiling at 112–115° (17 mm.) were obtained.

Benzyl Nicotinamide.—In a 200-ml. erlenmeyer flask, connected by ground glass joints to a calibrated water trap, in turn attached to a reflux condenser, were placed 12.3 g. (0.10 mole) of nicotinic acid and 10.7 g. (0.10 mole) of benzylamine. The mixture was heated gently until it became homogeneous. Seventy-five ml. of anhydrous xylene was added and the mixture refluxed for one hundred and fifty hours in an oil-bath kept at 165–170°. At the end of this time, 1.95 ml. of water was found in the trap (1.80 ml.—theoretical amount). On cooling, the product formed pure white crystals. A yield of 19.7 g. (93.0% of theoretical) of product, m. p. 72–73°, was obtained.

***n*-Amyl-α-picolinamide.**—In a 250-ml. round-bottomed flask fitted with a reflux condenser were placed 15.1 g. (0.10 mole) of ethyl α-picolinate and 17.4 g. (0.20 mole) of *n*-amylamine. The mixture was heated in an oil-bath maintained at 125° for twenty-five hours. Distillation *in vacuo* yielded 1.8 g. (11.9% recovery) of ethyl α-picolinate, 16.0 g. (83.3%) of product boiling at 135–136° (2 mm.) and 1.0 g. of residue.

(8) Weidel, *Ber.*, **12**, 1992 (1879); *Org. Syn.*, **20**, 79 (1940).
(9) LaForge, THIS JOURNAL, **50**, 2479 (1928).
(10) Claus and Collischonn, *Ber.*, **19**, 2763 (1886).
(11) Gilman and Spatz, THIS JOURNAL, **63**, 1553 (1941).
(12) Gabriel and Sonn, *Ber.*, **40**, 4850–4860 (1907).

Summary

1. Benzyl nicotinamide has been prepared and found to possess antispasmodic activity.

2. A series of fifteen other amides of nicotinic acid and related acids has been prepared and submitted for pharmacological testing.

BLOOMINGTON, INDIANA RECEIVED NOVEMBER 22, 1943

[CONTRIBUTION FROM THE FERMENTATION DIVISION, NORTHERN REGIONAL RESEARCH LABORATORY[1]]

Optical Isomers of 2,3-Butanediol Produced by Fermentation

BY GEORGE E. WARD, O. GLENN PETTIJOHN, LEWIS B. LOCKWOOD AND ROBERT D. COGHILL

In connection with fermentation studies conducted at this Laboratory on the production of 2,3-butanediol, some of the properties of the isolated products have been determined. *levo*-2,3-Butanediol, previously unknown in pure form and not recognized heretofore as a fermentation product, has been identified as the chief substance formed by the action of *Bacillus polymyxa* on grain mash substrates.

Previous reports concerning fermentation butanediol have stated it to be essentially optically inactive, the slight *dextro* rotation sometimes observed being attributed to the presence of a relatively small quantity of the *dextro* isomer. The butanediol produced by Harden and Walpole,[2] the first investigators in the field, was examined by Walpole[3] and was reported to be essentially a mixture of two optically inactive glycols. This product had resulted from the action of *Bacterium lactis aerogenes* (*Aerobacter aerogenes*) on glucose. The butanediol prepared by Kluyver's process,[4] presumably using *Aerobacter aerogenes*, was investigated by Böeseken and Cohen[5] and found to have a specific rotation of +2.42° and a melting point of +25°. Attempts at resolution were unsuccessful. These data suggested that the principal constituent was *meso*-2,3-butanediol and that a small quantity of the *dextro*-rotatory isomer was also present.

During the past three years we have conducted numerous fermentations with *Aerobacter aerogenes*. The 2,3-butanediol isolated *en masse* from such liquors has consistently had a specific rotation of approximately +1.0° and has shown a tendency to crystallize at room temperatures. These observations are in essential agreement with the data presented by Böeseken and Cohen. The discrepancy in specific rotation is not especially significant, since we have observed that appreciable fractionation occurs during distillation of the glycol. Unless a quantity of glycol is distilled *in toto*, the rotation exhibited by any

(1) The Northern Regional Research Laboratory is one of four regional laboratories operated by the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not subject to copyright.
(2) Harden and Walpole, *Proc. Roy. Soc.* (London), Series B, **77**, 399 (1906).
(3) Walpole, *ibid.*, Series B, **83**, 270 (1911).
(4) Kluyver and Scheffer, U. S. Patent 1,899,156.
(5) Böeseken and Cohen, *Rec. trav. chim.*, **47**, 839 (1928).

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given fraction may not be typical of that of the total product, the asymmetric isomers concentrating in the first fractions and the *meso* form appearing in the distillate in higher amounts toward the end of the distillation.

Besides studying the *Aerobacter* fermentation, we have investigated in some detail the fermentation of grain mashes by strains of *Bacillus polymyxa*. Although this species has long been known to produce 2,3-butanediol and acetylmethylcarbinol from starch, previous investigators have not reported differences between the butanediol of this origin and that formed by *Aerobacter* species. We have recently observed that the 2,3-butanediol produced by our preferred strain of *B. polymyxa* (N. R. R. L. No. B-510) differs markedly from the 2,3-butanediol produced by *Aerobacter aerogenes*, as shown in Table I.

TABLE I

	2,3-Butanediol isolated *en masse* from fermentation by	
	Bacillus polymyxa	*Aerobacter aerogenes*
Specific rotation (25°C.)	−13.0°	+1.0°
Melting point, °C.	+19	+25
Refractive index (25°C.)	1.4307	1.4384
Viscosity (25°C.), c. p.	41.0	118.0
Hydrate	None formed	Pentahydrate, m. p. +16.8°C.

Fractional distillation at 5 mm. pressure of butanediol possessing a specific rotation of approximately −13° has not yielded fractions of greater specific rotation than −13.19°, although such a procedure is effective in partially separating the *meso–dextro* mixture. It therefore seems probable that pure *levo*-2,3-butanediol has a specific rotation slightly in excess of −13.0°. It should be noted that we have not attempted resolution by procedures other than distillation, which would not separate the *dextro* and *levo* forms.

The highest specific rotation previously reported for optically active 2,3-butanediol was +6.9° for a sample of *dextro*-2,3-butanediol prepared from *dextro*-2,3-diaminobutane by Chappell.[6] There have been very few investigations of *levo*-2,3-butanediol. Neuberg and Nord[7] obtained small quantities of a substance possessing a specific rotation of −2.4° by the reducing action of yeast on diacetyl. Neuberg and Kobel[8] obtained an analogous preparation with a specific rotation of −5.51° by the action of yeast on acetylmethylcarbinol. In the light of our findings, it is apparent that these two products were composed principally of material other than *levo*-2,3-butanediol.

The fact that *levo*-2,3-butanediol does not form a hydrate is of importance in at least one of its possible applications, namely, as a constituent of antifreeze preparations. Freezing-point measurements of aqueous solutions show that whereas pure *meso*-butanediol with an equal weight of water forms a hydrate melting at +16.8°, the levorotatory isomer does not form such a hydrate, the freezing point depression decreasing regularly with increasing glycol concentration. *levo*-2,3-Butanediol appears to be approximately the equal of ethylene glycol in this respect.

Results are not yet at hand regarding the ability of other strains of *Bacillus polymyxa* to produce *levo*-2,3-butanediol. In view of the fact that the production of the *meso–dextro* mixture is characteristic of numerous strains of *Aerobacter*, it would not be surprising if many strains of *Bacillus polymyxa* will eventually be shown to be capable of producing the *levo* isomer.

Acknowledgment.—The authors gratefully acknowledge the determination of viscosity, freezing points of aqueous 2,3-butanediol systems, and fractional vacuum distillation observations by Drs. R. T. Milner, Duncan Macmillan, and N. C. Schieltz of the Analytical and Physical Chemical Division of this Laboratory. This work will be published in detail at a later date.

Summary

levo-2,3-Butanediol, possessing a specific rotation slightly in excess of −13.0°, has been isolated and identified as the chief substance formed by the action of *Bacillus polymyxa* (N. R. R. L. No. B-510) on grain mash substrates. This optical activity is far in excess of values previously ascribed to the asymmetric 2,3-butanediols.

In contrast to the *meso–dextro*-2,3-butanediol mixture produced in *Aerobacter aerogenes* fermentations, *levo*-2,3-butanediol possesses a relatively low viscosity and does not form a hydrate.

PEORIA, ILLINOIS RECEIVED JANUARY 12, 1944

(6) C. H. Chappell, "A Study of 2,3-Butylene Glycol and Its Derivatives," Thesis, 1935, Iowa State College, Ames, Iowa.

(7) Neuberg and Nord, *Ber.*, **52**, 2252 (1919).

(8) Neuberg and Kobel, *Biochem. Z.*, **160**, 250 (1925).

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY, AND THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Allylic Rearrangements. XV. The Carbonation of Butenylmagnesium Bromide

BY JOHN F. LANE, JOHN D. ROBERTS* AND WILLIAM G. YOUNG

In the course of independent investigations in these Laboratories, studies have been made of the products resulting from the carbonation of the Grignard reagent derived from crotyl and methylvinylcarbinyl bromides.

At the University of California, Los Angeles, this work was carried out as part of an extensive program of research on the nature of the allylic Grignard reagent and its reactions with a variety of substances. The approach, therefore, was one which gave detailed attention to all of the products formed in the reaction. On the other hand, certain studies now in progress at Princeton University on the reactions of the isomeric olefinic acids R—CH=CH—CH_2CO_2H(I), R—CH(CO_2H)—CH=CH_2(II), led to an investigation of the carbonation of allylic Grignard reagents with particular attention being focused on the acidic components of the reaction mixture, since it appeared that a convenient method of the synthesis for at least one and perhaps both of the isomerides I and II would be available if the reaction proved successful.

Previous attempts to obtain unsaturated monocarboxylic acids by carbonating allylic Grignard reagents have met with only moderate success. Thus Houben[1] was able to obtain but an 11% yield of 3-butenoic acid when magnesium was allowed to act on allyl bromide in an atmosphere of carbon dioxide. Using the same technique Gilman and Harris[2] obtained a similarly low yield of 2-phenyl-3-butenoic acid from cinnamyl chloride. Subsequent experiments by Gilman and co-workers[3] in which a stream of carbon dioxide was passed into a previously prepared solution of the Grignard reagent gave only slightly better results.

In the present work the Grignard reagent was prepared by the action of magnesium on a mixture of crotyl and methylvinylcarbinyl bromides and the carbonation was carried out by two different methods. (1) A dilute ethereal solution of the butenylmagnesium bromide was poured rapidly onto a large excess of solid carbon dioxide and, after decomposition of the complexes, alkaline extraction and careful fractionation a good yield (75%, based on the Grignard reagent) of practically pure 2-methyl-3-butenoic acid was obtained. The acid, b. p. 95.5° (35 mm.), was converted to its chloride, b. p. 55–58° (110 mm.), and thence to the crystalline amide, m. p. 98°. Catalytic hydrogenation of the latter compound gave 2-methylbutanoamide, m. p. 110°.

(2) The carbonation of butenylmagnesium bromide by the procedure of Arnold[4] followed by decomposition of the complexes gave on direct fractionation of the ethereal layer (without alkaline extraction) 2-methyl-3-butenoic acid (63%), b. p. 94° (30 mm.). Other fractions consisted of lesser amounts of octadienes, b. p. 52–53° (100 mm.), a dibutenyl ketone (13%), b. p. 93–94° (100 mm.), and a high boiling residue, b. p. 100–115° (30 mm.), which may be alcoholic material. The principal fraction, as well as the intermediates containing acidic substances, gave α-phenylethylamine salts,[5] all of which melted at 118–120° without recrystallization. The structure of the acid was confirmed by isomerization with strong alkali to 2-methyl-2-butenoic acid (tiglic acid), m. p. 64°, and by hydrogenation to 2-methylbutanoic acid; anilide, m. p. 109°. The structures of the other products have not yet been elucidated.

These results using butenylmagnesium bromide show that the carbonation of an allylic Grignard reagent may give good yields of acids provided that a large excess of carbon dioxide and a low reaction temperature are used. It is also to be noted that such reactions apparently lead exclusively to acids of type II rather than I. Not only in the present studies, but also in the experiments of Gilman and Harris,[2,3a] no appreciable amounts of the latter type of acid were formed.

Experimental Part

Materials.—The mixture of butenyl bromides used in these experiments was prepared by the method of Claisen and Tietze[6] from a mixture of crotyl alcohol and methylvinylcarbinol purchased from the Shell Chemical Company. The butenyl bromide mixture boiled at 90–105° (39–51° (100 mm.)) and had $n^{20}D$ 1.4781 corresponding to the composition 80% crotyl bromide, 20% methylvinylcarbinyl bromide.[7] Magnesium turnings were prepared as needed from bars of the pure metal.

A. Action of Carbon Dioxide on Butenylmagnesium Bromide (J. F. L.).—A dilute ethereal solution of the Grignard reagent was prepared from the butenyl bromide (67.5 g., 0.5 mole) according to the procedure of Young, Prater and Winstein.[8] The yield of Grignard reagent was 82% (estimated by titration of an aliquot portion with standard hydrochloric acid). This solution (555 cc.) was poured rapidly onto 400 g. of solid carbon dioxide broken into small lumps. After the excess of solid carbon dioxide had evaporated, the mixture was treated with ice and concentrated hydrochloric acid (75 cc.) to decompose the

(*) Abbott Laboratories Research Fellow 1943–44.

(1) Houben, *Ber.*, **36**, 2897 (1903).

(2) Gilman and Harris, THIS JOURNAL, **49**, 1825 (1927).

(3) (a) Gilman and Harris, *ibid.*, **53**, 3541 (1931); (b) Gilman and McGlumphy, *Bull. soc. chim.*, **43**, 1322 (1928).

(4) Arnold, Bank and Liggett, THIS JOURNAL, **63**, 3444 (1941).

(5) Buehler, Carson and Edds, *ibid.*, **57**, 2181 (1935).

(6) Claisen and Tietze, *Ber.*, **59**, 2344 (1926).

(7) *Cf.* Winstein and Young, THIS JOURNAL, **58**, 104 (1936).

(8) Young, Prater and Winstein, *ibid.*, **55**, 4908 (1933).

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magnesium complex. The ethereal layer was then removed and the aqueous residue saturated with salt and extracted three times with ether, these extracts being united with the original ethereal solution of the product. The resulting solution was extracted three times with 100-cc. portions of 10% sodium carbonate solution. The united carbonate extracts were washed with ether, acidified with concentrated hydrochloric acid, saturated with salt, and extracted four times with ether. The united ethereal extracts were dried over anhydrous sodium sulfate. Removal of the ether by distillation gave 33 g. of the crude organic acid.

The crude product (65 g.) obtained from two such runs was freed from a small amount of residual water by mixing it with 100 cc. of benzene and removing the benzene by distillation at 100 mm. The residue from this treatment was subjected to fractionation at 35 mm. through a 1-m. column packed with Fenske spirals. Fractions were collected as follows

1	94.5°	1.5 g.	$n^{25}D$	1.4213
2	95.5°	52.0 g.	$n^{25}D$	1.4210
Holdup		9.0 g.		

The holdup was distilled from a small Claisen flask at 17 mm. The bulk of the material (6.2 g.) distilled at 80.5° and had $n^{25}D$ 1.4210. The remainder distilled at 80.5–90° and had $n^{25}D$ 1.4230. If the impurity in this fraction was 3-pentenoic acid, b. p. 93° (14 mm.), $n^{25}D$ 1.4346,[9] the amount present could not be more than 0.34 g. (13% of this fraction) or 0.5% of the total amount of the product obtained. Titration of the acid in aqueous solution gave the values 100.3, 100.5 for the equivalent weight (calcd. for $C_4H_8O_2$, 100.1).

The acid (8 g.) was warmed on the water-bath for twenty minutes with 10 g. of phosphorus trichloride. At the end of this time the upper layer of crude acid chloride was decanted into a small Claisen flask and distilled under reduced pressure. The bulk of the material (7 g.) distilled at 55-58° (110 mm.).

The acid chloride so prepared was taken up in 100 cc. of absolute ether, and ammonia gas was passed into the solution for one-half hour. The precipitated ammonium chloride was removed by filtration and the solution evaporated to dryness. The amide so obtained was purified by recrystallization from a mixture of benzene and petroleum ether, 5.0 g., m. p. 98°.

Anal. Calcd. for C_5H_9ON: N, 14.13. Found: N, 13.8.

The amide (1.0 g.) was dissolved in 25 cc. of alcohol and hydrogenated over 0.05 g. of Adams catalyst. The uptake of hydrogen was rapid and ceased after twenty minutes (98%). The catalyst was removed by filtration and the solution evaporated to dryness under diminished pressure. The crystalline residue melted at 110°, and the melting point was not depressed on admixture with an authentic specimen of 2-methylbutanoamide, m. p. 110°.

B. Action of Carbon Dioxide on Butenylmagnesium Bromide (J. D. R.).—The Grignard reagent (0.91 mole) was prepared as previously reported[8] in 84% yield[10] from butenyl bromide, magnesium turnings and dry ether in the relative mole quantities 1, 3 and 12, respectively. Of this 0.32 mole was carbonated smoothly by the procedure of Arnold[4] over a period of two hours.

The magnesium complexes were decomposed by ice and saturated ammonium chloride, the mixture acidified with dilute hydrochloric acid and the resulting ethereal layer of the products dried over magnesium sulfate. After evaporating the bulk of the ether, fractionation through a 70-cm. column[11] packed with small glass helices gave the following cuts:

Fraction	B. p., °C.	Press., mm.	Wt., g.	$n^{20}D$
1	34– 35	753	5.2	....
2	46– 52	100	0.8	1.4232
3	52– 53	100	2.1	1.4239
4–6	53– 85	100	2.2	1.4253–1.4351
7	93– 94	100	1.8	1.4371
8–11	94–118	100	2.7	1.4388–1.4352
12–13	118–119	100	7.54	1.4251–1.4235
14	94	30	8.1	1.4226
15–16	94–115	30	4.69	1.4390–1.4625

Residue 1.5 g.

Fraction 1 is diethyl ether and Fractions 2–6 consist mainly of octadienes formed by the coupling of the butenylmagnesium bromide with butenyl bromide. Except for carbon–hydrogen analysis on Fraction 3, these were not further investigated.

Anal. Calcd. for C_8H_{14}: C, 87.19; H, 12.80. Found: C, 85.69; H, 12.85.

Fraction 7 gave a positive test with 2,4-dinitrophenylhydrazine reagent and the analysis indicated that the material was a dibutenyl ketone.

Anal. Calcd. for $C_9H_{14}O$: C, 78.21; H, 10.21. Found: C, 77.23; H, 10.10.

Fractions 11, 14 and 16, but not Fraction 7, gave nicely crystalline α-phenylethylamine salts[5] which without recrystallization melted from 118–120°. A sample crystallized from ethyl acetate for analysis showed m. p. 119.5–120.5°.

Anal. Calcd. for $C_{13}H_{19}O_2N$: C, 70.55; H, 9.11. Found: C, 70.22; H, 8.78.

The structure of the acid (Fraction 14) was confirmed in the following ways.

(1) Hydrogenation of a 2.13-g. sample over platinum oxide in ethyl acetate gave 2-methylbutanoic acid, b. p. 90–95° (35 mm.), $n^{20}D$ 1.4069; yield 1.9 g. (90%). Somewhat less than the theoretical amount of hydrogen was absorbed (83%). The saturated acid was identified by conversion to the anilide m. p. 109° (lit., 105.5–106.5°,[12a] 108°,[12b] 110–111°[12c]).

(2) A small sample of the acid was refluxed with 60% potassium hydroxide solution for ten minutes.[13] After dilution, acidification and purification of the product there was obtained tiglic acid, m. p. 64° (lit.,[14] 64°).

Anal. Calcd. for $C_5H_8O_2$ (2-methyl-3-butenoic acid): C, 59.98; H, 8.05; neut. eq., 100.1. Found: C, 59.35; H, 8.24; neut. eq., 104.2.

Investigation of the higher boiling material which is probably an alcoholic substance is in progress.

Summary

1. From the reaction of carbon dioxide with butenylmagnesium bromide 2-methyl-3-butenoic acid was obtained in excellent yield. No detectable amounts of the isomeric 3-pentenoic acid were isolated. Other non-acidic substances were formed in the reaction.

2. It is indicated that good yields of acids from carbonation of allylic Grignard reagents may be obtained by using a low reaction temperature and a large excess of carbon dioxide.

(9) Constants determined for a sample of pure 3-pentenoic acid prepared by the method of Linstead, Noble and Boorman, *J. Chem. Soc.*, 557 (1933).

(10) If very vigorous stirring is used, such as that afforded by a Model L "Lightning" mixer driving a large Hershberg stirrer, the time of addition may be cut to three hours or less without apparent diminution in the yield of Grignard reagent.

(11) Whitmore and Lux, THIS JOURNAL, 54, 3451 (1932).

(12) (a) Underwood and Gale, *ibid.*, 56, 2117 (1934); (b) Schwartz and Johnson, *ibid.*, 53, 1065 (1931); (c) Verkade, *Rec. trav. chim.*, 36, 204 (1916).

(13) *Cf.* Kon and Linstead, *J. Chem. Soc.*, 127, 616 (1925).

(14) Kamm, Collection and Buck, THIS JOURNAL, 51, 2528 (1929).

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3. The present results are in accord with those of Gilman and Harris, who isolated 2-phenyl-3-butenoic acid from the carbonation of cinnamylmagnesium chloride.

LOS ANGELES, CALIFORNIA RECEIVED NOVEMBER 15, 1943

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

Allylic Rearrangement in the Reaction of Cuprous Cyanide with Butenyl Halides[1]

BY JOHN F. LANE, JAMES FENTRESS AND L. T. SHERWOOD, JR.

That cuprous cyanide reacts smoothly with allyl halides to give good yields of 3-butenonitrile is well known.[2] Until the present time, however, the reaction has not been extended to α- and γ-substituted allyl halides; *i. e.*

$$R{-}CHX{-}CH{=}CH_2\ (I),\quad R{-}CH{=}CH{-}CH_2X\ (II)\qquad (X = Cl, Br)$$

In connection with studies being carried out in this Laboratory on the preparation and reactions of isomeric olefinic acids of the type

$$R{-}CH(CO_2H){-}CH{=}CH_2\ (III)$$
$$R{-}CH{=}CH{-}CH_2CO_2H\ (IV)$$

it seemed desirable to investigate the action of cuprous cyanide on a pair of allylic isomerides such as I and II in the hope of producing the nitriles

$$R{-}CH(CN){-}CH{=}CH_2\ (V)$$
$$R{-}CH{=}CH{-}CH_2CN\ (VI)$$

corresponding to the acids III and IV.

Replacement of halogen by cyanide in such a system might proceed either by normal (bimolecular) substitution to give the expected nitrile from each isomeride

$$(1)\quad R{-}CH{=}CH{-}CH_2X + CuCN \longrightarrow R{-}CH{=}CH{-}CH_2CN + CuX$$

or by an "ionic" mechanism

$$(2)\quad R{-}CH{=}CH{-}CH_2X \longrightarrow X^- + [R{-}CH{=}CH{=}CH_2]^+ \xrightarrow{CN^-} \begin{cases} R{-}CH{=}CH{-}CH_2CN \\ R{-}CH(CN){-}CH{=}CH_2 \end{cases}$$
(VII)

to give a mixture of the isomeric nitriles V and VI.[3] In the latter event the composition of the mixture obtained should be independent first of the isomeric halide (I or II) used, and second of the nature of X. There remains also the possibility that the replacement might proceed by an "inverse" (bimolecular) substitution process[3c] to give from each isomeric halide the nitrile corresponding to the other form

$$(3)\quad R{-}CH{=}CH{-}CH_2X + CuCN \longrightarrow R{-}CH(CN){-}CH{=}CH_2 + CuX$$

Of these three types of substitution process, all of which are known in reactions involving allylic systems, the process 2 is most frequently encountered, since the high resonance energy of ions such as VII greatly facilitates reaction by this path.

We have investigated the action of cuprous cyanide on the butenyl halides (R = CH_3, X = Cl, Br) and have found that at 60–70°, regardless of the nature of the halide used, the same mixture of isomeric nitriles is always produced

$$\left.\begin{matrix} CH_3{-}CH{=}CH{-}CH_2X + CuCN \\ CH_3{-}CHX{-}CH{=}CH_2 + CuCN \end{matrix}\right\rangle \begin{cases} CH_3{-}CH{=}CH{-}CH_2CN \\ CH_3{-}CH(CN){-}CH{=}CH_2 \end{cases} + CuX$$

After the two pure isomers had been isolated, it was possible to estimate the composition of this mixture by measurement of the refractive index. By this means we have determined that the mixture produced in each instance consisted of 91.5 ± 0.5% 3-pentenonitrile and 8.5 ± 0.5% 2-methyl-3-butenonitrile.

The simplest interpretation of these results is that the action of cuprous cyanide on halides such as I and II belongs to that class of allylic replacement reactions which are completely "ionic" in nature (mechanism 2 above). It has been pointed out,[3a] however, that assignment of such a mechanism may be most satisfactorily made only when the allylic reactants and products are not susceptible to thermal rearrangement under the conditions employed. While in the present investigation this requirement was fulfilled with respect to the products of the reaction, it could not be fulfilled with respect to the reacting halides. Even the butenyl chlorides, normally rather stable substances, are, under the conditions of the reaction (*i. e.*, at 60° in the presence of cuprous chloride), isomerized fairly rapidly to an equilibrium mixture containing 74.0 ± 0.5% 1-chloro-2-butene and 26.0 ± 0.5% 3-chloro-1-butene. The butenyl bromides, of course, are extremely labile substances which rearrange almost instantaneously at elevated temperatures to an equilibrium mixture containing 87% 1-bromo-2-butene and 13% 3-bromo-1-butene.[4]

(1) Abstracted in part from Senior Theses presented to the Faculty of Princeton University by James Fentress and L. T. Sherwood, Jr., in partial fulfilment of the requirements for the degree of Bachelor of Arts.

(2) Bruylants, *Bull. Soc. Chim. Belg.*, **31**, 175 (1922); Breckpot, *ibid.*, **39**, 465 (1930); Supniewski and Salzberg, *Org. Syn.*, Coll. Vol. I, 38 (1932).

(3) (a) Young and Lane, THIS JOURNAL, **60**, 847 (1938); (b) Roberts, Young and Winstein, *ibid.*, **64**, 2157 (1942); (c) Hughes, *Trans. Faraday Soc.*, **37**, 627 (1941).

(4) Winstein and Young, THIS JOURNAL, **58**, 104 (1936).

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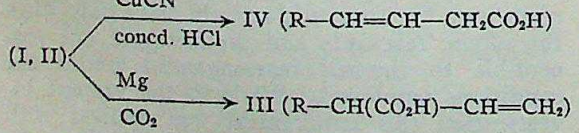
We feel, however, that an alternative mechanism presuming initial rearrangement of the butenyl halides followed by reaction of each isomer in normal fashion (mechanism 1 above) is improbable. It is scarcely possible that such normal reactions of the two isomeric halides present at equilibrium in each case could proceed at precisely those rates necessary to give the same mixture of nitriles regardless of whether the reactants were butenyl bromides or butenyl chlorides. We prefer to assume, therefore, that the composition of the nitrile mixture is governed entirely by the relative rates of coördination of the entering cyanide ion at positions 1 and 3 in the mesomeric carbonium ion

$$[CH_3—CH{=}{=}CH{=}{=}CH_2]^+ \quad (VII, R = CH_3)$$

We have also investigated the reaction of each of the two isomeric nitriles with concentrated hydrochloric acid according to the technique of Falaise and Frognier[5] for the preparation of 3-butenoic acid from 3-butenonitrile. It was found that while 3-pentenonitrile was readily converted to 3-pentenoic acid by this method, 2-methyl-3-butenonitrile was scarcely affected under the same conditions. Refluxing concentrated hydrochloric acid slowly attacked the latter nitrile to produce extensive charring but did not produce any appreciable amounts of the expected 2-methyl-3-butenoic acid.

From the results of this study it would appear that to derive an acid of type IV from either of the corresponding pair of halides (I, II) the proper procedure consists in treating the halides with cuprous cyanide and hydrolyzing the resulting nitrile with concentrated hydrochloric acid. On the other hand, the results previously reported[6] on the carbonation of butenylmagnesium bromide indicate that acids of type III will be exclusively produced when the corresponding halides (I, II) are converted to the Grignard reagent and the latter is treated with carbon dioxide. This may be summarized as follows



The general applicability of such methods to systems involving different alkyl and aryl groups R is being investigated.

Experimental Part

Materials.—1-Chloro-2-butene ($n^{20}D$ 1.4350), 2-chloro-1-butene ($n^{20}D$ 1.4150) and mixtures of these two butenyl chlorides were prepared by fractionation of a mixture containing approximately equal quantities of the two isomers which was purchased from the Shell Chemical Company. The composition of mixtures was determined before use in each instance by measurement of the refractive index. The mixture of butenyl bromides used in these experiments was prepared by the method of Claisen and Tietze[7] from a mixture of crotyl alcohol and methylvinylcarbinol purchased from the Shell Chemical Company. The cuprous cyanide employed in the preparation of nitriles was the Merck technical grade, dried for two hours at 110° before use. Cuprous chloride was prepared by the method of Marvel and McElvain,[8] washed successively with glacial acetic acid, alcohol, and ether, and dried in a vacuum desiccator over sulfuric acid before use.

Preparation of 3-Pentenonitrile and 2-Methyl-3-butenonitrile.—The method used was similar to that described by Bruylants, Breckpot and others[2] for the preparation of allyl cyanide from allyl halides. One hundred grams of a mixture of butenyl chlorides ($n^{20}D$ 1.4238: 56% 3-chloro-1-butene, 48% 1-chloro-2-butene) was mixed with dry cuprous cyanide (110 g.) in a flask equipped with a mechanical stirrer and an efficient reflux condenser protected by a calcium chloride tube. The mixture was heated on the water-bath with continuous stirring for one and one-half hours at 60–70°. The temperature of the bath was then increased to 95–100° for an additional half-hour in order to ensure complete reaction of the halide. The stirrer having been removed, the water-bath was replaced by an oil-bath, and at a bath temperature of 150–160° the volatile products were distilled under diminished pressure (200–100 mm.) into a trap immersed in an ice-salt bath. The crude product (70 g.) was dried over phosphorus pentoxide.

Fractionation of the product so obtained (200 g.) through a one meter column packed with glass helices, gave pure 3-pentenonitrile (133 g.); b. p. 146° (cor.); $n^{20}D$ 1.4228; d^{20}_4 0.8369[9]; M_D, calcd. 24.59, obs. 24.60, together with a low-boiling material, b. p. 120–143°. Systematic refractionation of this material gave pure 2-methyl-3-butenonitrile (22 g.); b. p. 126° (cor.); $n^{20}D$ 1.4063; d^{20}_4 0.8131; M_D, calcd. 24.59, obs. 24.57.

Anal. Calcd. for C_5H_7N: N, 17.26. Found: 3-pentenonitrile, N, 17.2, 2-methyl-3-butenonitrile, N, 17.5.

The identity of the low-boiling nitrile was further confirmed by preparation of an identical substance from 2-methyl-3-butenoamide[6] by dehydration with phosphorus pentoxide according to the technique of v. Auwers[9] for the preparation of 3-pentenonitrile from 3-pentenoamide. The nitrile so prepared boiled at 126° cor. and had $n^{20}D$ 1.4065; d^{20}_4 0.8131.

The refractive index of a mixture of the two nitriles was found to vary linearly with the composition. Mixtures of the two isomers could therefore be conveniently determined by measurement of this property.

TABLE I

REFRACTIVE INDICES OF MIXTURES OF 3-PENTENONITRILE AND 2-METHYL-3-BUTENONITRILE

Mixture	1	2	3
3-Pentenonitrile, %	30.0	50.0	74.0
2-Methyl-3-butenonitrile, %	70.0	50.0	26.0
$n^{20}D$ (calcd.)	1.4113	1.4146	1.4185
$n^{20}D$ (obs.)	1.4113	1.4146	1.4184

Action of Cuprous Cyanide on Different Butenyl Halides.—The procedure described above was repeated using (1) a mixture of butenyl chlorides (1 mole; $n^{20}D$ 1.4170) containing 90% 3-chloro-1-butene, 10% 1-chloro-2-butene; (2) pure 1-chloro-2-butene (1 mole, $n^{20}D$ 1.4350); (3) a mixture of butenyl bromides (⅔ mole, $n^{20}D$ 1.4781) containing 80% 1-bromo-2-butene, 20% 3-bromo-1-butene. These gave the following mixtures of nitriles: (1) 60 g., $n^{20}D$ 1.4215; (2) 58 g., $n^{20}D$ 1.4214; (3) 47 g., $n^{20}D$ 1.4212. The composition of the product in each instance was estimated first from the refractive index of the crude

(5) Falaise and Frognier, *Bull. soc. chim. belg.*, **42**, 427 (1933).

(6) Lane, Roberts and Young, THIS JOURNAL, **66**, 543 (1944).

(7) Claisen and Tietze, *Ber.*, **59**, 2344 (1926).

(8) Marvel and McElvain, "Org. Syn.," Coll. Vol. I, 163 (1932).

(9) V. Auwers, *et al.*, *Ann.*, **432**, 70 (1923), report $n^{20}He$ 1.4230; d^{20}_4 0.841 for this nitrile.

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mixture (method A) and then from the refractive indices and weights of the fractions obtained when the crude mixture was submitted to fractionation (method B). Thus, for mixture (1) the composition estimated by method A was 92.1% 3-pentenonitrile, 7.9% 2-methyl-3-butenonitrile, while fractionation gave the following results:

Fraction	Wt., g.	B. p. (755 mm.), °C.	$n^{20}D$	3-Pentenonitrile (g.)	2-Methyl-3-butenonitrile (g.)
(a)[10]	10.7	119–140	1.4154	5.91	4.79
(b)	1.8	140–141.5	1.4220	1.71	0.09
(c)	45.8	141.5	1.4228	45.8	.00
Total				53.4	4.88

from which the estimated percentage composition (method B) was 91.7% 3-pentenonitrile, 8.3% 2-methyl-3-butenonitrile. The residue (2 g.) was a viscous tarry material. The compositions of the three mixtures as estimated by both methods are given in Table II. Regardless of the

TABLE II

COMPOSITION OF THE NITRILE MIXTURE PRODUCED BY THE ACTION OF CUPROUS CYANIDE ON BUTENYL HALIDES

Mixture	$n^{20}D$ (crude)	Composition, % 3-Pentenonitrile A	3-Pentenonitrile B	2-Methyl-3-butenonitrile A	2-Methyl-3-butenonitrile B
(1)	1.4215	92.1	91.7	7.9	8.3
(2)	1.4214	91.5	91.2	8.5	8.8
(3)	1.4212	90.3	91.6	9.7	8.4
Av.	1.4214	91.3±0.6	91.5±0.2	8.7±0.6	8.5±0.2

butenyl halide used, the reaction leads to a mixture of nitriles having the composition 91.5 ± 0.5% 3-pentenonitrile, 8.5 ± 0.5% 2-methyl-3-butenonitrile.

Action of Cuprous Cyanide on the Isomeric Nitriles.—To 8 g. of a mixture of 3-pentenonitrile (44.3%) and 2-methylbutenonitrile (55.7%), $n^{20}D$ 1.4136, was added an equal weight of cuprous cyanide. The mixture was heated for three hours with frequent agitation on the boiling water-bath. At the end of this time the water-bath was replaced by an oil-bath, and at a temperature of 140–150° the nitriles were distilled completely into a trap cooled by an alcohol–dry-ice mixture. The last traces of volatile material were removed from the cuprous cyanide at a pressure of 20 mm. The refractive index of the nitrile mixture so obtained was $n^{20}D$ 1.4137, corresponding, within the experimental error of the measurement, to the same composition as that of the starting material. It may therefore be concluded that under conditions such as those employed in their synthesis and purification these nitriles are quite stable and show no tendency toward interconversion.

Action of Cuprous Chloride on the Butenyl Chlorides.—The butenyl chloride (30 g.) was stirred mechanically under reflux at 60° with an equal weight of cuprous chloride. Five-ml. samples were removed at intervals and transferred to a small distilling flask. The chloride was then distilled completely from the copper salt at a temperature of 30–35° and a pressure of 15 mm. into a trap cooled in an alcohol–dry-ice mixture. The composition of the purified sample was determined by measurement of the refractive index. The results are summarized in Table III. It is evident that an equilibrium mixture of the two chlorides having the composition crotyl chloride 74.0 ± 0.5%, methylvinylcarbinyl chloride 26.0 ± 0.5% is rapidly produced over cuprous chloride at this temperature.

Preparation of 3-Pentenoic Acid from 3-Pentenonitrile.—3-Pentenonitrile (81 g.) was treated

(10) Direct estimation of halogen by a slightly modified Volhard procedure, standardized against the pure butenyl halides, indicated that this fraction and the corresponding first fractions for mixtures (2) and (3) contained in each instance less than 0.2% unreacted butenyl chloride.

TABLE III

ISOMERIZATION OF BUTENYL CHLORIDES OVER CUPROUS CHLORIDE AT 60°

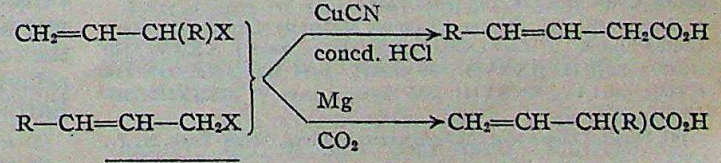
Expt.	Time, hr.	$n^{20}D$ of butenyl chloride mixture	Composition, % Crotyl chloride	Composition, % Methylvinylcarbinyl chloride
	0	1.4168	9.0	91.0
I	1.5	1.4298	74.0	26.0
	3.0	1.4299	74.5	25.5
	0	1.4331	90.5	9.5
II	1.0	1.4301	75.5	24.5
	2.0	1.4299	74.5	25.5
	3.0	1.4297	73.5	26.5

with concentrated hydrochloric acid (100 ml.) in the manner described by Falaise and Frognier[5] for the conversion of 3-butenonitrile to 3-butenoic acid. After twenty-five minutes the reaction mixture was diluted with water, saturated with salt and extracted four times with ether. The acid was obtained from the ethereal extract by alkaline extraction as previously described[6] for the isolation and purification of 2-methyl-3-butenoic acid. It distilled completely at 93° (14 mm.): m. p. −0.5°; $n^{20}D$ 1.4362; d^{20}_4 0.9876; M_D calcd. 26.36, obs., 26.50; eq. wt., calcd. 100.1, obs., 101. The melting point of the product was not depressed by admixture with 3-pentenoic acid prepared by the method of Linstead, Noble and Boorman.[11] When the acid was treated with bromine in carbon disulfide solution, the crystalline dibromide,[12] m. p. 64°, was obtained. The yield of pure acid was 70 g., 70% of the theoretical amount. This yield may be somewhat bettered when large quantities of the acid are to be prepared, since unreacted 3-pentenonitrile may then be profitably recovered from the neutral ethereal extracts of several runs and subjected again to hydrolysis in the manner described.

Attempted Hydrolysis of 2-Methyl-3-butenonitrile.—The experiment described above was repeated using 2-methyl-3-butenonitrile (10 g.) and 15 cc. of concentrated hydrochloric acid. On treatment of the reaction mixture by the purification methods described almost all of the nitrile was recovered in the neutral fraction (9 g.). The sodium carbonate extract was acidified and extracted with ether as before, but no appreciable amount of product was obtained on evaporation of this ethereal extract. When the nitrile (4 g.) was refluxed for one-half hour with concentrated hydrochloric acid, extensive charring took place. On working up the reaction mixture a neutral fraction of 3 g. was obtained. Less than 0.1 g. of acidic material was obtained by ether extraction of the acidified carbonate extract.

Summary

Cuprous cyanide acts on crotyl and methylvinylcarbinyl halides to produce a mixture of isomeric nitriles containing 91.5 ± 0.5% 3-pentenonitrile and 8.5 ± 0.5% 2-methyl-3-butenonitrile. It is suggested that this reaction belongs to that type of allylic replacement reaction which proceeds through a mesomeric carbonium ion.



(11) Linstead, Noble and Boorman, *J. Chem. Soc.*, 557 (1933).

(12) Thiele and Jehn, *Ber.*, **35**, 2320 (1902); Goldberg and Linstead, *J. Chem. Soc.*, 2343 (1928).

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It has been further shown that of the two isomeric nitriles produced by this reaction only 3-pentenonitrile is susceptible to acid hydrolysis.

These results and those of a previous study[6] on the carbonation of butenylmagnesium bromide indicate that either an α or γ-substituted butenoic acid may be prepared from either of a given pair of α- and γ-substituted allyl halides by an appropriate choice of method, as shown.

PRINCETON, NEW JERSEY RECEIVED OCTOBER 30, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NORTH CAROLINA]

Fish Poisons from *Ichthyomethia Piscipula*. I

BY ALFRED RUSSELL AND E. A. KACZKA[1]

Since the occurrence of toxic principles in various species in many genera of the family *Fabaceae* is well established and covered in several review articles,[2] it is unnecessary to give here a general survey of the field.

In connection with another study[3] there was collected on Key Largo, Florida, several hundred pounds of the roots, and wood, including bark, of the Jamaica dogwood. The powdered bark of the roots has been used extensively throughout tropical and subtropical America to narcotize fish but no exact information is available as to the nature of the toxic materials present.

The Jamaica dogwood has now been identified as *Ichthyomethia piscipula* (L) A. Hitchc. and it appears to be the same species as *Piscidia erythrina* L. Although six species in genus *Ichthyomethia* are stated[4] to occur in tropical and subtropical America, *I. piscipula* is the only member native to the United States.

E. Hart[5] separated, from a commercial liquid extract of *Piscidia erythrina*, a substance of m. p. 192° which he claimed was the toxic principle and named it piscidia. Freer and Clover[6] denied this, stating that Hart's product was not toxic and was not a chemical individual but a mixture of two distinct compounds, one melting at 201° and the other at 216°. They obtained a number of products from *Piscidia erythrina* "bark" by extraction with water and with petroleum ether. None of these was positively identified and apparently no toxicity tests were made since none was claimed to be toxic.

A drug known as "Cortex Piscidiae erythrinae," claimed to be an extract of the bark of *Piscidia erythrina*, was examined by Dankwortt and Schütte.[7] Ten assorted products were isolated by these workers and they came to the conclusion that the toxic principle was an amorphous saponin. Finally, Hauschild[8] made an examination of the bark of *Piscidia erythrina* and concluded that the toxic substance was a crystalline material m. p. 72° and not the saponin of Dankwortt and Schütte.

Obviously there is no way of correlating this earlier work since it appears that four different initial materials were used—root bark, tree bark, a commercial liquid extract and "Cortex Piscidiae erythrinae."

The physiological properties associated with *Piscidia erythrina* may be summarized: Ott[9] states that it is a direct sedative, producing narcotic effects that are refreshing and not followed, like those produced by opium, by hyperaemia of the brain, nausea and general nervous disturbance. It is claimed, also by Ott,[10] to be of value in treatment of bronchitis, asthma, nervous cough, writer's cramp, muscular spasms, chorea, tetanus and toothache. According to Reko[11] some quantity of *Piscidia erythrina* is included in "Sinicuichi"—a Mexican drink which causes rapid stupefaction. Drake and Spies[12] and Hauschild[8] report that an extract of the bark is toxic to goldfish.

In the present work, a few preliminary tests showed that the powdered root bark and root wood were very toxic to goldfish, two grams of either sprinkled into four liters of water producing death in a few minutes. Neither the powdered wood nor the powdered bark of the tree were noticeably toxic. Accordingly the work has been confined to a study of the extractives of the root bark and root wood.

Extraction of the ground bark with cold water followed by evaporation at low temperatures gave a large quantity (30% of the weight of the bark) of a dark colored resinous vitreous material. This extract was toxic to goldfish, the extracted bark was not. No satisfactory analytical separation of the components of aqueous extract could be achieved and the procedure was abandoned. Extractions with methanol, acetone and ethyl

(1) From a dissertation submitted to the Faculty of the University of North Carolina in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1943.

(2) H. King, *Ann. Rep.*, **29**, 186 (1932); LaForge, Haller and Smith, *Chem. Rev.*, **12**, 182 (1933), etc.

(3) Russell, *et al.*, "Natural Tanning Materials of the Southeastern United States," *J. Am. Leather Chem. Assoc.*, part I, XXXVI, 340 (1942); part II, XXXVIII, 30 (1943); part III, XXXVIII, 144 (1943); part IV, XXXVIII, 235 (1943); part V, XXXVIII, 355 (1943).

(4) Small, "Manual of the Southeastern Flora," New York, N. Y., 1933.

(5) E. Hart, *Am. Chem. J.*, **5**, 39 (1883).

(6) Freer and Clover, *ibid.*, **25**, 405 (1901).

(7) Dankwortt and Schütte, *Arch. Pharm.*, **272**, 201 (1934).

(8) Hauschild, *ibid.*, **274**, 388 (1936).

(9) Ott, *Detroit Lancet*, June, 1880.

(10) Ott, *Archives of Medicine*, February, 1881.

(11) Reko, *Pharm. Monatsh.*, **16**, 155 (1937).

(12) Drake and Spies, *J. Econ. Entomol.*, **25**, 129 (1932).

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acetate were similarly unsatisfactory. Finally it was found that prolonged extraction (Soxhlet) of the dried bark with petroleum ether (30–60°) removed all the toxic material with a small quantity of wax. The latter was easily removed from the dried petroleum ether extract by washing with ether. The ether washed residue formed a white crystalline mass. After this preliminary trial, the extraction was carried out on a much larger scale using a continuous type extractor handling about two kilos of bark at one time. The crystalline material was most easily separated by interrupting the extraction when much of the more soluble part had been removed (continued extraction gave the less soluble portion). Final purification was accomplished by repeated crystallizations from ethanol. Two pure compounds A and B were isolated.

The same two compounds occur to the same extent and in about the same proportion in the root wood. Extraction of the root wood by the same process as applied to the bark was, comparatively, very easy and the wood was used as the source of most of the toxic material examined.

Extraction of the root bark or root wood (Soxhlet) with chloroform gave some low-melting, wax-like material that had toxic properties. This product has not been further examined.

Both A and B are very toxic to goldfish, causing death in less than two hours at a dilution of about one part in a million. The compound A is identical with rotenone; the compound B is new and is, very likely, closely related to rotenone, its molecular formula is $C_{23}H_{20}O_7$ and it has been named "ichthynone."

Experimental

Qualitative Extractions of Root Bark and Root Wood of *I. piscipula* with Petroleum Ether.—I. Root bark: 50 g. of air dry bark (milled to the consistency of tea) was extracted in a large Soxhlet apparatus. The apparatus functioned about twenty times an hour and the bark was exhausted of toxic materials after twenty-four hours. The solvent was distilled and the residue collected—this was a pale yellow crystalline mass containing a little wax. The wax was removed by washing three times with 10-cc. portions of ether. The wax-free residue formed a white crystalline mass that was very toxic. The yield was 0.04 g.

II. Root wood: 50 g. of air-dry wood (chipped to about the size of rice) was extracted and treated as described for the bark. The yield of mixed crystalline, wax-free, toxic material was 0.039 g.

The large-scale extraction process was run fifteen times and a total of 18 g. of wax-free crystalline toxic material was obtained.

Separation of Rotenone.—The more soluble fraction, obtained when the extraction process was interrupted, was freed from traces of wax by washing with ether—the ether washed residue melted at 150–155°. After eight crystallizations from ethanol, a pure compound of m. p. 164° resulted. Its solubility in various solvents were in agreement with those recorded for rotenone and it gave a positive Durham test identical with that given by rotenone. *Anal.* Calcd. for $C_{23}H_{22}O_6$: C, 70.05; H, 5.58. Found: C, 70.08; H, 5.72. Mixed m. p. (with sample of authentic rotenone) was 163°.

Isolation of Icthynone.—The less soluble fraction obtained during the second extraction period was collected, freed from traces of wax by washing twice with 10-cc. portions of ether and crystallized four times from ethanol. A pure compound crystallizing in stout hexagonal rodlets was obtained m. p. 203–204°. *Anal.* Calcd. for $C_{23}H_{20}O_7$: C, 67.65; H, 4.92; mol. wt., 408. Found: C, 67.50; H, 5.07; C, 67.61; H, 5.14; C, 67.49; H, 5.09; mol. wt. 398, 416, 384, 390, av. 397. (The low solubility of ichthynone in all suitable solvents made it difficult to get consistent values for molecular weight. The above values were obtained by the boiling point method using chloroform as a solvent.)

Ichthynone is insoluble in water, acids or alkalies, very slightly soluble in petroleum ether, diethyl ether and acetone, and rather more soluble in ethanol, chloroform, and carbon tetrachloride. Ichthynone is optically inactive and is an unsaturated ketone containing two methoxyl groups. There is no evidence indicating the presence of either an alcoholic or a phenolic hydroxyl group. This distinguishes ichthynone from toxicarol, sumatrol and tephrosin since toxicarol and sumatrol are phenolic in character while tephrosin contains an alcoholic hydroxyl group that is easily removed by dehydration. However, all attempts to dehydrate ichthynone were unsuccessful. *Estimation of methoxyl:* Calcd. for $C_{21}H_{14}O_5(OCH_3)_2$: OCH_3, 15.2. Found: OCH_3, 15.1, 15.2, 15.8.

Estimation of Unsaturation: I. Ichthynone Dibromide.—0.25 g. ichthynone was dissolved in 26 cc. of carbon tetrachloride containing 0.12 g. of bromine and the solution refluxed for three hours. The carbon tetrachloride was evaporated, the white crystalline residue washed with a little ether and dried, m. p. 234–235°. *Anal.* Calcd. for $C_{23}H_{20}O_7Br_2$: Br, 28.2. Found: Br, 27.2. 26.0.

II. Tetrahydroichthynone.—1.00 g. of ichthynone, dissolved in 150 cc. ethyl acetate containing 0.1 g. of platinum black, was reduced (room temperature) in a low pressure (semi-micro) bomb (30 cm. pressure). After three hours no more hydrogen was taken up and the reduced product, which had precipitated, was collected, separated from the catalyst by dissolving in sufficient hot alcohol and filtering. On cooling tetrahydroichthynone separated in slender white needles, m. p. 233–234° after one recrystallization. *Anal.* Calcd. for $C_{23}H_{24}O_7$: C, 66.99; H, 5.82. Found: C, 67.30; H, 5.83.

Carbonyl Derivatives. I. Ichthynone Hydrazone.—0.20 g. of ichthynone and 0.20 g. of hydrazine hydrate were dissolved in 50 cc. of ethanol and 2 cc. of 0.1 *N* KOH added. The solution was refluxed for four hours, cooled and neutralized, whereupon the hydrazone crystallized. It was collected, washed with a little ethanol and crystallized twice from ethanol as pale yellow needles, m. p. 215–217°. *Anal.* Calcd. for $C_{23}H_{22}O_6N_2$: N, 6.63. Found: N, 6.70, 6.77.

II. Ichthynone Phenylhydrazone.—0.50 g. of ichthynone was dissolved in 100 cc. of ethanol and 5 cc. of phenylhydrazine, followed by 2.5 cc. of 0.2 *N* KOH, added. After refluxing for four hours the reaction mixture was cooled and neutralized. After standing for twelve hours the phenylhydrazone separated. Recrystallized twice from ethanol it formed brilliant yellow needles m. p. 195–200° (d.). *Anal.* Calcd. for $C_{29}H_{26}O_6N_2$: N, 5.62. Found: N, 5.76, 5.77.

Toxicity Tests on Goldfish.—0.001 g. of ichthynone dispersed (by dissolving in 1 cc. of acetone and then adding the solution to water) in 1000 cc. of water was fatal to goldfish in less than two hours. Ichthynone is, then, toxic to goldfish at a concentration of approximately one part in a million.

Summary

Extraction of the root bark or root wood of *Ichthyomethia piscipula* with petroleum ether gives a mixture of crystalline materials very toxic to goldfish.

Two pure compounds have been isolated, rotenone and a new compound "ichthynone." Ichthynone crystallizes difficultly from ethanol in sturdy hexagonal rodlets m. p. 203–204°. It

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has the molecular formula $C_{23}H_{20}O_7$ and is an unsaturated ketone containing two methoxyl groups.

Ichthynone kills goldfish at a concentration of, approximately, one part in a million.

CHAPEL HILL, N. C. RECEIVED NOVEMBER 29, 1943

[CONTRIBUTION NO. 330 FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF TEXAS]

The Nitrogen Compounds in Petroleum Distillates. XXV. Isolation and Identification of 3- and 4-Cyclopentylpyridines from California Petroleum

BY H. L. LOCHTE, E. D. THOMAS[1,2] AND PRICE TRUITT[3]

In a recent communication from this Laboratory[4] the chloroform extraction method of Bailey and co-workers[5] was extended to the hydrochlorides of petroleum bases boiling below the quinolines in the hope that, just as in the higher boiling range where the quinolines are found in the water layer and those of the substituted pyridines in the chloroform layer, so in the lower range the water layer might selectively dissolve the hydrochlorides of pyridines carrying cyclic substituents while the chloroform layer might hold the alkyl substituted pyridines. The chloroform layer was indeed found to contain alkyl substituted pyridines of which *dl*-2-(*s*-butyl)-4,5-dimethylpyridine was identified and several others isolated and analyzed.[4]

The water layer from the chloroform extraction of hydrochlorides of bases boiling at 210–213° reported in the previous communication[4] has been studied to determine what type of bases predominate.

Using a combination of fractionation by distillation and by fractional neutralization two isomeric cyclopentylpyridines were isolated. Since 2-cyclopentylpyridine is easily prepared by the interesting reaction of Emmert,[6] this compound was synthesized but it was found that neither of the petroleum compounds was identical with it.

Since one of the petroleum pyridines must then be the 3- and the other the 4-cyclopentylpyridine and since there was not enough pure base available to warrant a study of conditions required to obtain nicotinic or isonicotinic acids by oxidation, the synthesis of 3- and 4-substituted pyridines was studied. The new method of Crouch and Lochte[7] was finally used to prepare both 3- and 4-cyclopentylpyridines and thus show that the base yielding a picrate melting at 117.5° is 3-cyclopentylpyridine and the other one is the 4-cyclopentyl isomer.

Experimental

Fractional Distillation of Bases from Water Layer of Chloroform Extraction of 210–213° California Petroleum Bases.—Approximately three liters of bases were obtained from the water layer of the extraction reported in the previous paper.[4] These bases were distilled through a 12-foot Berl saddle-packed steel column at 20 mm. pressure using a 10:1 reflux ratio to yield 13 fractions of 240 cc. boiling at 207–219° with 9 fractions boiling between 212.5 and 214.0°. The index of refraction ranged from 1.502 to 1.516, that of the 9 fractions lay between 1.510 and 1.511, thus indicating that unsaturated or cyclic substituents might be expected.

Fractional Acid Extraction.—Fraction 6 (b. p. 213°; $n^{20}D$ 1.5102) was dissolved in 500 cc. of petroleum ether and extracted in the counter-current apparatus described in the previous paper,[4] Fig. 1, to yield 21 fractions with an average volume of 8 cc. and index of refraction, $n^{20}D$, ranging from 1.505 to 1.515.

Isolation of 3-Cyclopentylpyridine.—Since the index of refraction of the acid extraction fractions indicated that the alkyl substituted pyridines preceded those with cyclic side chain, fraction 19, with a volume of 25 cc. and $n^{20}D$ 1.5152, was selected to determine what type of substituents are present in the fractions with the high index of refraction. The base was dissolved in sulfurous acid and treated with picric acid. A crystalline picrate formed on standing in the ice-box. It melted at 117.5° after repeated recrystallizations from dilute ethanol and from 50% acetic acid. Additional amounts of the same picrate were obtained from fractions 17 and 18 of the same series.

Anal. Calcd. for $C_{16}H_{16}O_7N_4$: C, 51.06; H, 4.26; N, 14.89. Found: C, 50.97; H, 4.16; N, 15.03.

One gram of the picrate was heated with concentrated ammonium hydroxide to liberate the base which was extracted in benzene, dried and distilled in a semi-micro distillation apparatus. A middle fraction gave the following constants: b. p. 215.5° (747 mm.); $n^{20}D$ 1.5173.

Anal. Calcd. for $C_{10}H_{13}N$: N, 9.52. Found: N, 9.55.

Isolation of 4-Cyclopentylpyridine.—Fraction 21, volume 30 cc., $n^{20}D$ 1.5116, yielded a new crystalline picrate which after repeated recrystallizations from dilute ethanol and from 50% acetic acid melted at 145–146° but only a few grams of the pure crystalline picrate were obtained. Since this new base was isolated from the higher boiling fraction of fraction 6 of the distillation series it seemed probable that greater amounts could be isolated from a higher boiling fraction and fraction 11 was fractionally neutralized in the counter current column to yield 21 neutralization fractions. Fractions 10 through 12 yielded only oily picrates but 13 through 21 yielded larger amounts of a picrate melting at 145–146° and showing no depression when mixed with the previous picrate.

Anal. Calcd. for $C_{16}H_{16}O_7N_4$: C, 51.06; H, 4.26; N, 14.89. Found: C, 51.20; H, 4.45; N, 14.96.

One gram of the picrate was decomposed as before and fractionated, b. p. 218° (744 mm.); $n^{20}D$ 1.5167. Both of the cyclopentylpyridines were difficult to analyze, probably because of their tendency to take up moisture.

Anal. Calcd. for $C_{10}H_{13}N$: N, 9.52. Found: N, 9.30.

The chloroplatinate of this base crystallizes readily, forming orange needles decomposing at 225–227°.

(1) A part of this material was presented in partial fulfillment of requirements for the Master's Degree at the University of Texas by E. D. Thomas, 1942.

(2) Present address: Harvard Medical School.

(3) General Aniline Fellow, 1942–1944.

(4) Lochte, Crouch and Thomas, THIS JOURNAL, **64**, 2753 (1942).

(5) Perrin and Bailey, *ibid.*, **55**, 4136 (1933).

(6) Emmert and Pirot, *Ber.*, **74**, 714 (1941).

(7) Crouch and Lochte, THIS JOURNAL, **65**, 270 (1943).

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Anal. Calcd. for $(C_{10}H_{13}N)_2H_2PtCl_6$: Pt, 27.71. Found: Pt, 27.50.

Synthesis of 2-Cyclopentylpyridine

1-(2-Pyridyl)-cyclopentanol.—This compound was prepared by the method of Emmert and Pirot.[6] Into a three-necked flask fitted with stirrer, condenser, and dropping funnel was placed 155 g. of pyridine, 30 g. of aluminum turnings, and a crystal of iodine. Twenty-three grams of mercuric chloride dissolved in 154 g. of cyclopentanone was placed in the dropping funnel. A reaction started after about 10 cc. of this solution had been added to the flask and the remainder of the solution was now added, a few drops at a time, at such a rate as to keep the reaction mixture refluxing slowly. Finally the mixture was stirred for five hours on a steam-bath before the mixture was poured into cold dilute sodium hydroxide. The base was extracted with ether, dried over potassium hydroxide, and distilled at 5 mm. pressure. The material boiling at 130–140° was collected. It solidified on cooling and was recrystallized from petroleum ether; yield 30.5 g. of white solid melting at 83°.

Anal. Calcd. for $C_{10}H_{13}ON$: C, 73.63; H, 8.03. Found: C, 73.63; H, 8.26.

Dehydration of 1-(2-Pyridyl)-cyclopentanol.—Six cubic centimeters of concentrated sulfuric acid was added drop by drop to 2 g. of the cyclopentanol. This solution was heated for one hour on a steam-bath, poured on ice, neutralized with sodium hydroxide, and extracted with ether. The yield was practically quantitative; however, when this operation was repeated with 14 times these quantities, a viscous tar formed from which only 8 cc. of 1-(2-pyridyl)-cyclopentene-1 could be isolated. The cyclopentene readily decolorized 2% potassium permanganate. It boiled at 238–239° (748 mm.).

Hydrogenation of 1-(2-Pyridyl)-cyclopentene-1.—An acetic acid solution of the cyclopentene was hydrogenated at atmospheric pressure in six hours over Adams catalyst. The resulting base was dried over potassium hydroxide and fractionated, b. p. 217–218° (750 mm.), $n^{20}D$ 1.5205.

The picrate after recrystallization from dilute ethanol and from 50% acetic acid melted at 106.5°. A mixture of this picrate with the picrates of the two petroleum base cyclopentylpyridines melted below 100° thus showing that neither of these was 2-cyclopentylpyridine.

Anal. Calcd. for $C_{16}H_{16}O_7N_4$: C, 51.06; H, 4.26; N, 14.89. Found: C, 51.17; H, 4.36; N, 15.03.

Synthesis of 3-Cyclopentylpyridine

Diethyl 2-Cyclopentyl-2-(2-cyanoethyl)-malonate.—Following the general procedure of Bruson and Riener,[8] 19 g. of acrylonitrile was added to a stirred solution of 40 g. of cyclopentylmalonic ester,[9] 40 g. of dioxane, and 1.2 g. of sodium ethylate at 35–40°. The solution was stirred for one hour, the temperature raised to 50° for several hours or overnight with continued stirring. The reaction mixture was neutralized with 10% hydrochloric acid, and extracted with 100 cc. of benzene. The benzene layer was washed twice with 50-cc. portions of distilled water, and the benzene removed on a steam-bath. The residual oil was fractionated at 2 mm. pressure and 30 g. of the cyanoethylation product obtained, b. p. 162° at 2 mm., $n^{20}D$ 1.4612, d^{20}_4 1.0614.

Anal. Calcd. for $C_{15}H_{23}O_4N$: C, 64.03; H, 8.24; N, 4.98. Found: C, 64.02; H, 8.26; N, 4.94.

2-Cyclopentylglutaric Acid[10] (low melting form).—One hundred grams of the cyanoethylation product obtained as above was hydrolyzed by refluxing with 300 cc. of concentrated hydrochloric acid for twenty hours. The solution was evaporated on a steam-bath and the residue extracted with ether. The ether was evaporated off and the residue heated to 200° *in vacuo* until carbon dioxide ceased to be liberated. The sirupy material remaining was distilled at reduced pressure yielding 44 g. of the very viscous acid, b. p. 176–177° at 1.5 mm. pressure. The acid solidified on standing and was recrystallized from petroleum ether (b. p. 60–75°) to a constant melting point of 69°.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 60.03; H, 8.03.

Diethyl 2-Cyclopentyl-2-(ethyl-3-propionate)-malonate.—To a stirred solution of 90 g. (0.395 mole) of cyclopentylmalonic ester and 500 cc. of anhydrous xylene was added 8.5 g. (0.37 mole) of clean sodium and the mixture refluxed for three hours. A solution of 75 g. of ethyl 3-bromopropionate and 30 cc. of xylene was added slowly to the refluxing solution and the heating continued for fifteen hours. At the end of this time the solution was allowed to cool, 75 cc. of water added to dissolve the sodium bromide, and the aqueous layer removed. The xylene solution was washed twice with water and the xylene distilled under 40–50 mm. pressure. The residual liquid was fractionated at 2–3 mm. pressure. Sixty-seven grams of the tricarboxylic ester (72% conversion, with 25 g. of cyclopentylmalonic ester recovered) was obtained, b. p. 168–170° at 2.4 mm. pressure; $n^{20}D$ 1.4589; d^{20}_4 1.068.

Anal. Calcd. for $C_{17}H_{28}O_6$: C, 62.17; H, 8.59. Found: C, 62.13; H, 8.57.

2-Cyclopentylglutaric Acid (high melting form).—Sixty-seven grams of the tricarboxylic ester was hydrolyzed by refluxing with 500 cc. of 10% aqueous potassium hydroxide for forty-eight hours. Concentrated hydrochloric acid was added to neutralize the solution which was then evaporated to dryness on a steam-bath in a stream of air. The sodium chloride–organic acid residue was extracted twice with an ether–alcohol solution, the two extracts combined, and the solvents evaporated on a steam-bath. The sirupy product which remained evolved carbon dioxide on continued heating at 100°. When carbon dioxide ceased to be evolved the residue was dissolved in boiling benzene–petroleum ether and the acid allowed to crystallize out of the solution. After two recrystallizations from petroleum ether 30 g. of 2-cyclopentylglutaric acid, m. p. 152.5°, was obtained.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 59.84; H, 8.09.

2-Cyclopentylglutaryl Dichloride.—By a modification of Scheiber's[11] procedure 17 g. of the low melting cyclopentylglutaric acid was dissolved in 27.4 g. of thionyl chloride. The solution was warmed to 60° for three hours and finally refluxed for two hours. The excess thionyl chloride was removed under vacuum and the residual oil fractionated at 4–5 mm. pressure. Twenty grams (90%) of the dichloride was obtained, b. p. 140–142° at 4.5 mm. pressure.

Anal. Calcd. for $C_{10}H_{14}O_2Cl_2$: Cl, 30.10. Found: Cl, 29.93.

2-Cyclopentylglutaryl Diamide.—Eight grams of the acid chloride was poured slowly into 50 cc. of concentrated ammonia and the crystals, which formed after standing in the ice-box overnight, were filtered off. Recrystallization from concentrated ammonia gave 2 g. of white crystals which melted at 174° with the evolution of ammonia.

Anal. Calcd. for $C_{10}H_{18}O_2N_2$: C, 60.60; H, 9.13; N, 14.13. Found: C, 60.48; H, 9.18; N, 14.19.

3-Cyclopentylglutarimide.—Two grams of the diamide was heated to 200° at 5 mm. pressure in a 10-cc. flask equipped with an internal condenser until the evolution of ammonia ceased. A charred mass remained in the flask but a white solid, m. p. 131°, collected on the condenser. Recrystallization from petroleum ether gave 0.5 g. of white flakes melting at 131°.

Anal. Calcd. for $C_{10}H_{15}O_2N$: N, 7.73. Found: N, 7.84.

Eight grams of the cyclopentylglutaric acid (high melting form) was converted to the anhydride by refluxing one

(8) Bruson and Riener, THIS JOURNAL, **65**, 23 (1943).

(9) Verwey, *Ber.*, **29**, 1996 (1896).

(10) Godchot and Taboury, *Compt. rend.*, **153**, 1011 (1911), oxidized 1-cyclopentyl-cyclopentanone-2 and obtained an oil which was identified as 2-cyclopentylglutaric acid merely by means of its copper salt.

(11) Scheiber, *Ber.*, **42**, 1322 (1909).

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hour with 12 g. of acetyl chloride, after which the excess acetyl chloride and acetic acid were distilled *in vacuo*. Dry ammonia was passed into the residue at 130–140° for one hour and the product heated to 210° to form the imide which was then purified by recrystallization from benzene and petroleum ether. Four grams of the fine white flakes, m. p. 131°, was obtained. A mixture of this imide and that obtained from the diamide of the low melting cyclopentylglutaric acid showed no depression of melting point, thus showing the two imides to be identical.

Anal. Calcd. for $C_{10}H_{15}O_2N$: N, 7.73. Found: N, 7.85, 7.81.

2,5,6-Trichloro-3-cyclopentylpyridine.—By a modification of the procedure of Crouch and Lochte[7] an intimate mixture of 1.8 g. of 3-cyclopentylglutarimide and 6.4 g. of phosphorus pentachloride was warmed slowly in a water-bath to 43° at which temperature a vigorous reaction began. When this initial reaction had subsided the mixture was heated to 100° for fifteen minutes and the viscous liquid poured into shallow dishes and allowed to evaporate in a hood. The crystals, which soon formed, were washed into a beaker with ice-water, filtered off, and recrystallized from dilute ethanol and dilute acetic acid. Three grams of the trichloride was obtained, m. p. 141°.

Anal. Calcd. for $C_{10}H_{10}NCl_3$: N, 5.59; Cl, 42.46. Found: N, 5.62; Cl, 42.31.

3-Cyclopentylpyridine.—A methanol solution of 1.3 g. of the trichlorocyclopentylpyridine was reduced using hydrogen at 20 pounds pressure over palladium–charcoal[12] catalyst. Ninety-five per cent. of the calculated quantity of hydrogen was absorbed in four hours. The solution was now filtered, concentrated, and 15 cc. of 20% sodium hydroxide solution added. The oil, which immediately separated, was extracted with ether, separated from the aqueous layer, and the ether evaporated. The free pyridine base was dissolved in sulfurous acid solution and 1.5 g. of picric acid in a saturated aqueous solution was added. The picrate separated as an oil which crystallized on standing in the ice-box. After alternate recrystallizations from dilute acetic acid and dilute ethanol it melted at 118.7°.

Anal. Calcd. for $C_{10}H_{13}N \cdot C_6H_3O_7N_3$: C, 51.06; H, 4.26; N, 14.89. Found: C, 50.98, 51.03; H, 4.32, 4.24; N, 15.00, 14.97.

The picrate showed no depression in melting point when mixed with the petroleum base picrate melting at 117.5°, but did show a depression when mixed with the picrate of the isomeric petroleum base.

Synthesis of 4-Cyclopentylpyridine

Cyclopentyl Aldehyde.—Cyclopentyl aldehyde was prepared by the action of magnesium bromide etherate on cyclohexene oxide according to the procedure of Clemo and Ormston.[13] One hundred and twenty grams of cyclohexene oxide gave 9 g. of cyclopentyl aldehyde, b. p. 136°, $n^{20}D$ 1.4432. Clemo and Ormston give the boiling point as 135°.

3-Cyclopentyl-2,4-dicyanoglutaryl Diamide.—Following the general procedure of Day and Thorpe,[14] 15.4 g. of recrystallized cyanoacetamide was dissolved in 75 cc. of water, 9 g. of cyclopentyl aldehyde added, the solution clarified by adding 35 cc. of alcohol, then 0.2 cc. of 50% potassium hydroxide added. The solution was shaken vigorously for a few minutes and allowed to stand for two days at room temperature. The white solid which separated was removed by filtration. After two recrystallizations from 95% alcohol 4 g. of a white powdery substance was obtained, m. p. 213° (effervescence).

Anal. Calcd. for $C_{12}H_{16}O_2N_4$: C, 58.22; H, 6.51; N, 22.62. Found: C, 58.00; H, 6.55; N, 22.62, 22.55.

3-Cyclopentylglutaric Acid.—To 3.3 g. of 3-cyclopentyl-2,4-dicyanoglutaryl diamide was added 8 cc. of concentrated hydrochloric acid and the mixture heated until the solid dissolved. Eight cubic centimeters of water was added and the solution refluxed for five hours. The mixture was allowed to cool and the acid extracted with 50 cc. of ether. After evaporating off the ether, the acid was recrystallized twice from petroleum ether to give 1.7 g. of 3-cyclopentylglutaric acid, m. p. 111.5°.

Anal. Calcd. for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 59.82; H, 8.09.

4-Cyclopentylpyridine.—One and one-half grams of 3-cyclopentylglutaric acid was refluxed with 5 g. of acetyl chloride for one hour, the acetic acid and excess acetyl chloride were distilled under vacuum, and dry ammonia passed into the anhydride at 130° for one hour. The product was heated to 210–230° for fifteen minutes to form the imide which was extracted with benzene. This extract gave 1 g. (damp weight) of the imide which was subsequently treated with phosphorus pentachloride to give the corresponding trichloropyridine as before.

The trichloro compound was hydrogenated in methanol–hydrogen chloride solution over palladium chloride–charcoal catalyst.[12] The resulting cyclopentylpyridine was removed as before and the picrate prepared. After several recrystallizations from water the melting point was constant at 146°. The picrate showed no depression in the melting point when mixed with the petroleum base picrate melting at 145°, but did show a depression when mixed with the picrate of the isomeric petroleum base.

Summary

1. In an extension of a study of California petroleum bases boiling in the 210–213° range, 3-cyclopentyl- and 4-cyclopentylpyridine have been isolated and identified.

2. 2-, 3- and 4-cyclopentylpyridine have been synthesized and characterized.

AUSTIN, TEXAS RECEIVED DECEMBER 8, 1943

(12) Stevens, Beutel and Chamberlin, THIS JOURNAL, **64**, 1095 (1942).

(13) Clemo and Ormston, *J. Chem. Soc.*, 362 (1933).

(14) Day and Thorpe, *J. Chem. Soc.*, **117**, 1465 (1920).

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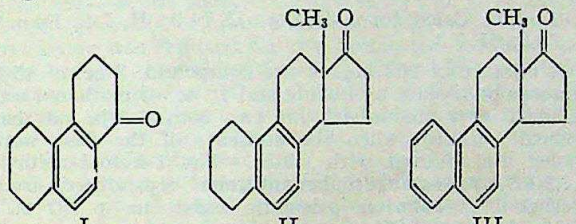
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

The Synthesis of Compounds Related to the Sex Hormones

BY W. E. BACHMANN AND R. D. MORIN[1]

From 1-keto-*sym*-octahydrophenanthrene (I), the *cis* and *trans* forms of 1,2,3,4-tetrahydro-17-equilenone[2] (II), an isomer of desoxyestrone, were prepared by the method employed for the synthesis of equilenin[3] and related compounds. Since the configurations of the two forms of II (m. p. 72–73° and 114–115°) are not known, they are designated by the prefixes α and β. The structures of the two forms were established by dehydrogenation. When heated with sulfur the α-form

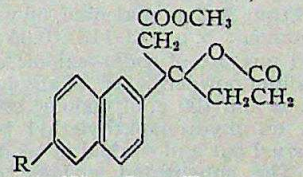


I II III

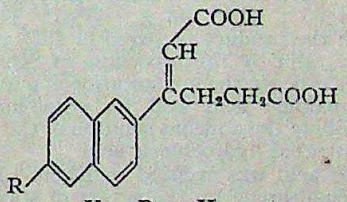
of II gave the α-form of 17-equilenone[2] (III) and the β-form yielded the β-form of 17-equilenone. These reactions relate the configurations of the compounds in the two series. The new compounds should prove useful in studies of the sex hormones and compounds derivable from neoergosterol. Marker and Rohrmann[3a] prepared one of the optically active forms (m. p. 107–109°) of II from equilenin.

A number of 3-arylcyclopentenones and 3-arylcyclopentanones were synthesized from the β-3-aroylpropionic acids. In the synthesis of VIc, the methyl ester of β-6-methoxy-2-naphthoylpropionic acid was treated with zinc and methyl bromoacetate to yield the lactone (IVb) of the Reformatsky ester. When the lactone was hydrolyzed by methanolic sodium hydroxide and a solution of the resulting sodium salt was acidified, the unsaturated dicarboxylic acid (Vb) was formed. The double bond is probably in the position indicated, for the acid is reduced readily by means of sodium amalgam and water. By cyclization of the dimethyl ester of this acid by means of sodium methoxide, followed by treatment of the product with a boiling mixture of acetic acid and hydrochloric acid, a mixture of 3-(6′-hydroxy-2′-naphthyl)-cyclopenten-2-one-1 (VIc) and its methyl ether (VIb) was obtained. 3-(6′-Hydroxy-2′-naphthyl)-cyclopentanone-1 was obtained by catalytic reduction of VIc and also by cyclization of the ester of the saturated dicarboxylic acid, obtained by reduction of Vb by means of sodium amalgam and water. Banerjee[4] prepared 3-(*p*-hydroxyphenyl)-cyclohexanone by a similar procedure.

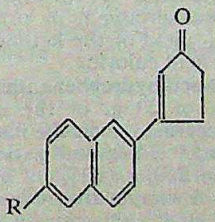
By a similar series of reactions 3-(2′-naphthyl)-cyclopenten-2-one-1 (VIa), 3-(2′-naphthyl)-cyclopentanone, 3-(5′,6′,7′,8′-tetrahydro-2′-naphthyl)-cyclopenten-2-one-1 (VII) and the corresponding cyclopentanone were prepared. By catalytic dehydrogenation, the tetralylcyclopentenone (VII) was converted to the naphthylcyclopentenone (VIa). VIa and the corresponding cyclopentanone had been prepared previously by Weidlich and Daniels by another method.[5] The 2-methyl derivatives, of VIa,[5] of VIc[6] and of the corresponding cyclopentanones have been prepared by other methods.



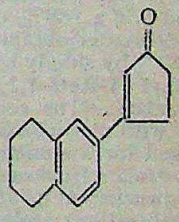
IVa R = H
IVb R = OCH_3



Va R = H
Vb R = OCH_3



VIa R = H
VIb R = OCH_3
VIc R = OH



VII

The ring structures of these compounds were confirmed completely by Wolf–Kishner reduction of VIa to 1-β-naphthylcyclopentene and of VIb to 1-(6′-methoxy-2′-naphthyl)-cyclopentene. Both of these reference compounds have been prepared previously by another method.[7]

Experimental

1-Keto-1,2,3,4,5,6,7,8-octahydrophenanthrene (I).—α-Naphthylamine (20 g.) was reduced by sodium and fusel oil by the procedure described for the β-isomer.[8] After all

(1) From the Ph. D. Dissertation of R. D. Morin.
(2) For the nomenclature of these compounds see Bachmann and Wilds, THIS JOURNAL, 62, 2084 (1940).
(3) Bachmann, Cole and Wilds, *ibid.*, 62, 824 (1940).
(3a) Marker and Rohrmann, *ibid.*, 61, 3314 (1939).
(4) Banerjee, *Science and Culture*, 5, 586 (1940).
(5) Weidlich and Daniels, *Ber.*, 72, 1590 (1939).
(6) Koebner and Robinson, *J. Chem. Soc.*, 566 (1941).
(7) Bachmann and Kloetzel, THIS JOURNAL, 60, 2204 (1938).
(8) Waser and Möllering, "Organic Syntheses," Coll. Vol. I, 1941, 2nd ed., p. 490.

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the sodium had reacted, the hot mixture was poured into water and after separation of the layers, the organic layer was acidified with hydrochloric acid. Six such runs were combined and concentrated by distillation until the *ar*-tetrahydro-α-naphthylamine hydrochloride began to crystallize from the hot solution. The cooled solution was filtered and the crystalline hydrochloride was washed several times with ether to remove colored impurities; the product obtained was sufficiently pure for the next step; yield, 131 g. (84%).

Diazotization and conversion to 1-iodo-5,6,7,8-tetrahydronaphthalene was carried out according to the directions for 1-iodo-6-methoxynaphthalene.[9] From 110 g. of *ar*-tetrahydro-α-naphthylamine, 102 g. (66%) of 1-iodo-5,6,7,8-tetrahydronaphthalene, b. p. 153–158° (20 mm.), was obtained.

The Grignard reagent of the iodotetralin was prepared and allowed to react with ethylene oxide according to the procedure described for *m*-iodoanisole.[10] From 51.6 g. of the 1-iodotetralin, 20 g. (57%) of β-(5,6,7,8)-tetrahydro-1-naphthylethyl alcohol was obtained as a viscous yellow oil; b. p. 125–135° (0.4 mm.).

Conversion of the alcohol to β-5,6,7,8-tetrahydro-1-naphthylethyl bromide by means of phosphorus tribromide was carried out in the same manner as described for a similar case.[3] From 35.2 g. of alcohol, 30 g. (62%) of the bromide was obtained; b. p. 113–118° (0.05 mm.).

To the cooled mixture of sodio-malonic ester obtained from 10 g. of sodium powder, 30 cc. of absolute alcohol, 25 cc. of dry benzene and 100 g. of malonic ester was added 71.7 g. of the tetrahydronaphthylethyl bromide. The reaction was carried out and worked up as described for a similar case.[3] The substituted malonic acid was decarboxylated at 180° to γ-5,6,7,8-tetrahydro-1-naphthylbutyric acid. After recrystallization from ligroin, the acid melted at 94–95°; yield, 42 g. (65%). The acid was identical with the product prepared in 45% yield from 1-chloroacetyltetralin by the procedure of Schroeter.[11] In one step of his process, the precipitation of a mixture of the substituted malonic acid and its potassium salt was avoided by adding the aqueous solution of the dipotassium salt to concentrated hydrochloric acid.

The butyric acid was cyclized to 1-keto-1,2,3,4,5,6,7,8-octahydrophenanthrene by the action of stannic chloride on the acid chloride according to the procedure described by Wilds[10] for γ-1-naphthylbutyric acid. From 21.8 g. of the acid 17.6 g. (88%) of ketone was obtained; m. p. 80.5–82°. Schroeter obtained an 80% yield of the ketone (m. p. 81–82°) by simply heating the acid chloride.

Methyl 1-Keto-1,2,3,4,5,6,7,8-octahydrophenanthrene-2-glyoxalate.—The condensation of 20 g. of the cyclic ketone with methyl oxalate was carried out in the manner described for a similar compound.[3] Recrystallization of the glyoxalate from methanol gave 25.5 g. (89%) of bright yellow prisms; m. p. 101–102°. A sample after two more recrystallizations melted at 103–104°. It gave a dark purple-brown color with alcoholic ferric chloride.

Anal.[12] Calcd. for $C_{17}H_{18}O_4$: C, 71.3; H, 6.3. Found: C, 71.4; H, 6.3.

1-Keto-2-carbomethoxy-1,2,3,4,5,6,7,8-octahydrophenanthrene.—Following the procedure described,[3] 10 g. of the glyoxalate and 5 g. of powdered soft glass were heated at 180° for exactly one-half hour. The product was separated from the glass with hot benzene and the benzene solution was washed with 2% aqueous sodium hydroxide to remove any unreacted glyoxalate. The product after recrystallization from methanol was suitable for the next step; yield, 7.95 g. (88%); m. p. 81–84°. A sample after three more recrystallizations formed stout colorless prisms which melted at 83–85°. It gave an immediate dark blue-green color with alcoholic ferric chloride.

Anal.[12] Calcd. for $C_{16}H_{18}O_3$: C, 74.4; H, 7.0. Found: C, 74.3; H, 7.1.

1-Keto-2-methyl-2-carbomethoxy-1,2,3,4,5,6,7,8-octahydrophenanthrene.—A solution of 10.32 g. (0.04 mole) of the aforementioned keto ester in 50 cc. of dry benzene was added to a solution of sodium methoxide prepared from 4.6 g. of sodium and 90 cc. of absolute methanol. After being warmed for one-half hour and then cooled, the mixture was treated with 14 cc. of methyl iodide and kept at room temperature until nearly all of the sodio derivative had disappeared. An additional 14 cc. of methyl iodide was added and within thirty minutes all of the solid had reacted. The product was isolated according to the procedure described[3] and recrystallized from methanol; yield, 9.42 g. (86%) of nearly colorless material sufficiently pure for the next step; m. p. 72–75°. A sample after two more recrystallizations formed colorless prisms which melted at 77–78°. It gave no color with alcoholic ferric chloride.

Anal.[12] Calcd. for $C_{17}H_{20}O_3$: C, 74.9; H, 7.4. Found: C, 74.3; H, 7.3.

A mixture of 262 mg. of the compound, 3 cc. of 45% aqueous potassium hydroxide and 10 cc. of methanol was refluxed on a steam-bath for two hours. The oil that formed solidified when the contents of the flask were cooled and diluted with water. The **1-keto-2-methyl-1,2,3,4,5,6,7,8-octahydrophenanthrene** crystallized from methanol in colorless prismatic rods; m. p. 87–88°; yield, 171 mg. (80%).

Anal.[12] Calcd. for $C_{15}H_{17}O$: C, 84.0; H, 8.5. Found: C, 83.6; H, 8.6.

Dimethyl Ester of 2-Methyl-2-carboxy-1-hydroxy-1,2,3,-4,5,6,7,8-octahydrophenanthrene-1-acetic Acid.—The Reformatsky reaction between the methyl keto ester (5.44 g.), zinc and methyl bromoacetate was carried out as described for a similar compound,[3] except that extremely vigorous stirring was employed. The product crystallized from methanol in stout colorless prisms; yield, 5.3–5.6 g. (76–81%); m. p. 100–101°. A sample after two more recrystallizations melted at 102–103°.

Anal.[12] Calcd. for $C_{20}H_{26}O_5$: C, 69.3; H, 7.6. Found: C, 69.5; H, 7.7.

When a mixture of 346 mg. of the Reformatsky ester, 3 cc. of 45% aqueous potassium hydroxide and 10 cc. of methanol was refluxed on a steam-bath for two hours, 150 mg. (after recrystallization from methanol) of 1-keto-2-methyl-1,2,3,4,5,6,7,8-octahydrophenanthrene; m. p. 87–88°, was obtained.

Conversion of the Reformatsky Ester to the Unsaturated Acids.—The hydroxy ester (1.52 g.) was converted to the chloride by means of thionyl chloride and pyridine and the product was treated with aqueous alcoholic potassium hydroxide in the manner described.[3] The **2-methyl-2-carboxy-1,2,3,4,5,6,7,8-octahydrophenanthrylidene-1-acetic acid** which precipitated on acidification of the aqueous solution of the potassium salt weighed 1.21 g. (92%); m. p. 137–140°. It crystallized from acetone–ligroin in colorless prisms; m. p. 140–141° with evolution of gas.

Anal. Calcd. for $C_{18}H_{20}O_4$: C, 72.0; H, 6.7. Found: C, 71.8; H, 6.7.

Preparation of α- and β-2-Methyl-2-carboxyl-1,2,3,4,5,-6,7,8-octahydrophenanthrene-1-acetic Acid.—Usually the Reformatsky ester (6.92 g.) was converted directly to the α- and β-reduced acids without isolation of the unsaturated acid. The aqueous solution of the potassium salts of the unsaturated acids was shaken vigorously for one-half hour with 150 g. of 2% sodium amalgam. The dried mixture of reduced acids (5.5–5.7 g.) was dissolved in a hot mixture of 20 cc. of acetic acid and 30 cc. of xylene. Without filtering, the solution was allowed to cool; 2.4–2.6 g. (40–43%) of the α acid crystallized; m. p. 208–211°. A sample crystallized from acetic acid in short stout colorless prisms; m. p. 218–219°.

By evaporation of the filtrate and recrystallization of the residue from benzene-ligroin 1.8–2.0 g. (46–50%) of the β acid

(9) Cohen, Cook, Hewett and Girard, *J. Chem. Soc.*, 653 (1934).

(10) Bachmann and Thomas, THIS JOURNAL, **64**, 95 (1942); see also Wilds, *ibid.*, **64**, 1424 (1942).

(11) Schroeter, *Ber.*, **57**, 2029 (1924).

(12) Microanalysis by T. S. Ma.

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was obtained; m. p. 160–161°. A sample of the β acid crystallized from ethyl acetate–ligroin in small colorless prisms; m. p. 162–163°.

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.5; H, 7.3. Found: (α-form) C, 71.4; H, 7.4; (β-form) C, 71.6; H, 7.4.

Dimethyl Ester of 2-Methyl-2-carboxy-1,2,3,4,5,6,7,8-octahydrophenanthrene-1-acetic Acid.—The α-form of this compound, prepared in 97% yield from the α-acid by means of diazomethane, crystallized from methanol in stout colorless prisms; m. p. 70–71.5°. A sample after one more recrystallization melted at 70.5–71°.

The **β-form**, prepared from 6.04 g. of the β-acid and diazomethane, crystallized from methanol in colorless prisms; yield, 6.07 g. (92%); m. p. 79–81°. After two more recrystallizations a sample melted at 81.5–82.5°.

Anal.[12] Calcd. for $C_{20}H_{26}O_4$: C, 72.7; H, 7.9. Found: (α-form) C, 73.0; H, 7.6; (β-form) C, 73.3; H, 7.8.

2-Methyl-2-carbomethoxy-1,2,3,4,5,6,7,8-octahydrophenanthrene-1-acetic Acid.—A mixture of 4.62 g. of the dimethyl ester, 100 cc. of methanol and 14.3 cc. of *N* sodium hydroxide was refluxed for two hours, the methanol was removed and the residue dissolved in about 25 cc. of warm water. About 3 cc. of ethyl acetate was added and the mixture was acidified. The acid ester, which gradually crystallized as the ethyl acetate evaporated, was sufficiently pure for the next step.

In this manner 4.21 g. (95%) of the α-form melting at 120–122° was obtained. A sample after two recrystallizations from acetone–ligroin formed colorless prisms; m. p. 121–122°.

The β-form was obtained in 98% yield; m. p. 136–139°. From ethyl acetate it crystallized in small colorless prisms melting at 141–142°.

Anal. Calcd. for $C_{19}H_{24}O_4$: C, 72.2; H, 7.6; neut. equiv., 316. Found: (α-form) C, 72.3; H, 7.7; neut. equiv., 317. (β-form) C, 72.0; H, 7.6; neut. equiv., 318.

Arndt–Eistert Reaction on the Acid Esters.—This was carried out on 1.58 g. of the acid esters as described for a similar compound.[3] The solution of the product obtained by the action of silver oxide on the diazoketone in methanol was filtered and evaporated, and the residue was evaporatively distilled at 180° (0.05 mm.).

The **dimethyl ester of α-2-methyl-2-carboxy-1,2,3,4,5,6,7,8-octahydrophenanthrene-1-β-propionic acid** crystallized from methanol in small colorless prisms; yield, 1.29 g. (75%); m. p. 63.5–64.5°.

Anal.[12] Calcd. for $C_{21}H_{28}O_4$: C, 73.2; H, 8.2. Found: (α-form) C, 73.0; H, 8.0.

The β-isomer, a pale yellow liquid, was used directly in the next step; yield, 1.59 g.

1,2,3,4-Tetrahydro-16-carbomethoxy-17-equilenone.—Cyclization of 1.38 g. of the aforementioned esters by sodium methoxide in benzene (ten hours of refluxing) was accomplished by the procedure described.[3]

The **α-form** crystallized from methanol in fine colorless needles; yield, 1.12 g. (90%); m. p. 124–124.5°. After two more recrystallizations a sample melted at 124–125°. The compound gave a dark green color with alcoholic ferric chloride.

By recrystallization from methanol the **β-form** was obtained as colorless prisms; yield, 1.08 g. (85%); m. p. 118–121°. After three recrystallizations a sample melted at 121–122°. The compound gave an immediate greenish-brown color with alcoholic ferric chloride.

Anal.[12] Calcd. for $C_{20}H_{24}O_3$: C, 76.9; H, 7.8. Found: (α-form) C, 76.8; H, 7.7; (β-form) C, 76.9; H, 8.1.

1,2,3,4-Tetrahydro-17-equilenone (II).—A mixture of 0.9 g. of the 16-carbomethoxy derivative, 45 cc. of acetic acid, 22 cc. of concentrated hydrochloric acid and 4 cc. of water was refluxed for two hours in an atmosphere of nitrogen. The residue remaining after removal of the solvents under reduced pressure was dissolved in benzene and washed with 2% aqueous sodium hydroxide. The benzene solution was concentrated and the residue was dissolved in hot methanol from which the product crystallized.

The α-form crystallized in stout colorless prisms; yield, 0.65 g. (88%); m. p. 72–73°. After evaporative distillation at 100° (0.05 mm.) and two recrystallizations from methanol it melted at the same temperature.

The β-form crystallized in small colorless prisms; yield, 0.60 g. (79%); m. p. 113–114°. After evaporative distillation at 110° (0.05 mm.) and two recrystallizations from methanol, it melted at 114–115° (vac.).

Anal.[12] Calcd. for $C_{18}H_{22}O$: C, 85.0; H, 8.6. Found: (α-form) C, 84.7; H, 8.3; (β-form) C, 84.4; H, 8.4.

The **semicarbazones** were prepared with semicarbazide hydrochloride in a mixture of absolute alcohol and pyridine. The **α-form** crystallized from alcohol in colorless prisms; m. p. 243–244°. The **β-form** was obtained in colorless prisms; m. p. 274–275° (vac.).

Anal. Calcd. for $C_{19}H_{25}ON_3$: N, 13.5. Found: (α-form) N, 13.3; (β-form) N, 13.4.

Dehydrogenation of 1,2,3,4-Tetrahydro-17-equilenone.—A mixture of 50 mg. of II and 15 mg. of sulfur was heated at 210° for two hours. The product was purified by sublimation at 100° (0.05 mm.) and recrystallization from methanol. The **α-form** gave 20 mg. of α-17-equilenone (41%) melting at 97–98.5°; when mixed with α-17-equilenone (III) (m. p. 100–101°)[2] it melted at 98–99°. The **β-form** gave 24 mg. (49%) of β-17-equilenone melting at 186–187.5° (vac.); when mixed with β-17-equilenone (m. p. 188.5–189.5°) it melted at 187–188.5° (vac.).

Lactone of the Monomethyl Ester of β-Hydroxy-β-(6-methoxy-2-naphthoyl)-adipic Acid (IVb).—β-Naphthyl methyl ether (158 g.) and 110 g. of succinic anhydride were brought into reaction according to the procedure of Short, Stromberg and Wiles.[13] Fractional crystallization of the mixture of isomeric acids from acetone gave 49 g. of β-(6-methoxy-2-naphthoyl)-propionic acid (m. p. 147–148°). Esterification of this acid by alcoholic hydrogen chloride yielded 52.5 g. of the ethyl ester (m. p. 107.5–108°). By esterification of the mixture of acids in the acetone mother liquor an additional 40 g. of the ethyl ester was obtained.

The Reformatsky reaction on the above keto ester (8.05 g.) was carried out in the manner previously described[3] except that vigorous stirring was employed; in working up the reaction mixture washing with ammonium hydroxide was omitted in order to avoid hydrolysis of the product. The lactone ester crystallized from methanol in yellowish prisms; yield, 8.02 g. (84%); m. p. 115–119°. This was sufficiently pure for the next step. A sample after evaporative distillation at 115° (0.05 mm.) crystallized from methanol in fine colorless prisms; m. p. 121–122°.

Anal.[12] Calcd. for $C_{18}H_{18}O_5$: C, 68.8; H, 5.8. Found: C, 69.2; H, 5.7.

3-(6′-Methoxy-2′-naphthyl)-2-hexendioic Acid (Vb).—A mixture of 12.4 g. of the above crude lactone ester, 300 cc. of methanol and 80 cc. of *N* sodium hydroxide was refluxed for three hours on a steam-bath. The methanol was removed in a current of air, some water was added to the residue, and this solution was filtered and acidified. The unsaturated acid which precipitated was filtered and dried; yield, 11.27 g. (98%); m. p. 194–195°. A sample crystallized from acetone–ligroin in small colorless prisms which melted at the same temperature.

Anal. Calcd. for $C_{17}H_{16}O_5$: C, 68.0; H, 5.3. Found: C, 68.2; H, 5.4.

3-(6′-Hydroxy-2′-naphthyl)-cyclopenten-2-one-1 (VIc).—Ethereal diazomethane was added to 4.2 g. of the above unsaturated acid to form the dimethyl ester. The product was an oil which was purified by evaporative distillation at 190° (0.05 mm.). Cyclization of 3.28 g. of the ester was accomplished by the procedure described[3] (twelve hours of refluxing). The cyclic keto ester crystallized from methanol as a light tan powder; yield, 2.36 g. (80%); m. p. 123–125°. A sample of the **3-(6′-methoxy-2′-naphthyl)-5-carbomethoxycyclopenten-2-one-1** after three more recrystallizations from methanol formed small colorless prisms; m. p. 125–126°.

(13) Short, Stromberg and Wiles, *J. Chem. Soc.*, 320 (1936).

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Anal. Calcd. for $C_{18}H_{16}O_4$: C, 73.0; H, 5.4. Found: C, 73.1; H, 5.5.

Two grams of the crude material was refluxed for ten hours with a mixture of 75 cc. of acetic acid, 37 cc. of concentrated hydrochloric acid and 7 cc. of water in an atmosphere of nitrogen. The cooled solution was poured into one liter of water. The crystalline product was filtered off, dissolved in 100 cc. of hot 2.5% aqueous potassium hydroxide and the solution was filtered from a small amount of the methyl ether. The **3-(6′-hydroxy-2′-naphthyl)-cyclopenten-2-one-1 (VIc)** obtained by acidification of the alkaline solution was purified by sublimation at 200° (0.05 mm.) and subsequent recrystallization from methanol; yield, 0.22 g. of small stout prisms; m. p. 252–253° (vac.) to red liquid. The m. p. was unchanged after two more recrystallizations.

Anal.[12] Calcd. for $C_{16}H_{12}O_2$: C, 80.3; H, 5.4. Found: C, 79.8; H, 5.4.

The **semicarbazone** melted at 260–262° (vac.).

Anal. Calcd. for $C_{16}H_{15}O_2N_3$: N, 14.9. Found: N, 15.1.

The **methyl ether (VIb)** after evaporative distillation at 190° (0.05 mm.) crystallized from methanol in fine needles; m. p. 169–170°.

Anal. Calcd. for $C_{16}H_{14}O_2$: C, 80.7; H, 5.9. Found: C, 80.4; H, 6.0.

The **semicarbazone of the methyl ether** melted at 250–251° (vac.).

Anal. Calcd. for $C_{17}H_{17}O_2N_3$: N, 14.2. Found: N, 14.0.

A mixture of 118 mg. of the semicarbazone and a solution of sodium methoxide prepared from 0.3 g. of sodium and 6 cc. of absolute alcohol was heated in a sealed tube at 180° for twenty hours. From the reaction mixture 34 mg. (37%) of 1-(6′-methoxy-2-naphthyl)-cyclopentene was obtained; m. p. 141–142°, alone and when mixed with an authentic specimen.[7]

3-(6′-Hydroxy-2′-naphthyl)-cyclopentanone.—A solution of 3.0 g. of the substituted hexendioic acid (Vb) in 1.75 cc. of 45% aqueous potassium hydroxide and 20 cc. of water was shaken with 75 g. of 2% sodium amalgam for one-half hour. The **β-(6-methoxy-2-naphthyl)-adipic acid** obtained by acidification of the filtered solution crystallized from acetone–ligroin in colorless prisms; yield, 3.01 g. (99%); m. p. 164–165°.

Anal. Calcd. for $C_{17}H_{18}O_5$: C, 67.5; H, 6.0. Found: C, 67.8; H, 6.1.

The liquid dimethyl ester of the acid, prepared by means of diazomethane, was evaporatively distilled at 180–190° (0.05 mm.). Cyclization of 1.98 g. of the ester and hydrolysis, decarboxylation and demethylation were accomplished as previously described for similar cases.[3] A solution of the phenolic product in 125 cc. of hot 2.5% potassium hydroxide was filtered and acidified. The **3-(6′-hydroxy-2′-naphthyl)-cyclopentanone** after evaporative distillation at 200° (0.05 mm.) crystallized from methanol in small colorless prisms; yield, 1.14 g. (83%); m. p. 176–176.5°. The m. p. remained unchanged after two more recrystallizations.

The same compound was obtained by shaking a solution of 100 mg. of VIc in 10 cc. of acetic acid with 25 mg. of palladium–charcoal catalyst[14] and hydrogen for four hours. The filtered solution was evaporated and the residue was crystallized from methanol; yield, 70 mg. (70%); m. p. 176–176.5°.

Anal.[12] Calcd. for $C_{15}H_{14}O_2$: C, 77.9; H, 6.2. Found: C, 77.5; H, 6.3.

The **semicarbazone** crystallized in cream-colored prisms; m. p. 212–213°.

Anal. Calcd. for $C_{16}H_{17}O_2N_3$: N, 14.8. Found: N, 15.1.

3-(2′-Naphthyl)-cyclopenten-2-one-1.—The Reformatsky reaction was carried out on 7.5 g. of methyl-β-2-naphthoylpropionate (m. p. 74–75°), which was prepared from the acid in quantitative yield by means of diazomethane. The **lactone of the monomethyl ester of β-hydroxy-β-(2-naphthyl)-adipic acid (IVa)** (5.7 g.; m. p. 106–108°) was sufficiently pure for the next step. A sample after evaporative distillation at 170° (0.05 mm.), followed by two recrystallizations from methanol formed fine colorless needles; m. p. 111–112°.

Anal.[12] Calcd. for $C_{17}H_{16}O_4$: C, 71.8; H, 5.7. Found: C, 72.0; H, 5.5.

A mixture of 8.9 g. of the crude lactone ester, 150 cc. of methanol and 63 cc. of *N* sodium hydroxide was refluxed for three hours. The **3-(2′-naphthyl)-2-hexendioic acid (Va)** was isolated as described for the methoxy compound; yield, 8.06 g. (96%); m. p. 179–180°. The crude product was pure enough for the next step. After two recrystallizations from acetone–ligroin a sample was obtained as colorless prisms with the same m. p.

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.0; H, 5.2. Found: C, 71.3; H, 5.2.

The liquid dimethyl ester of the unsaturated dicarboxylic acid, prepared by means of diazomethane, was evaporatively distilled at 170–180° (0.05 mm.). Cyclization of 1.64 g. of the ester and hydrolysis and decarboxylation of the product was carried out as described.[3] The **3-(2′-naphthyl)-cyclopenten-2-one-1 (VIa)** was evaporatively distilled at 160–170° (0.05 mm.) and then recrystallized twice from methanol; yield, 0.93 g. (81%) of small colorless prisms; m. p. 126–127° (reported,[5] 126–127°).

Anal.[12] Calcd. for $C_{15}H_{12}O$: C, 86.6; H, 5.8. Found: C, 87.2; H, 5.9.

The **semicarbazone** melted at 240–241° (reported, 244°[5]).

Anal. Calcd. for $C_{16}H_{15}ON_3$: N, 15.8. Found: N, 16.0.

The Wolff–Kishner reduction of 115 mg. of the above semicarbazone was carried out exactly as described for the methoxy compound and yielded 40 mg. (49%) of 1-(2′-naphthyl)-cyclopentene; m. p. 84.5–86° (reported,[7] 85–86°).

3-(2′-Naphthyl)-cyclopentanone.—Reduction of 3.24 g. of the naphthylhexendioic acid by 2% sodium amalgam was carried out as described for the methoxy derivative; yield, 3.14 g. (96%) of **β-(2-naphthyl)-adipic acid** sufficiently pure for the next step; m. p. 151–153°. After two recrystallizations from acetone–ligroin a sample formed colorless prisms; m. p. 153–154°.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.6; H, 5.9. Found: C, 70.7; H, 5.9.

The liquid dimethyl ester of the acid prepared by means of diazomethane was evaporatively distilled at 180° (0.05 mm.). Cyclization of 2.4 g. of the diester and hydrolysis and decarboxylation of the cyclic keto ester were carried out as described. The **3-(2′-naphthyl)-cyclopentanone** after evaporative distillation at 150° (0.05 mm.) followed by two recrystallizations from methanol formed small colorless prisms; yield, 1.47 g. (87%); m. p. 65–66° (reported,[5] 61°).

The same compound was obtained in 75% yield by catalytic hydrogenation of 200 mg. of VIa in acetic acid in the presence of 50 mg. of palladium-charcoal catalyst.

Anal.[12] Calcd. for $C_{15}H_{14}O$: C, 85.7; H, 6.7. Found: C, 85.7; H, 6.7.

The **semicarbazone** crystallized in colorless prisms; m. p. 199–199.5° (reported,[5] 196–197°).

Anal. Calcd. for $C_{16}H_{17}ON_3$: N, 15.7. Found: N, 15.5.

3-(5′,6′,7′,8′-Tetrahydro-2′-naphthyl)-cyclopenten-2-one-1 (VII).—A malonic ester synthesis was carried out on 104.5 g. of 2-chloroacetyl-5,6,7,8-tetrahydronaphthalene as described[11] except that benzene was used as the solvent and one hour of refluxing was employed. By adding the aqueous solution of the potassium salt of the substituted malonic acid to concentrated hydrochloric acid, the free

(14) Zelinsky and Turowa-Pollak, *Ber.*, **58**, 1295 (1925).

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acid was obtained. After decarboxylation of the substituted malonic acid at 150–170°, the β-(5,6,7,8-tetrahydro-2-naphthoyl)-propionic acid was recrystallized from benzene using Norite; yield, 94.5 g. (85%); m. p. 120.5–121.5° (reported,[11] 121–122°). The methyl ester, prepared from 23 g. of the acid by means of diazomethane, solidified after distillation (b. p. 168–173° at 0.1 mm.) to a colorless solid; yield, 22 g.; m. p. 31–32° (reported,[15] 31°).

A Reformatsky reaction was carried out on 7.38 g. of the methyl ester as described. The product was an oil which was purified by evaporative distillation at 180° (0.05 mm.) and heated with 50 cc. of *N* sodium hydroxide in 50 cc. of methanol for three hours. The **3-(5′,6′,7′,8′-tetrahydro-2′-naphthyl)-2-hexendioic acid** (4.9 g., m. p. 183–185°) was sufficiently pure for the next step. A sample twice recrystallized from acetone–ligroin formed colorless prisms which melted at 185–186°.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 70.1; H, 6.6. Found: C, 70.0; H, 6.7.

The liquid dimethyl ester, prepared by means of diazomethane was evaporatively distilled at 180° (0.05 mm.); and 2.8 g. of it was cyclized as described. The cyclic keto ester was hydrolyzed and decarboxylated by heating with hydrochloric and acetic acids,[3] and the **3-(5′,6′,7′,8′-tetrahydro-2′-naphthyl)-cyclopenten-2-one-1** (VII) was evaporatively distilled at 150° (0.05 mm.) and recrystallized twice from methanol from which it crystallized in small colorless prisms; yield, 1.64 g. (77%); m. p. 82–82.5°.

Anal. Calcd. for $C_{15}H_{16}O$: C, 84.8; H, 7.6. Found: C, 84.6; H, 7.5.

The **semicarbazone** melted at 235–236°.

Anal. Calcd. for $C_{16}H_{19}ON_3$: N, 15.6. Found: N, 15.8.

A mixture of 50 mg. of VII and 10 mg. of palladium–charcoal catalyst was heated for fifteen minutes at 320° in an atmosphere of nitrogen. The 3-(2′-naphthyl)-cyclopenten-2-one-1 was evaporatively distilled at 150° (0.05 mm.); yield, 30 mg. (61%); m. p. 125–126°, alone and when mixed with a sample of VIa.

(15) Newman and Zahm, THIS JOURNAL, **65**, 1099 (1943).

3-(5′,6′,7′,8′-Tetrahydro-2′-naphthyl)-cyclopentanone.—Reduction of 2.0 g. of the tetralylhexendioic acid by 2% sodium amalgam gave 2.0 g. (98%) of β-(5,6,7,8-tetrahydro-2-naphthyl)-adipic acid sufficiently pure for the next step; m. p. 159–160°. After two recrystallizations from acetone–ligroin a sample formed small colorless prisms which melted at 159.5–160°.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.5; H, 7.2. Found: C, 69.8; H, 7.2.

The liquid dimethyl ester, prepared by means of diazomethane, was evaporatively distilled at 160° (0.05 mm.), 1.06 g. of it was cyclized (eight hours of refluxing), and the cyclic keto ester was hydrolyzed and decarboxylated as described.[3] The ketone was evaporatively distilled at 170° (0.05 mm.) and recrystallized twice from methanol; yield, 0.63 g. (83%) of colorless prisms; m. p. 73–74°. The same compound was formed in 74% yield when VII was hydrogenated in acetic acid in the presence of palladium–charcoal.

Anal. Calcd. for $C_{15}H_{18}O$: C, 84.1; H, 8.4. Found: C, 83.6; H, 8.5.

The **semicarbazone** crystallized in colorless prisms; m. p. 207–208°.

Anal. Calcd. for $C_{16}H_{21}ON_3$: N, 15.5. Found: N, 15.3.

Summary

The *cis* and *trans* forms of 1,2,3,4-tetrahydro-17-equilenone, an isomer of desoxyestrone, have been synthesized from 1-keto-*sym*-octahydrophenanthrene. The compounds were dehydrogenated by sulfur to the *cis* and *trans* forms of 17-equilenone (desoxyequilenin).

Three 3-arylcyclopentenones and the corresponding 3-arylcyclopentanones were prepared in which the aryl groups were 2′-naphthyl-, 2′-tetralyl- and 6′-methoxy-2′-naphthyl.

ANN ARBOR, MICHIGAN RECEIVED DECEMBER 31, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF IOWA STATE COLLEGE]

Relationship between Solution Viscosity and Molecular Weight in the Amylose Series[1]

BY JOSEPH F. FOSTER[2] AND R. M. HIXON

Data on the solution viscosities of a series of amyloses prepared from various starch sources have recently been given.[3] Investigations of the osmotic behavior of some of these materials have been carried out with a view to establishing a relationship between molecular weight and viscosity for this series of glucose polymers. Unfortunately, it has been necessary to discontinue these investigations, temporarily, in the present rather preliminary stage.

Attempts to relate the solution viscosities of high polymers with their molecular weights through simple equations, of which that of Staudinger is best known, have been complicated by several factors. In the first place it is essential that the polymers be either linear or, if branched, have a constant degree of branching, so that the length or axial ratio may be expressed as a simple function of molecular weight. Much confusion has been caused in attempting to apply the Staudinger equation to starch and its degradation products, due to the fact that this polymer apparently consists of two types of molecules,[3,4,5] the one highly branched and the other linear. Obviously the same equations could not be expected to apply to both types of polymer.

In the second place it is now recognized that viscosity measurements on high polymers yield not a simple number average molecular weight as in the case of osmotic studies but one which is weighted in some manner.[6] Therefore it is essen-

(1) Journal Paper No. J-1139 of the Iowa Agricultural Experiment Station, Ames, Iowa; Project No. 817. Supported in part by a grant from the Corn Industries Research Foundation.

(2) Present address, Department of Physical Chemistry, Harvard Medical School, Boston, Mass.

(3) Foster and Hixon, THIS JOURNAL, **65**, 813 (1943).

(4) K. H. Meyer, "Natural and Synthetic High Polymers," Interscience Publishers, Inc., New York, N. Y., 1942, pp. 387–417.

(5) Bates, French and Rundle, THIS JOURNAL, **65**, 142 (1943).

(6) Kraemer and Lansing, *J. Phys. Chem.*, **39**, 153 (1935); Flory, THIS JOURNAL, **65**, 372 (1943).

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tial that the material used be well fractionated if a comparison of values from the two methods is to be made.

A third point of very great importance which must also be considered is the degree of flexibility (randomness of kinking) of the polymer chains. Theoretical derivations of Kuhn[7] and more recently Huggins[8] predict, for the case of rigid rods, a linear relationship between the intrinsic viscosity and the square of the molecular weight (or length). However, if the chain is kinked in a random manner the result is compatible, according to Huggins, with the Staudinger equation

$$\eta_i = KM \qquad (I)$$

Kuhn,[9] in fact, predicts for such molecules a dependence of η_i on a power of M even lower than 1.0, the lower limit being 0.5. Most actual long-chain molecules would be expected to behave in a manner intermediate between these extremes and a general form for the equation relating these quantities would be[10] where α takes on values between the limits 0.5 and 2.0 depending on the flexibility of the chains. Values for α of 0.64 for the polyisobutylene series[11a] and 0.67 for cellulose acetates[11b] have been found.

$$\eta_i = KM^{\alpha} \qquad (II)$$

The evidence is quite conclusive that the amyloses are linear polymers,[3,4,5] and there is some evidence that they are fairly homogeneous with respect to molecular size.[5] With regard to the third point mentioned above, the amyloses are of peculiar interest. Inspection of molecular models[12] emphasizes in a striking manner the difference between this polymer and a polymer such as a simple hydrocarbon or rubber, or even cellulose. The amylose molecule is remarkably rigid due to restricted rotation about the glucosidic linkages. Thus in this case it might be expected that the value of the exponent in Equation (II) would be considerably greater than unity, perhaps approaching the maximum value of 2.0. The present paper presents evidence that this is the case.

Osmotic Pressure Measurements

Apparatus.—The osmotic cell used for this investigation was of the dynamic type working on the counter-pressure principle, patterned after a cell previously described by Hepp.[13] Peters and Saslow[14] have found this type of cell satisfactory for aqueous solutions. The design was considerably simplified in the present cell through the use of all-brass construction. A flat, circular brass block was drilled vertically and then horizontally to meet the glass capillary which was platinized and set in Wood's metal to provide a tight seal. The membrane was placed on top of this block over a disk of bolting silk and clamped in place by means of a brass ring. To prevent upward motion of the membrane, it was weighted with a grooved brass block which fitted inside the brass ring. Evaporation of solvent was minimized by covering the cell with an inverted glass funnel, open to the atmosphere through a fine capillary.

Suitable pressures (positive and negative) were obtained by means of leveling bulbs containing water and were measured with a water manometer.

Membranes.—Cellophane[15] was found to be the most satisfactory membrane material for this work in spite of its low permeability to organic solvents. Three grades of cellophane were tried, numbers 300, 450 and 600. In general the thinner grades, 300 and 450, were somewhat more satisfactory. Swelling in water–alcohol as recommended by McBain and Stuewer,[16] was found to increase the permeability temporarily but this decreased again after a few hours contact with the organic solvent. Ordinary parchment was also fairly satisfactory, being much more permeable than cellophane and hence giving more rapid attainment of equilibrium (about one hour as compared to four to eight hours with cellophane). In a few cases parchment disks were found permeable to the solute molecules. This was in no case observed with cellophane.

Materials.—Inasmuch as there is no solvent for amylose suitable for osmotic pressure work it was necessary to render the material soluble in organic solvents. This was done by acetylating, using pyridine and acetic anhydride which have been shown to produce no degradation.[17] The amyloses were the same preparations used in the viscosity work.[3] Chloroform was the solvent for all measurements reported here.

Procedure.—It is necessary to correct the equilibrium pressure in the cell for head of solvent and capillarity. This zero point was ascertained experimentally prior to each run by filling the cell with solvent and permitting it to come to equilibrium. The value varied somewhat from run to run, apparently due to slight leakage around the membrane which affects the rate of flow. This variation constitutes the chief uncertainty of the measurements.

Following the determination of the zero point the solvent was withdrawn from the chamber above the membrane and the top of the membrane pressed dry with filter paper. The cell was now filled with solution and permitted to come to equilibrium. The rate of flow of the meniscus was ascertained at various pressures using a low power microscope mounted on a micrometer, and the equilibrium point obtained by interpolating to zero flow rate.

Results and Calculations

The osmotic pressure results are given in Table I, and in Fig. 1 the quantity π/C is given as a function of concentration.

Substituting the limiting values of π/C in the van't Hoff equation the molecular weights of corn and tapioca amylose are found to be 42,000 and 75,000, respectively, corresponding to 260 and 460 glucose units.

Viscosity of Amylose Acetates in Chloroform.—The viscosities of the acetates of corn, tapioca and potato amyloses (butanol method) were determined. An Ostwald viscometer (capillary dimensions 15 by 0.04 cm., capacity 10 ml., flow time with chloroform about 21 sec.) equipped with ground-glass joints to cut down solvent evaporation was used. All measurements were at 25 ± 0.01° and all the usual precautions were observed. Results are shown graphically in Fig. 2.

(7) Kuhn, *Z. physik. Chem.*, **A161**, 1 (1932).
(8) Huggins, *J. Phys. Chem.*, **42**, 911 (1938); **43**, 439 (1939).
(9) Kuhn, *Kolloid-Z.*, **68**, 2 (1934); *Angew. Chem.*, **49**, 858 (1936).
(10) In this connection see Simha, *J. Applied Phys.*, **13**, 147 (1942).
(11) (a) Flory, THIS JOURNAL, **65**, 372 (1943); (b) Bartovics and Mark, *ibid.*, **65**, 1901 (1943).
(12) Photographs of such models of amylose have been published by Caesar and Cushing, *J. Phys. Chem.*, **45**, 776 (1941).
(13) Hepp, *Z. ges. expl. Med.*, **99**, 709 (1936).
(14) Peters and Saslow, *J. Gen. Physiol.*, **23**, 177 (1939).
(15) Supplied through the courtesy of E. I. du Pont de Nemours and Company, Inc., Wilmington, Delaware.
(16) McBain and Stuewer, *J. Phys. Chem.*, **40**, 1157 (1936).
(17) Karrer and Goldschmid, *Helv. Chim. Acta*, *Ann.*, **527**, 195 (1937).

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TABLE I

SUMMARY OF RESULTS

Material	Concn., g./100 ml.	Pressure π, mm. of H_2O	π/C	Membrane
Corn	0.237	9.0	38	Parchment
amylose	.474	2.10	44	Parchment
acetate	.860	46.0	53	Cellophane
	.860	49.0	57	Cellophane
	1.440	92.0	64	Cellophane
	2.400	214.0	89	Cellophane
	2.480	234.0	94	Cellophane
Tapioca	0.197	4.0	20	Cellophane
amylose	.197	4.0	20	Parchment
acetate	.197	5.5	28	Parchment
	.396	10.5	26	Parchment
	.596	17.5	29	Parchment
	.996	33.0	33	Parchment
	.996	33.5	34	Parchment

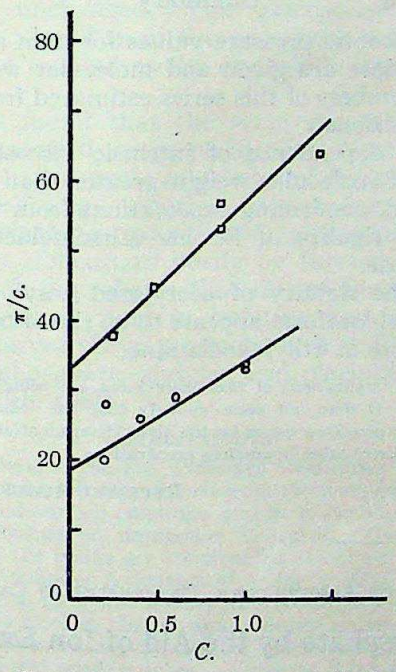

Fig. 1.—Concentration dependence of the function π/c. Concentration is given in g. per 100 ml., π in mm. of water. Squares are experimental points for corn amylose, circles for tapioca amylose.

Discussion

Unfortunately, of the materials whose viscosity behavior was studied earlier,[3] only three were available in large enough quantities for acetylation and osmometric study, namely, corn, tapioca and potato butanol precipitates. Discordant results were obtained with the latter, at least in part due to a strong tendency of even 1% solutions in chloroform to gel. Nevertheless, other evidence is available as to molecular weight of some of these preparations. Schoch[18] has recently reported "alkali numbers" for the potato and corn amyloses. The method is admittedly empirical but

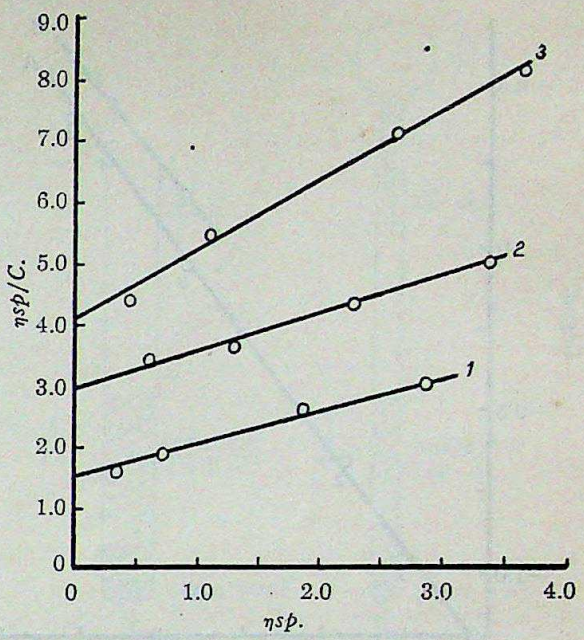

Fig. 2.—Calculation of the intrinsic viscosities of: 1, corn; 2, tapioca and 3, potato amylose acetates.

it is apparently a measure of the number of reducing groups present. It does not seem unlikely that for molecules of this size, where any inconsistencies should enter equally in the two cases, the ratio of the molecular weights would be approximately inversely proportional to the ratio of the alkali numbers which are about 25 for corn and 11 for potato amylose. This would correspond to a value of about 600 glucose units for potato amylose based on the osmometric value for corn.

Haworth, *et al.*,[19] have determined the chain length of a synthetic starch preparation, prepared in identically the same manner as the one used here, by means of analysis for end-groups (tetramethyl glucose analysis). They report a value of 80–90 glucose units.

Reducing value measurements,[20] both by hypoiodite and ferricyanide, on the amylodextrin fraction number 4 give values of the order of 50 glucose units for the molecular size.

In Fig. 3 these various values are plotted as log N *versus* log η_i where N is the number of glucose units in the molecule. The slope of this curve, 1.5, corresponds to α in Equation II.

All of the molecular weight calculations made above yield number average molecular weights. Too much emphasis cannot be placed on the value of 1.5 for α in view of uncertainty as to the homogeneity of these materials. Fraction 4 of amylodextrin was prepared by careful fractionation and should be reasonably homogeneous. The other materials have not been fractionated except in that the preparation itself probably gives fractionation, the longer amylose molecules precipitating preferentially. However, in view of the fact

(18) Schoch, THIS JOURNAL, 64, 2957 (1942).

(19) Haworth, Heath and Peat, *J. Chem. Soc.*, 55 (1942).

(20) Bates, unpublished data in this Laboratory.

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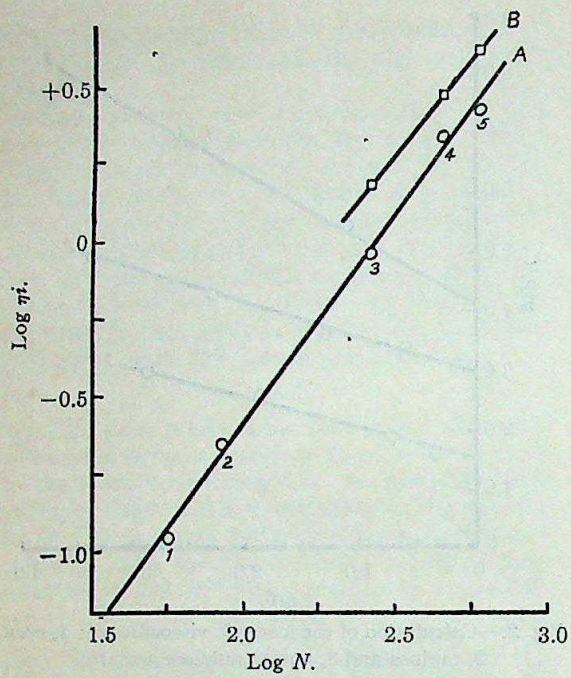

Fig. 3.—Relation between intrinsic viscosity and degree of polymerization for amyloses in ethylenediamine (A) and amylose acetates in chloroform (B): 1, amylodextrin 4; 2, synthetic starch; 3, corn; 4, tapioca and 5, potato amylose.

that most of these materials are prepared from natural sources with little if any degradation it does not seem unlikely that their homogeneity approaches that of materials prepared by fractional precipitation of originally highly polydisperse materials such as synthetic polymers (or even such natural polymers as cellulose where considerable degradation is involved in the preparation). Also the fact that these different materials can be titrated quantitatively with iodine in mixtures[5,21] would seem to indicate that the molecular weight distributions are fairly small relative to the magnitude of the differences between them. For the present, however, it is perhaps best to consider the value 1.5 as an upper limit for α in this series. There would seem to be little doubt that the value is greater than unity confirming the expectations from the rigidity of Fischer–Hirschfelder models of amylose.

The fact that α for the acetates in chloroform is the same, within the experimental error, as for the amyloses in ethylenediamine (as shown by the similar slopes in Fig. 3) is somewhat surprising. This would seem to indicate the molecules to be equally rigid in the two cases.

Summary

1. Osmotic pressure values for corn and tapioca amylose are given and molecular weights of other members of this series estimated from other considerations.

2. A dependence of intrinsic viscosity on a power of molecular weight greater than unity is indicated, confirming expectations from the comparative rigidity of Fischer–Hirschfelder models of amylose.

3. The rigidity of acetylated amylose molecules in chloroform appears to be the same as that of amylose in ethylenediamine.

(21) The implications of this observation are being further investigated. It does not seem unlikely that the iodine titration method may provide a means for the direct determination of molecular weight distribution in amylose preparations.

Ames, Iowa Received August 20, 1943

[Contribution from the Division of Plant Nutrition, College of Agriculture, University of California]

The Preparation and Purification of Glucose 1-Phosphate by the Aid of Ion Exchange Adsorbents

By R. M. McCready[1] and W. Z. Hassid

The establishment of glucose-1-phosphate (Cori ester) as an important intermediary product in the synthesis and breakdown of glycogen and starch[2,3] contributed much toward the stimulation of further study of the mechanism of carbohydrate formation in general. Since studies along these lines require an available supply of glucose-1-phosphate, it is important to have a satisfactory method whereby this ester can readily be prepared. Although Hanes' method[3] of preparing the ester from starch in fairly large quantities is satisfactory, the product is usually contaminated with small amounts of dextrins, which are very difficult to remove, and which are objectionable in certain types of experiments. Green and Stumpf[4] for example, in studying the influence of different carbohydrates on the synthesis of starch from glucose-1-phosphate *in vitro*, were obliged to use synthetic glucose-1-phosphate, which is laborious to prepare. Hanes' procedure can be very much shortened and improved by using ion exchange adsorbents,[5,6] whereby the following steps are eliminated: concentration of large volumes of

(1) Present address, Western Regional Research Laboratory, U. S. Department of Agriculture, Albany, Calif.

(2) C. F. Cori, *Endocrinology*, **26**, 285 (1940).

(3) C. S. Hanes, *Proc. Roy. Soc.* (London), **B129**, 174 (1940).

(4) D. E. Green and P. K. Stumpf, *J. Biol. Chem.*, **142**, 355 (1942).

(5) The synthetic resins IR-100 and IR-4 were obtained from the Resinous Products and Chemical Company, Inc., Philadelphia, Penna.

(6) For a review on the use of ion exchange adsorbents see: R. J. Myers, *Ind. Eng. Chem.*, **35**, 858 (1943).

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solution, precipitation of the ester with considerable quantities of alcohol, addition of trichloroacetic acid to precipitate the proteins, and the enzymatic hydrolysis of dextrin impurities.

In the present procedure the phosphorolysis of starch in the presence of phosphate buffer and the precipitation of the inorganic phosphate were carried out according to a modified procedure of Hanes, but the purification of the ester was accomplished by ion exchange adsorbents. The reaction mixture containing the ester was first passed through a column of cation exchange adsorbent, which removed the cations from solution, exchanging them for hydrogen ions. The effluent was then run through an acid adsorbing column. In this operation the Cori ester, being a strong acid with a high exchange capacity, was adsorbed, while the soluble impurities, including dextrins, proteins and weak organic acids, passed through unchanged. The glucose-1-phosphate was then eluted from the adsorbent with dilute alkali and isolated as the crystalline dipotassium salt.

It was found that the same general method could be applied to the purification of other hexosephosphates, such as fructose-1,6-diphosphate (Harden–Young ester), fructose-6-monophosphate (Neuberg ester), and glycerophosphate which are difficult to purify by the usual methods,[7,8,9] It is probable that this method may be advantageously used in isolating and purifying other phosphorylated products, such as dihydroxyacetone phosphate, glyceric acid phosphates, and also organic acids.

Experimental

Preparation of the Ion Exchange Columns.—The resin exchange materials as obtained from the manufacturer are in moist and swollen condition and little swelling or disintegration occurs on immersion in water. The columns containing the resins are constructed as shown in Fig. 1. The larger cylinder A consists of a 100 × 1000 mm. tube containing a 1200 ml. Amberlite IR-100 bed and some Pyrex glass wool at the bottom. Tubes cc_1 are attached to distilled water; aa_1 are outflow tubes for backwashing; bb_1 are effluent outflow tubes. Cylinder B is a 35 × 1000 mm. tube containing a 200 ml. bed of Amberlite IR-4 and a glass wool plug at the bottom. C is a 1-liter flask arranged to give a constant level of influent. After filling the columns the exchange material should be "classified" to size by washing before use in a particular process. The classification is accomplished by backwashing with water at such a rate as to produce a 50% bed volume expansion.[10] Flow resistance is thus reduced by the elimination of fines and the classification to a desirable particle size. The bed should be "broken in" by three or four exchange cycles followed by regeneration and washing to eliminate any color discharge and fines.

In the present work 4% hydrochloric acid was used to regenerate a 1200-ml. bed volume of Amberlite IR-100.

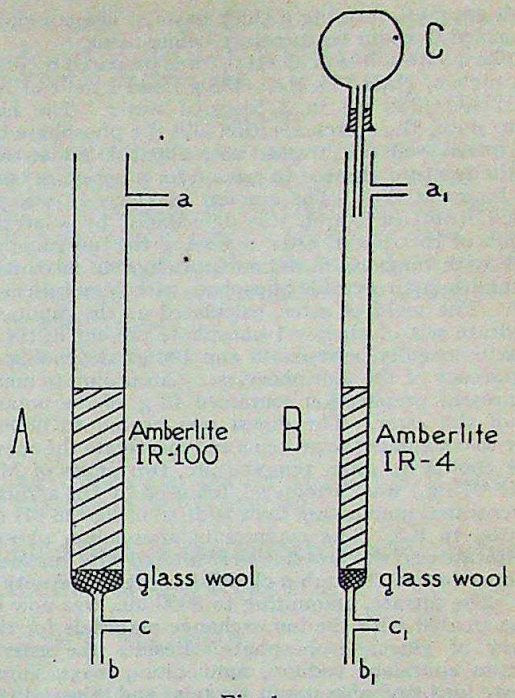

Fig. 1.

The acid was passed through the resin at the rate of seven bed volumes per hour, followed by thorough washing until the titratable acidity was negligible. Under these conditions the wash water effluent did not rise above *p*H 3. The resin in the form of the hydrogen derivative was treated with 4% sodium chloride solution to exchange the hydrogen of the resin for the cation of the sodium chloride solution. After 3000 ml. of the sodium chloride solution was allowed to pass through the resin at the rate of ten bed volumes per hour, the resin was completely saturated with sodium ions. The resin was then backwashed with distilled water and again regenerated with 3000 ml. of 4% hydrochloric acid solution by allowing it to pass through the column at the rate of 10 bed volumes per hour. The titratable acidity of the effluent then became the same as that of the influent, and the regeneration was considered complete. The column was put through three more exchange cycles as previously described, before it was ready for use.

The acid adsorbing Amberlite IR-4 was "broken in" in the same manner as the IR-100, except that ammonium hydroxide was used in the regeneration and 4% hydrochloric acid to saturate its acid binding capacity. In treating the IR-4 resin with ammonium hydroxide, its regeneration was considered complete when the reaction of the effluent became *p*H 11. When the column was subsequently treated with hydrochloric acid in the "breaking in" treatment, the *p*H value of 4.0 was used as an index of saturation of the resin with acid. Four exchange cycles were carried out on the Amberlite IR-4 before it was put into operation.

Preparation of the Digest.—Two kilograms of fresh potatoes were peeled and ground through a meat grinder fitted with a peanut butter cutter and the juice pressed through cheesecloth. Approximately 1200 ml. of the juice obtained from this weight of raw potatoes was then filtered through a canvas precoated with a thin layer of filter aid[11] on a Buchner funnel, using suction.

One hundred grams of air-dried potato starch was stirred into 600 ml. of cold water, then poured with stirring into 3500 ml. of boiling water and maintained at 100° for half an hour. This treatment completely ruptures the

(7) M. Kobel and C. Neuberg, "Handbuch der Pflanzenanalyse," edited by G. Klein, Julius Springer, Wien, 1932, Vol. II, part 1, pp. 546–577.

(8) C. Neuberg and H. Lustig, THIS JOURNAL, **64**, 2722 (1942).

(9) K. P. DuBois and V. R. Potter, *J. Biol. Chem.*, **147**, 41 (1943).

(10) The bed volume of a resin is known as the backwashed and drained volume and is measured by backwashing to 50% bed volume expansion, followed by draining the wash water to one inch of the top of the resin bed.

(11) "Hyflo-Super-Cel" obtained from Johns-Manville Co., New York, was employed. Other diatomaceous silica of similar grade may be used.

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starch granules, forming a thick paste. The starch paste was cooled to room temperature before using.

A phosphate solution of *p*H 6.7 was prepared by dissolving 1 mole of $NaH_2PO_4 \cdot H_2O$ (138 g.) and 1 mole of $Na_2HPO_4 \cdot 12H_2O$ (358 g.) in 3 liters of water. The filtered potato juice, the starch solution and the phosphate buffer were mixed well, and treated with about 50 ml. of toluene and the mixture allowed to remain for a period of twenty-four hours at 25°. The amount of glucose-1-phosphate formed from the starch was determined by analyzing a portion of the digest, after removing the inorganic phosphate with magnesium ammonium chloride mixture[12] for ten-minute hydrolyzable phosphate with *N* sulfuric acid at 100°. The yield of ester, calculated as the dipotassium dihydrate salt of glucose-1-phosphate present in the total digest, is usually between 40 and 100 g., depending upon the potency of the phosphorylase. According to analysis, the present preparation contained 43 g. of the potassium salt of the ester. The digest was heated to boiling in order to coagulate the proteins and inactivate the enzymes. After cooling to room temperature, two moles of $MgAc_2 \cdot 4H_2O$ (428 g.) was introduced, followed by the addition of concentrated ammonium hydroxide to bring the *p*H of the solution to 8.5. The magnesium ammonium phosphate precipitate and the proteins were filtered with suction on a Buchner funnel through a cloth filter precoated with filter aid. The filtrate, amounting to 8000 ml., was now ready to be treated with the ion exchange materials for the recovery of glucose-1-phosphate. Besides the ester, the solution contained sodium, ammonium, magnesium and acetate ions, and also starch, proteins and other impurities from the potato juice.

Treatment of the Digest with Amberlite IR-100.—The solution containing the glucose-1-phosphate and impurities was passed through a column of 1200-ml. bed volume of Amberlite IR-100 at the rate of 10 bed volumes per hour, taking the *p*H of the effluent as an index of saturation capacity of the resin. The cations in the solution were exchanged for hydrogen ions by this treatment. When the *p*H value rose to 4 the resin was considered to be near its saturation capacity and was regenerated with acid. To pass eight liters of solution through this column required four regenerations with hydrochloric acid followed by washing as previously described.

Adsorption of the Glucose-1-phosphoric Acid on Amberlite IR-4.—The solution was run through a column of Amberlite IR-4 of a 200-ml. bed volume at the rate of seven bed volumes per hour. When the reaction of the effluent from the Amberlite IR-4 falls to a value of *p*H 4 its saturation capacity has been reached and the Amberlite should be regenerated. However, in the case of glucose-1-phosphoric acid, it is still being adsorbed, although according to the *p*H value, the resin appears to be saturated. The glucose-1-phosphoric acid, having a stronger affinity for combination with this resin than acetic acid, is preferentially adsorbed, thus facilitating the removal of the glucose-1-phosphoric acid present in relatively low concentration as compared to the acetic acid. Analysis of samples of effluent for ten-minute hydrolyzable phosphate showed that practically all the glucose-1-phosphoric acid was removed from the solution. After the eight liters of the solution containing the glucose-1-phosphoric acid passed through the Amberlite IR-4, the resin was washed with three liters of water to remove soluble impurities such as starch or protein.

Recovery of Glucose-1-phosphate and Regeneration of the Amberlite IR-4.—A 4% solution of ammonium hydroxide was passed through the Amberlite IR-4 at a rate of five bed volumes per hour, and the *p*H of successive 50-ml. portions of effluent was determined. When 500 ml. of the solution had passed through the resin the reaction of the effluent became *p*H 11. An additional 200 ml. of 4% ammonium hydroxide was passed through this column to ensure complete regeneration of the resin, but it was not combined with the first 500 ml. of effluent, containing at least 99% of the glucose-1-phosphate. A concentration of 8000 ml. to 500 ml. in terms of glucose-1-phosphate had thus been effected by the use of the exchange materials.

The solution containing the glucose-1-phosphate was treated with 50 g. of potassium acetate and the reaction adjusted to *p*H 12 with 10% potassium hydroxide. One and a half volumes of methanol was then added to the solution and the potassium salt allowed to crystallize at 4°. After twenty-four hours the crystals of dipotassium glucose-1-phosphate dihydrate were removed by filtration, washed with methanol and ether, and dried *in vacuo* at 50°. A yield of 40.5 g. was obtained. This yield constitutes 94% recovery of the ester, formed from starch after treatment with potato phosphorylase, shown to be present in the digest according to analysis of acid hydrolyzable phosphorus. The product was free of inorganic phosphorus, nitrogen and dextrins. Its reducing value in terms of glucose, after hydrolysis with *N* sulfuric acid, was 48.4% (calculated reducing value, 48.38%).

Anal. Calcd. for $C_6H_{11}O_5OPO_3K_2 \cdot 2H_2O$: P, 8.33. Found: P, 8.3. Specific rotation: $[\alpha]_D$ +78° (in water, $c = 2$).

Adsorption Capacity of Amberlite IR-4 with Various Acids at their "Break through" Points.—When the resin is saturated with acid to its full capacity, the concentration of the effluent becomes equal to that of the influent. When quantitative adsorption of an acid is desired, it is of interest to determine the point at which the resin is not fully saturated, but only to the degree where some or the acid begins to appear in the effluent. This point is termed by Myers, *et al.*,[13] as the "break through" capacity of the resin.

The adsorption capacities of Amberlite IR-4 with respect to hexose phosphate esters were determined as follows: a 500-ml. solution, containing two hundred milli-equivalents of hexose phosphate, was passed through a 300-ml. bed of Amberlite IR-100 to remove cations, and then through a bed of Amberlite IR-4 to adsorb the phosphoric acid ester. The weight of the Amberlite IR-4 bed in the column was equivalent to 10 g. of resin on the dry weight basis. The results of the adsorption capacities are expressed in terms of grams of acid adsorbed per gram of dry resin. Table I shows the break through capacities of the resins when treated with various hexose phosphoric acids and also of glycerophosphoric acid.

TABLE I

ADSORPTION CAPACITY OF AMBERLITE IR-4

Acid	Influent concn., milli-moles/liter	Capacity at break through g. acid/g. dry resin	Capacity at break through millimoles acid/g. dry resin
Hydrochloric[a]	11.1	0.174	4.77
Nitric[a]	5.9	.495	7.86
Sulfuric[a]	5.1	.389	3.97
Phosphoric[a]	15.3	.508	5.18
Acetic[a]	33.3	.231	3.85
Glycerophosphoric	200	1.59	9.25
Glucose-1-phosphoric	200	2.28	8.77
Fructose-6-phosphoric	200	2.34	9.00
Glucose-6-phosphoric	200	2.34	9.00
Fructose-1,6-diphosphoric	100	1.49	4.38

[a] Data presented by Myers[6] and recalculated to compare with the hexose phosphoric acids.

The resin exchange adsorbents have been very successfully used for the purification of crude preparations of fructose-6-phosphate and fructose-1,6-diphosphate. A crude preparation of fructose-1,6-diphosphate prepared

(12) The magnesium mixture is made up as follows: 55 g. of $MgCl_2 \cdot 6H_2O$ and 70 g. of NH_4Cl are dissolved in 650 ml. of water; 350 ml. of 10% ammonium hydroxide is added and allowed to remain at room temperature for two or three days, until the solution becomes clear, and then filtered.

(13) R. J. Myers, J. W. Eastes and D. Urquhart, *Ind. Eng. Chem.*, 38, [illegible]

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according to Kobel and Neuberg[7] was treated with the resin exchange adsorbents and recovered as the amorphous calcium salt by precipitation with alcohol. Analysis of this hexosediphosphate before treatment with the ion exchange adsorbents showed only 70% purity, the chief contaminants being proteins and calcium phosphate. After purification by the aid of the resin exchange adsorbents the calcium salt of the fructose diphosphoric acid was obtained in pure condition. *Anal.* Calcd. for $C_6H_{10}O_6(PO_3Ca)_2$: P, 14.9; Ca, 19.2. Found: P, 15.3; Ca, 19.4.

Crude fructose-6-monophosphate (75% purity) was similarly treated with the resin exchange adsorbents and the ester recovered as the barium salt. *Anal.* Calcd. for $C_6H_{11}O_6(PO_3Ba)$: P, 7.8; fructose, 45.5. Found: P, 8.0; fructose, 45.5.

The authors wish to thank Drs. J. R. Matchett, R. R. Le Gault and J. F. Carson for their interest and valuable suggestions.

Summary

A method for preparation of dipotassium glucose-1-phosphate dihydrate is described. The glucose-1-phosphate is obtained by digesting a starch with crude potato phosphorylase in the presence of inorganic phosphate and the purification of the ester is accomplished by using ion exchange adsorbents.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY AND PHARMACOLOGY AND THE DEPARTMENT OF RADIOLOGY, SCHOOL OF MEDICINE AND DENTISTRY, THE UNIVERSITY OF ROCHESTER]

The Autoxidation of β-Eleostearic Acid. The Application of the Spectrophotometer to the Study of the Course and the Kinetics of the Reaction[1,2]

BY RALPH W. BRAUER[3] AND LUVILLE T. STEADMAN

The course and mechanism of the reactions between unsaturated fatty acids and molecular oxygen have remained obscure in spite of a vast amount of careful investigation. The solution of this important problem has been held up by a dilemma which the conventional approach has been unable to evade: Either the autoxidation takes a complicated destructive course, with the formation of numerous secondary products, or there are several centers within the molecule capable of undergoing reaction. In either case the methods hitherto employed measure a number of simultaneously occurring reactions which cannot be disentangled for theoretical studies.

Of the known fatty acids, those which contain a conjugated system of unsaturation show the least breakdown and the most clearly defined oxygen uptake. Due to their conjugated double bonds, these compounds all show strong absorption of light in the middle or remote ultraviolet region. This property permits the determination, impracticable by other methods, of a particular grouping throughout the course of the autoxidation reaction. Thus, in spite of the fact that more than one center in these molecules is capable of absorbing oxygen, it becomes possible to dissociate the various reactions from one another to some degree.

The work reported in this paper has been performed upon β-eleostearic acid, an octadecatrienoic acid of structure

$$CH_3(CH_2)_3(CH{=}CH)_3(CH_2)_7COOH$$

which is readily obtained in a state of high purity from tung oil. The autoxidation of this material was followed by spectrophotometric means and by simultaneous oxygen uptake measurements.

In order to attain a satisfactory degree of accuracy and reproducibility, it was deemed desirable to carry out the reactions in liquid solutions in an inert solvent. This required the development of a special technique for the oxygen uptake measurements, which will be described below in some detail, not only as an integral part of the spectrographic studies, but also because the procedure permits the investigation of the relation between the concentration of autoxidizable substrate and the rate of autoxidation. In the opinion of the authors such studies are of vital importance to the further elucidation of the mechanism of autoxidation of ethylenic systems.

Experimental

β-Eleostearic Acid.—Sulfur isomerized tung oil[4] was saponified according to the method of Dann, *et al.*,[5] and the non-saponifiable matter was extracted with ether from the alkaline mixture diluted 1:1 with water. The aqueous layer was separated and acidified after heating to about 90°. The liberated fatty acids were washed repeatedly with hot water, and finally solidified by the addition of ice water, and were then separated by filtration. β-Eleostearic acid was isolated from the mixed fatty acids by crystallization, once from methyl alcohol and three times from petroleum ether (b. p. 40–60°) at 0°.

The β-eleostearic acid thus obtained consisted of white platelets of m. p. 71.5–71.8°. The entire isolation was performed under nitrogen. The final product was stored in the dark in nitrogen-flushed containers, kept evacuated to less than 1 mm. of mercury.

***n*-Amyl Acetate.**—The commercial product (Eastman Kodak Co., C. P. grade) was purified by two different pro-

(1) Submitted by Ralph W. Brauer in partial fulfillment of the requirements for the degree of Doctor of Philosophy to the Division of Graduate Studies of the University of Rochester.

(2) Read in part before the Division of Biological Chemistry at the 104th meeting of the American Chemical Society, Detroit, April, 1943.

(3) Present address: Distillation Products, Inc., Rochester, N. Y.

(4) The authors hereby acknowledge the kindness of Mr. C. F. Goodyear, President of the Bogalusa Tung Oil Corp., Bogalusa, La., in providing the oil employed in this work.

(5) Dann, Morton, Heilbron and Kon, *Biochem. J.*, **29**, 133 (1935).

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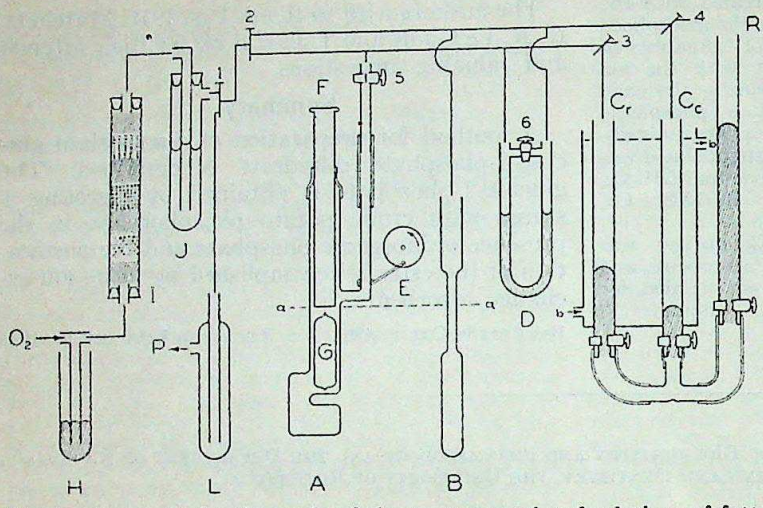

Fig. 1.—Apparatus for the study of the oxygen uptake of solutions of fatty acids.

cedures, namely, that of Likhtman[6] and that recommended by Weissberger and Proskauer.[7] The physical constants of samples prepared by either procedure were identical and indicated the presence of some lower esters in the product. Neither sample showed any oxygen uptake when shaken for twenty-four hours at 64.5° under 1 atmosphere of oxygen in the dark.

Preparation of Solutions.—In all, five solutions were employed in the experiments here reported. The concentrations are shown in Table I. These solutions were

TABLE I

Solution no.	1	2	3	4	5
Concn. in g. β-eleostearic acid per 10 cc. soln.	0.204	0.315	0.397	0.890	1.490

made up by weight under nitrogen in 5-g. lots and were freed of air by passing a stream of solvent-saturated nitrogen through the liquid for five minutes. Aliquots of 0.2–0.5 g. were weighed under nitrogen into thin-walled ampules, which were then cooled to −80°, evacuated and sealed. The finished ampules were kept in a dark vacuum desiccator, evacuated to below 1 mm.

Apparatus and Procedure.—The apparatus employed in these experiments consisted essentially of the following parts (see Fig. 1): the reaction cell A attached to the shaking eccentric E and connected to the manometer D and the gas buret C_r; the compensating cell B attached to the other side of the manometer D and to the gas buret C_c; the gas and vacuum train, consisting of the mercury trap H, the drying tower I, the solvent saturating tube J and the dry-ice trap L placed before the vacuum pump P; the stopcock manifold 1, 2, 3, 4, 5, 6, which permitted the connection of the various parts of the system with one another and the atmosphere. Cells A and B were kept in the water thermostat a-a which was maintained at 64.5 ± 0.2°. The gas burets C_r and C_c were placed in the circulating water jacket b-b thermostated at 28.0 ± 0.3°. A shaking rate of 40 cycles per minute was found to be well above the critical rate of shaking and was employed throughout.

The apparatus was operated as follows: Stopcock 6 was opened, thus putting the manometer D out of operation. The glass rod F was removed from cell A and the solution to be tested was introduced in ampule G. A was then closed by replacing F into its rubber collar, and the shaking mechanism was started. The entire apparatus was next evacuated and tested for leaks. After the system had been made completely gas-tight, dry oxygen, saturated with *n*-amyl acetate vapor, was admitted through H, I, J into all parts of the apparatus. This procedure of alternately evacuating and filling with oxygen was repeated three times and finally the oxygen pressure within the apparatus was brought to 10–15 mm. of mercury above atmospheric pressure. After fifteen minutes the apparatus had reached temperature equilibrium. The reaction was then started by crushing ampule G with the rod F. Gas pressure within the apparatus was adjusted to atmospheric pressure by momentarily opening stopcocks 3 and 4 to the outside, and finally the manometer arms were separated by closing 6. Oxygen uptake was measured directly by introducing mercury from the reservoir R into the gas buret so as to maintain a constant oxygen pressure differential between A and B. The geometry of the apparatus was such that distillation of solvent from A into C_r did not take place to any detectable amount under the conditions of the experiments. All volume changes employed in the calculations are uncorrected for the partial pressure of the solvent since suitable data are not available in the literature. When such data become available a downward correction of all oxygen values reported below will have to be made which will probably not exceed 2–3%.

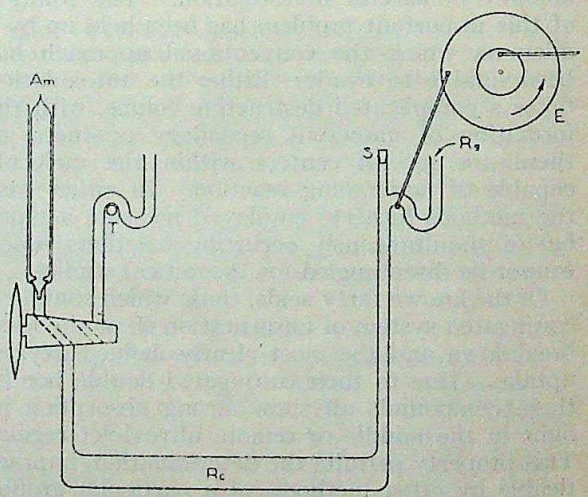

Fig. 2.—Oxidation cell for the spectrographic studies.

For the spectrographic experiments the cell shown in Fig. 2 was connected to the shaking eccentric and simultaneous oxygen uptake and spectrophotometric determinations were performed. The sample was introduced into the spectrographic cell by cracking both ends of the ampule Am. The cell R_c was next flushed with oxygen and connected to the gas reservoir R_g which was kept filled with oxygen at atmospheric pressure. From time to time samples for spectrographic analysis were withdrawn from the cell through the stud S. Such samples were weighed and diluted with a calculated amount of ether to a concentration of 1.84 mg. of β-eleostearic acid per liter of ether for the initial samples; for the later samples the concentrations were adjusted so that the density at 2685 Å. was between 1.5 and 2.0. The spectrographic examination was performed by means of a medium size Bausch and Lomb quartz spectrograph using a rotating sector spectrophotometer with an iron spark as light source.

(6) Likhtman, USSR Patent 52,647; *cf. C. A.*, **34**, 5468 (1940).

(7) Weissberger and Proskauer, "Organic Solvents," Oxford University Press, 1935.

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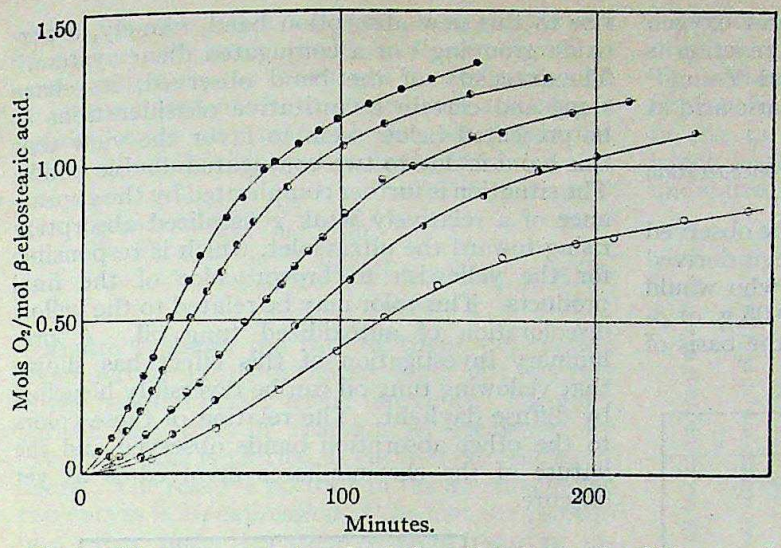

Fig. 3.—The oxygen uptake of solutions of β-eleostearic acid in *n*-amyl acetate: ○, solution no. 1; ◑, solution no. 2; ◒, solution no. 3; ◐, solution no. 4; ●, solution no. 5 (*cf.* Table I).

Results and Discussion

Figure 3 shows the oxygen uptake of different concentrations of solutions of β-eleostearic acid in *n*-amyl acetate as a function of time.

In all cases induction periods of from twenty to forty minutes were observed. These, however, were found to be irreproducible even with duplicate samples of the same solutions.[8] The variations observed in the induction periods apparently were not due to impurities present in the solvents, since no differences could be observed between the solvent purified by the two procedures.[6,7] Neither can the blame be laid upon impurities of the acid employed, since all samples were prepared from the same batch of material. The oxygen tension was substantially the same in any duplicate experiments; the extremes of the variation of total pressure of the entire series of experiments were 755.5 and 729.8 mm. of mercury, respectively; hence, this factor can hardly be responsible for the results obtained. A plausible explanation might be found in the persistence of minute traces of dissolved oxygen in the solvent in spite of the precautions taken.

But for their induction periods, duplicate oxygen uptake curves were found to be superimposable within an accuracy of ±1–2%. The induction periods shown in Fig. 3 were arbitrarily chosen to permit convenient representation.

Several samples were studied for twenty-four to thirty-six hours. In all cases it was found that the uptake of oxygen became extremely small after 2 mols of oxygen per mol of β-eleostearic acid had been absorbed. These observations agree with those of Myers, Kass and Burr,[8] who studied the autoxidation of the acid spread upon filter paper at 40° and with the results of Miller and Claxton,[9] who worked with the molten acid at 80°. The agreement of these various experiments suggests that the main reaction is terminated when 2 mols of oxygen have been taken up per mol of β-eleostearic acid, and that any further oxygen absorption represents a side reaction, possibly of a degradative type.

The final product of the autoxidation has been isolated by the dilution of the completely oxidized solutions with petroleum ether. This procedure precipitates the oxidized material, a dark brown, viscous, non-volatile oil. Analysis[10] showed a composition $C_{36}H_{58.8}O_{12.2}$, a neutral equivalent of 312.4 and a molecular weight of about 600 (ebullioscopic determination in acetone). These properties would agree closely with those expected for a dimer of β-eleostearic acid, formed with the uptake of 2 mols of oxygen per mol of acid and without the participation of the carboxyl groups: $C_{36}H_{58-60}O_{12}$, neutral equivalent 315, molecular weight 630. All attempts to crystallize this material have failed so far, and it is suggested that several isomers are present which differ in the relative orientation of the chains (head-to-head or head-to-tail), the sites of mutual attachment and possibly in geometric configuration.

The rate of oxygen uptake in each experiment increased from 0 to a maximum after the absorption of 0.3 to 0.5 mol of oxygen per mol of β-eleostearic acid, and thereafter decreased slowly, to reach 0 when the limiting amount of oxygen had been consumed (see, *e. g.*, Fig. 7). The re-

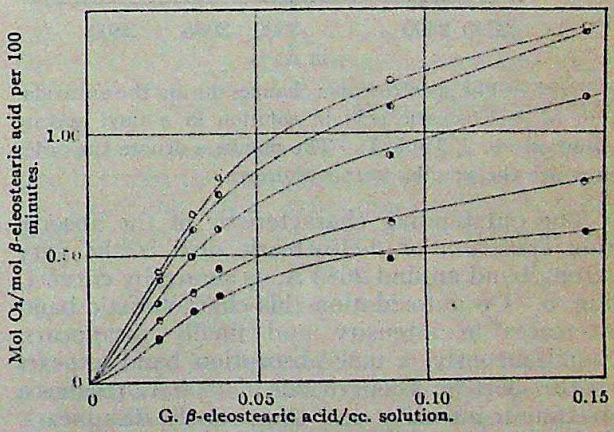

Fig. 4.—The rate of oxygen uptake of solutions of β-eleostearic acid in *n*-amyl acetate as a function of the initial concentration: ●, after the absorption of 0.025; ◒, of 0.050; ◑, of 0.100; ◐, of 0.200; and ○, of 0.300 mol of oxygen per mol of β-eleostearic acid.

(8) Myers, Kass and Burr, *Oil and Soap*, **18**, 107 (1941).

(9) Miller and Claxton, *Ind. Eng. Chem.*, **20**, 43 (1928).

(10) The authors are indebted to Mr. H. Baumann of the Department of Chemistry of this University for the combustion analyses performed in connection with this work.

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lation between initial concentration and oxygen uptake rates for various stages of the reaction is represented in Fig. 4. Henderson and Young[11] working with oleic acid dissolved in stearic acid at 70° reported a relation

$$\text{Rate of oxygen uptake} = A + B \times (\text{initial concentration of oleic acid})$$

where A and B are constants. It will be observed that a similar equation might have been derived for β-eleostearic acid by an observer who would employ a concentration greater than 0.05 g. of β-eleostearic acid per cc. of solution as the basis of his considerations.

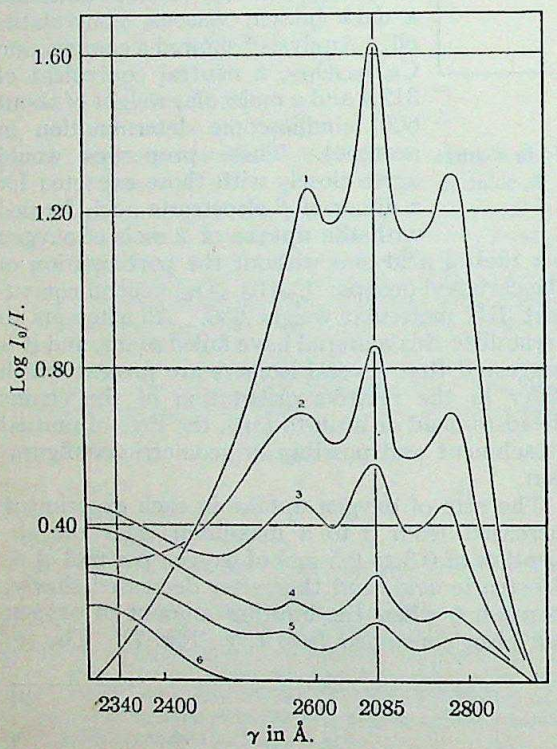

Fig. 5.—The spectroscopic changes during the autoxidation of β-eleostearic acid in solution in *n*-amyl acetate (solution no. 2, Table I). The numbers denote the order in which the samples were withdrawn.

The outstanding characteristic of the absorption spectrum of β-eleostearic acid is the very strong band around 2685 Å. as shown by curve 1, Fig. 5. On autoxidation this characteristic band decreases in intensity and finally disappears. Simultaneously, a new absorption band appears on the short wave length side of 2500 Å., reaches a maximum intensity and then slowly disappears. Unfortunately, the spectrograph employed does not permit measurements below 2330 Å., so that only one side of the new band can be observed. This restriction makes it impossible to definitely identify the new band as due to a particular chromophore. Under the conditions of these experiments, two groupings might plausibly give rise to this new absorption band, namely, a peroxide grouping[12] or a conjugated diene system.[13] The intensity of the band observed, its sharp slope and certain quantitative considerations to be presented below seem to favor the view that this band is due to two conjugated double bonds. The situation is further complicated by the appearance of a relatively weak generalized absorption rising toward the ultraviolet, which is responsible for the yellowish to brown color of the final products. This color may be related to the yellow discoloration of autoxidized tung oil. A preliminary investigation of this effect has shown that yellowing tung oil can be reversibly bleached by diffuse daylight. The relation of these colors to the other absorption bands observed and the nature of the chromophores involved is as yet obscure.

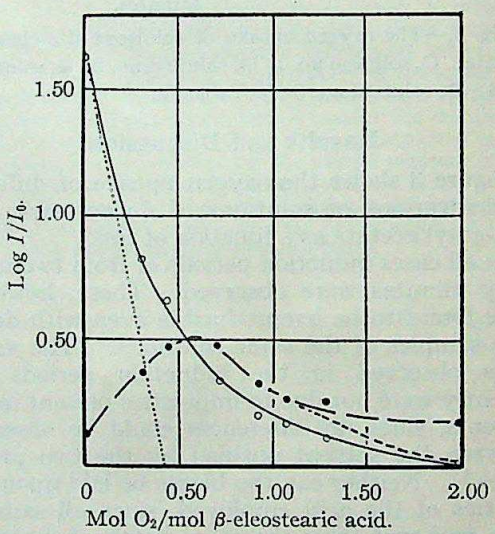

Fig. 6.—The extinction coefficients of autoxidizing β-eleostearic acid as a function of oxygen taken up: ○, log I_0/I at 2685 Å.; ●, log I_0/I at 2340 Å.; ———, calculated from equation 1; – – – –, late course of diene curve as predicted from reactions A and B.

Figure 6 shows the relation between the amount of oxygen absorbed and the extinction coefficient of the autoxidizing solution at 2685 and at 2340 Å., respectively. The relation between the extinction coefficient of the triene band and the amount of oxygen taken up is given by the empirical expression:

$$K_{3\Delta_t} = K_{3\Delta_0} \frac{O_{2\infty} - O_{2t}}{(1.265\, O_{2t} + \sqrt{O_{2\infty}})^2}$$

where $O_{2\infty}$ and O_{2t} represent the amount of oxygen taken up at infinite time and at time t, respectively, and where $K_{3\Delta_0}$ and $K_{3\Delta_t}$ represent the extinction coefficient at 2680 Å. at zero time and at time t, respectively. In view of what has been said

(11) Henderson and Young, *J. Phys. Chem.*, **46**, 670 (1942).

(12) E. Rieche, "Alkylperoxyde und Ozonide," T. Steinkopff, Leipzig, 1931.

(13) D. T. Mowry, W. R. Borde and J. B. Brown, *J. Biol. Chem.*, **142**, 671 (1942); J. H. Mitchell, Jr., H. R. Kraybill and F. D. Zscheile, *Ind. Eng. Chem., Anal. Ed.*, **15**, 2 (1943).

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above, $O_{2\infty}$ is equal to 2.0 mols of oxygen per mol of β-eleostearic acid. From this expression it is possible to compute the rate of triene destruction at any moment of the reaction from the oxygen uptake curve and relatively few spectrographic data. The following relation is obtained

$$(1)\qquad \frac{d}{dt}K_{3\Delta_t} = \frac{\partial K_{3\Delta_t}}{\partial O_2}\frac{dO_2}{dt} = \frac{dO_2}{dt} \times K_{3\Delta_0} \times \frac{1.265(O_{2t} - 2O_{2\infty}) - \sqrt{O_{2\infty}}}{(1.265\,O_{2t} + \sqrt{O_{2\infty}})^3}$$

Figure 7 shows the rate of triene destruction computed by means of this equation as a function of the residual intact triene (curve a). For comparison the rate of reaction as measured by oxygen uptake is plotted as curve b into the same figure. The relative position of the maxima of the two curves is an expression of the fact that groupings other than the triene system take an increasingly important part in the absorption of oxygen as the reaction progresses.

The marked asymmetry of curve a is of theoretical interest. Either a simple autocatalytic mechanism or a mechanism involving an autocatalytic chain reaction would lead to the prediction of a symmetrical shape for this curve. The asymmetry of curve a, Fig. 7, is therefore indicative of one of two possibilities: either a catalyst which is formed in the first stages of the reaction is destroyed in later phases, or an inhibitor substance gradually accumulates during the course of the reaction. Which of these possibilities is the correct one cannot be determined on the basis of available data.

The data presented in Fig. 6 also give some indication of the fate of the absorbed oxygen. Inspection of the triene decay curve will reveal the fact that the intercept with the O_2 axis of the tangent drawn to this curve at the value $O_2 = 0$, yields directly the value of the ratio (O_2 taken up)/(triene destroyed) at the start of the reaction. Calculation shows this value to be equal to 0.44. Thus, a little less than $1/2$ mol of oxygen suffices initially to destroy 1 mol of triene system. Present evidence indicates that the uptake of oxygen by unchanged molecules does not involve the initial rupture of the strong O–O bond. The results here obtained can be explained in terms of either of two hypotheses: (A) the peroxidation is succeeded by a very rapid decompostion reaction involving the peroxidized molecule and one intact molecule; or (B) the initial peroxidation may lead either directly or in a rapid secondary reaction to the formation of dimeric products with the formation of additional C–C and C–O bonds. These products may or may not be peroxidic. The fact that low molecular weight decomposition products are not observed in the course of the autoxidation of β-eleostearic acid makes the first of these possibilities improbable, while the assumption that dimerization is an essential part of the reaction between the triene and molecular oxygen is supported by the appearance of dimers of the original acid as the major product of the reaction. The somewhat low value obtained for the initial oxygen to triene ratio (0.44 instead of 0.50) may be due to a reaction caused by the peroxide and which leads to the formation of polymers of the unoxidized acid.[14]

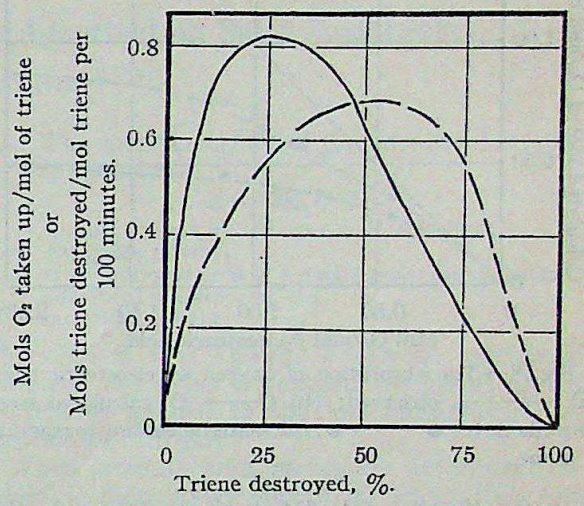

Fig. 7.—Rate of autoxidation as measured by oxygen uptake or by triene destruction: (a) ———, triene destruction; (b) – – – – –, oxygen uptake.

The oxygen–triene curve very soon deviates from the tangent which would represent the course of the reaction if only the step described above took place. A closer approach to the observed oxygen uptake can be achieved if it be assumed that the absorption at 2340 Å. is due to a conjugated diene which is formed directly from the triene and which in turn is capable of absorbing oxygen. The sequence of the reactions which would represent this hypothesis is

(A) $2(\text{—C=C—})_3 + O_2 \longrightarrow n(\text{—C=C—})_2$

(B) $(\text{—C=C—})_2 + mO_2 \longrightarrow$ spectrographically inert product capable of absorbing $(3\text{-}nm)$ mols of O_2

These formulas permit the calculation of the relation between the amount of oxygen taken up and the diene and triene extinction coefficients after various periods of reaction. The relation obtained is

$$(2)\qquad O_2 = \frac{K_{3\Delta_0} - K_{3\Delta_t}}{2K_{3\Delta_0}}(1 + mn) - m\frac{K_{2\Delta_t}}{K_{3\Delta_0}}\frac{\epsilon_{3\Delta}}{\epsilon_{2\Delta}}$$

where $\epsilon_{3\Delta}$ and $\epsilon_{2\Delta}$ designate the specific extinction coefficients of the triene and the diene, respectively. The ratio $\epsilon_{3\Delta}/\epsilon_{2\Delta}$ has been determined by extrapolation from the experimental data. If n is assumed to be $1/2$, or 1, or 2, then $\epsilon_{3\Delta}/\epsilon_{2\Delta}$ equals 2, or 1, or $1/2$, respectively. From the authors' data for β-eleostearic acid and from those of Van der Hulst[15] for 9,11-linoleic acid, this ratio can be computed and is found to be 1.5, thus eliminating

(14) Tatimori, *J. Soc. Chem. Ind., Japan*, **44**, suppl. 8 (1941).

(15) Van der Hulst, *Rec. trav. chim.*, **54**, 639 (1935).

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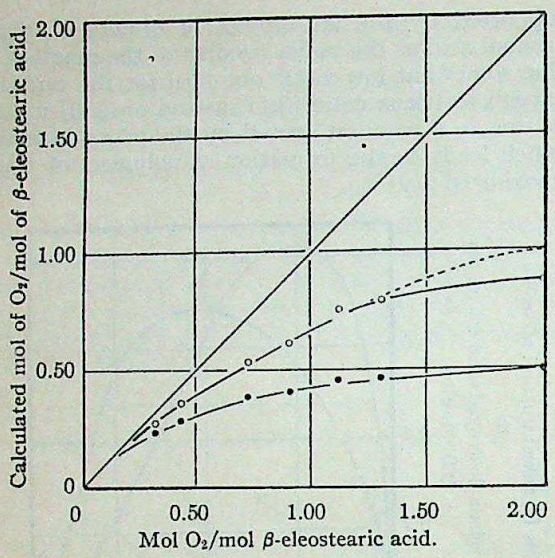

Fig. 8.—The absorption of oxygen by eleostearic acid: (a) ————, observed; (b) O————O, calculated from formula 2; (c) ●— — —●, calculated according to reaction A alone.

$n = 2$. Further calculation shows that only the case $n = 1$, $m = 1$ yields satisfactory results. The curve calculated on this basis is shown as curve b, Fig. 8. For comparison, the curve computed on the assumption that the oxygen uptake value = $^1/_2 \times$ (mols of triene destroyed) is shown in the same figure as curve c and the experimental values are indicated by the straight line a. The course of curve b deviates in its later part from that expected on the basis of the proposed scheme of reactions as indicated by the dotted line on the graph. This deviation might be due to the generalized light absorption mentioned earlier in this paper and which becomes more prominent as the reaction progresses. The difference between the value of $\epsilon_{3\Delta}/\epsilon_{2\Delta}$ as observed in these experiments and as calculated from the studies on pure compounds is hardly surprising in view of the fact that the hypothetical diene certainly must possess a structure differing widely from that of the straight chain fatty acid investigated by Van der Hulst.

The results reported in this paper permit no more than a tentative description of the autoxidation of β-eleostearic acid. Further progress will depend largely upon an elucidation of the structure of the several compounds[16] formed as intermediate and final products of the reaction. Some preliminary work has been performed in this connection and has indicated marked differences in the stability of differently combined oxygen. In the dimeric acid already described, all but $^1/_2$ mol of oxygen per mol of β-eleostearic acid is unstable and can be removed by boiling for one hour with 2% aqueous potassium hydroxide. The product obtained from such treatment is still a dibasic dimer of β-eleostearic acid of composition $C_{36}H_{58.0}O_{5.92}$[10] (formula for 2 mols β-eleostearic acid + $^1/_2$ mol O_2 = $C_{36}H_{60}O_6$). In view of the fact that $^1/_2$ mol of oxygen initially accounts for the destruction of one triene system, this observation may hold a valuable clue.

(16) It would seem inadvisable, therefore, to make use of structural formulas in this paper; such formulas at the best could only represent one of a very considerable number of possible reaction courses, and their use would thus obscure rather than clarify the results actually obtained.

Acknowledgment.—Ralph W. Brauer wishes to acknowledge gratefully the constant friendly advice and encouragement of Dr. Harold C. Hodge. He also desires to express his gratitude toward Professor W. R. Bloor for his friendly attitude which has materially aided in the completion of this research.

Summary

1. A method has been described for the study of the autoxidation of fatty acids in liquid solution by oxygen uptake measurements and by the simultaneous determination of the absorption spectra of the autoxidizing solutions.

2. Curves showing the relation between the rate of oxygen uptake of β-eleostearic acid and the initial concentration of the substrate have been presented.

3. From the spectrographic changes observed in autoxidizing solutions of β-eleostearic acid, it has been suggested that during the reaction a conjugated diene is formed which in turn undergoes autoxidation.

4. A method has been described which permits the computation of the rate of triene destruction employing (a) the oxygen uptake curves and (b) the relation between absorbed oxygen and residual intact triene groups.

5. In order to destroy 1 mol of β-eleostearic acid, slightly less than one-half mol of oxygen is required initially. Consequently, it has been assumed (a) that the initial uptake of oxygen by β-eleostearic acid results in a dimerization involving the formation of some carbon to carbon bonds and (b) that a parasitic polymerization reaction is induced by the peroxides formed in the course of the reaction. The formation of dimeric products in the reaction has been verified by molecular weight determinations.

6. The amount of oxygen taken up can be computed approximately for the early stages of the reaction from the extinction coefficients of the diene and the triene bands if the following sequence of reactions is assumed

$$2(\text{—C=C—})_3 + O_2 \longrightarrow (\text{—C=C—})_2$$

$(\text{—C=C—})_2 + O_2 \longrightarrow$ spectrographically inert products capable of taking up 2 mols of oxygen per mol of original β-eleostearic acid

7. The rate of oxygen absorption by β-eleostearic acid becomes insignificant after an uptake of 2 mols of oxygen per mol of β-eleostearic acid.

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This amount of oxygen can be recovered in a dibasic acid which is probably a dimer of the original acid. Three-fourths of the absorbed oxygen in this product is removed by treatment with alkali.

ROCHESTER, N. Y. RECEIVED SEPTEMBER 28, 1943

[CONTRIBUTION FROM KENT CHEMICAL LABORATORY, THE UNIVERSITY OF CHICAGO]

Cross-Sectional Areas of Molecules Adsorbed on Solid Surfaces[1a]

BY H. K. LIVINGSTON[1b]

The data relating to the cross-sectional areas of molecules in insoluble monolayers adsorbed on water are quite extensive. Adam[2] has listed limiting area values for 26 different classes of molecules. Recently, an increasing number of adsorption studies for gases and vapors adsorbed on solid surfaces of *known area* have been reported.[3] This is principally due to the development of an adsorption theory[4] which permits the calculation of the specific surface of any solid for which vapor adsorption data are available. Therefore, it should be possible to establish a body of area data for vapor molecules adsorbed on solid surfaces analogous to the data for insoluble molecules adsorbed on liquid surfaces.

As will be explained in the following section, cross-sectional area data for molecules adsorbed on solid surfaces are subject to restriction in that they are based on specific surface data which, in turn, are based on cross-sectional area data. If the experimental results are properly interrelated, however, it is possible to obtain accurate relative values for molecular cross-sectional areas.

Theoretical.—Brunauer, Emmett and Teller[4] have developed an equation in the form

$$q_m = \frac{q(p_0 - p)(p_0 - p + cp)}{cpp_0} \qquad (1)$$

q_m = quantity of vapor adsorbed when a monomolecular layer exists, g. per g. of adsorbent.
q = quantity of vapor adsorbed at any pressure, g. per g. of adsorbent.
p = pressure; p_0 = saturation pressure.
c = $(a_1b_1/a_ib_i)\exp.(E_1 - RT.E_i)/$
E = energy of adsorption.
a and b are probability factors in the equations:
ap = number of molecules condensing per unit area;
$b \exp.(E/RT)$ = number of molecules evaporating per unit area.
Subscripts "1" refer to first layer of adsorbed molecules.
Subscripts "i" refer to all other layers (average values).

As pointed out in their paper, the equation may be transposed to give

$$p/q(p_0 - p) = 1/cq_m + p(c - 1)/cq_mp_0 \qquad (2)$$

Since p and q can be measured, this straight-line form of the equation can be used to evaluate c and q_m. The specific surface of the adsorbent is given by the equation

$$\Sigma = Nq_m\sigma/M \qquad (3)$$

Σ = specific surface, sq. cm. per g. of adsorbent.
N = Avogadro number.
σ = cross-sectional area of a single molecule (in plane of adsorbent surface), sq. cm.
M = molecular weight.

Therefore if σ is known, Σ can be calculated. Emmett[5] has given a detailed treatment of this method as applied to the low temperature adsorption of nitrogen.

When pressure–area curves are determined for insoluble monolayers spread on water, the area per molecule is obtained from the equation

$$A = MS/WN \qquad (4)$$

A = area per molecule, sq. cm.
W = weight of insoluble material spread on surface, g.
S = total area available to monolayer, sq. cm.

In the same manner, the area available to each molecule adsorbed on a solid surface can be calculated from the analogous equation

$$A = M\Sigma/qN \qquad (5)$$

With pressure–area data for insoluble monolayers, it is possible to recognize one portion of the curve as corresponding to close-packed chains. The area per molecule in this region is accepted as being equivalent to the actual area of the molecule in a plane parallel to the adsorbing surface, that is, the cross-sectional area (hereafter referred to as "section area"). This section area is found to be approximately equal to that which would be predicted from measurements of molecular dimensions in the normal condensed phases (liquid or solid).

Section area data obtained from pressure–area data for insoluble monolayers are known to vary with the temperature or surface pressure. It would be expected that similar results would be obtained with adsorbed layers on solids, and therefore σ-values used in equation (3) would vary somewhat with temperature, surface pressure, and solid surface.

By use of equation (2), the adsorption corresponding to a complete monolayer can be calculated. The molecular area, A, at this point is equivalent to the actual cross-sectional area occupied by the molecules measured in a plane parallel to the adsorbing surface. Accordingly, when

(1a) Original manuscript received October 21, 1943.
(1b) Present address: Jackson Laboratory, E. I. du Pont de Nemours and Co., Deepwater Point, N. J.
(2) Adam, "The Physics and Chemistry of Surfaces," Oxford Press, New York, N. Y., 1941, p. 50.
(3) Brunauer, "The Adsorption of Gases and Vapors. Vol. I. Physical Adsorption," Princeton University Press, Princeton, 1943.
(4) Brunauer, Emmett and Teller, THIS JOURNAL, 60, 309 (1938).
(5) Emmett, *Advances in Colloid Sci.*, 1, 1 (1942).

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$q = q_m$, $A = \sigma$, and equation (5) is identical with equation (3) at this point. Thus, A is the area available to each molecule, which will be very great at the beginning of adsorption, while σ is the area which is effectively occupied by each molecule. This area will be very similar to that which is determined from considerations of the atomic volumes involved, but will depend on the packing which the molecules adopt.

It should be emphasized that this treatment is based on the monomolecular adsorption as calculated by the equation of Brunauer, Emmett and Teller, and the results are subject to the same limitations as is their theory. Recent publications have questioned the validity of the equation. Kistler, Fischer and Freeman[6] have objected to the derivation on two counts. They point out that if E_1 is greater than E_i (see equation (1)), as Brunauer, Emmett and Teller assume, molecules in the second layer will distill to fill any bare space in the first layer if that layer is not yet complete. However, one would not expect the energy of adsorption on the bare solid surface to be a constant throughout the process of adsorption. It would seem that E_1 represents an average value, and when the solid surface is almost completely covered, the energy of adsorption on the few bare spaces remaining is so small that condensation in the second or subsequent layers is more probable. Statistically, however, the rate of evaporation over the entire first layer remains equal to b exp. (E_1/RT). Thus E_1 and E_i, like a and b, are constants of the equation and should be interpreted primarily as such. The second objection of Kistler, Fischer and Freeman is that capillary condensation is neglected in equation (1). Inasmuch as the equation fits experimental data very well for pressures up to $p/p_0 = 0.3$, even for many porous solids, the objection is not serious for the portion of the isotherm which determines q_m. This would be especially true for crystalline nonporous adsorbents such as those used in the present work.

Rowley and Innes[7] have applied a two-dimensional phase rule to determine that multilayers adsorbed from vapors onto solids must exist as gaseous two-dimensional films. They conclude that the energy of vaporization in layers after the first cannot be a factor in equation (1). Again, this objection does not appear to invalidate the equation in its original form. Although Brunauer, Emmett and Teller have suggested that E_i is approximately equal to the energy of vaporization of the bulk liquid, this assumption has no effect on the fundamental theory. It is only necessary that E_i be equal to the energy involved in multilayer formation, whatever the source of the energy. The layers may be gaseous, liquid, or solid without affecting the result. If E_i is not equal to the energy of vaporization, equation (1) must be modified to a form in which p_0 is replaced by a new constant. The writer has studied this possibility and found that the value of this constant has relatively little effect on the form of the theoretical isotherm when p/p_0 is less than 0.3; that is, in the range where the equation fits experimental data.

In this connection, it is interesting that the new adsorption isotherm of Jura and Harkins[8] is based on the assumption that the adsorbed films obey the pressure–area relations developed for condensed monolayers on water surfaces. This would seem to contradict the conclusion of Rowley and Innes to the effect that the films are gaseous rather than condensed. The Gibbs equation for vapor–solid adsorption (see Boyd and Livingston,[9] equation (15)) is

$$\pi = (RT/M\Sigma)\int_0^p (q/p)\,dp \qquad (6)$$

π = surface pressure of the adsorbed film on the solid surface. If equations (1) and (3) are substituted into this equation

$$\pi = (RT/N\sigma)\ln[(p_0 - p + cp)/(p_0 - p)] \qquad (7)$$

This is the relation between π, the surface pressure, and the gas pressure for adsorptions to which the equation of Brunauer, Emmett and Teller applies. It can be shown that pressure–area plots constructed from equations (7) and (5) show a considerable portion which is approximately a straight line. That is, the basic equation of Jura and Harkins

$$\pi = a - bA \qquad (8)$$

is in agreement with the equation of Brunauer, Emmett and Teller over a considerable range of pressure. For example, the data of Table I can be fitted to the equation

$$(N\sigma/RT)\pi = 2.58 - 1.65\,A/\sigma \qquad (9)$$

over the pressure range $p/p_0 = 0.07$ to $p/p_0 = 0.5$. This is very similar to the range of agreement reported for the isotherm of Jura and Harkins.

TABLE I

THEORETICAL PRESSURE–AREA DATA

Calculated from equations (7), (1) and (5), with $c = 50$.

p/p_0	$(N\sigma/RT)\pi$	A/σ
0.01	0.176	2.95
.05	.559	1.31
.06	.622	1.23
.075	.704	1.15
.09	.774	1.09
.10	.816	1.06
.125	.910	0.996
.15	.992	.946
.175	1.06	.903
.20	1.13	.865
.30	1.35	.733
.40	1.54	.619
.50	1.71	.510

Accordingly, the new isotherm seems to be closely related to that of Brunauer, Emmett and

(6) Kistler, Fischer and Freeman, THIS JOURNAL, 65, 1909 (1943).

(7) Rowley and Innes, *J. Phys. Chem.*, 45, 1041 (1941).

(8) Jura and Harkins, *J. Chem. Phys.*, 11, 430 (1943).

(9) Boyd and Livingston, THIS JOURNAL, 64, 2383 (1942).

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Teller, although it is perhaps superior at higher pressures. The success of the Jura–Harkins isotherm increases our confidence in the Brunauer–Emmett–Teller theory.

Measurements.—Emmett and Burnauer have described the adsorption apparatus which they have used for measurement with oxygen or nitrogen at or near their boiling points.[10] A facsimile of this apparatus has been used in this work for determining the nitrogen isotherms. Boyd and Livingston[9] have described an apparatus which is very satisfactory for adsorption studies with vapors which liquefy at room temperature and atmospheric pressure. They use a gravimetric method employing the McBain–Bakr silica spring balance,[11] which is especially designed for use with organic vapors which attack stopcock grease. This apparatus was used for determining the adsorption isotherms of water, *n*-propyl alcohol, and *n*-heptane on the same sample of four different crystalline powders: quartz, anatase, barium sulfate and graphite. These adsorption isotherms have been reported previously.[9] All of the isotherms have been fitted to the Brunauer–Emmett–Teller equation with least square calculations, using the straight line form, equation (2). Thus, for any single sample of powdered solid, it was possible to determine the constants of the Brunauer, Emmett and Teller equation with several different vapors. These are reported in Table II.

TABLE II

THE CONSTANTS OF THE BRUNAUER–EMMETT–TELLER EQUATION

Adsorption measurements at 24°

Solid	Water q_m	Water c	Propyl alcohol q_m	Propyl alcohol c	Heptane q_m	Heptane c
Anatase	2.32	82.2	4.09	66.8	2.22	37.6
Quartz	0.85	72.0	1.47	106.8	0.92	29.1
$BaSO_4$	0.57	218	0.86	132	0.64	44.1
Graphite					9.36	72.0

The Section Area of Adsorbed Molecules.—For many molecules there are a number of independent methods for determining the molecular area, so that a most probable value can be developed from the consideration of the several methods. The effective dimensions of a molecule can be calculated from the density of the bulk phase if the nature of the packing is known and the molecules are spherical. The value of σ can be calculated for all combinations of the three simplest three-dimensional packings and the two simplest two-dimensional packings. The equation which is used is

$$\sigma = F(M/N\rho)^{2/3} \qquad (10)$$

where ρ = the density of the bulk phase. The values of F, the packing factor, are given in Table III.

For the closest possible packing, $F = 1.091$. This is the factor which Emmett and Brunauer[10] have used in their calculations. For nitrogen, this leads to cross-sectional areas of 16.2 and 13.8 Å. per molecule, based on liquid density at −196° and solid density at −252°, respectively. In their early publications, Emmett and Brunauer used both areas, but Emmett and DeWitt[13] used the liquid value exclusively. Ruhemann[14] reports that β-nitrogen (the form which is stable above 35° K.) crystallizes in the form of spheres with closest possible packing. This indicates that 1.091 is the correct packing factor and the section area at −196° is between 13.8 and 16.2 sq. Å.

TABLE III

PACKING FACTORS[12]

Type of three-dimensional lattice	Packing Factor: Square Two-dimensional packing, 4 nearest neighbors	Packing Factor: Hexagonal Two-dimensional packing, 6 nearest neighbors
Simple cubic, 6 nearest neighbors	1.000	0.866
Body-centered cubic, 8 nearest neighbors	1.190	1.023
Face-centered cubic, 12 nearest neighbors	1.260	1.091

The water molecule is not spherical, but the volume of hydrogen is so small in comparison with oxygen that the molecule must be almost a sphere. Ice crystals exhibit low symmetry, indicating that packing is somewhat looser than for any of the types referred to in Table III. It is very difficult to predict the area of the water molecule by use of equation (10), but if F is taken to be 1.091, the section area can be calculated to be 11.1 sq. Å., based on the solid density at 0°, or 10.6 sq. Å., based on the liquid density at 24°.

From X-ray crystallographic measurements, Müller[15] has concluded that the distance of nearest approach between normal hydrocarbon molecules is 4.75 Å. and the length of the molecules is 1.29 Å. per carbon. Accordingly, the *n*-heptane molecule may be treated as a cylinder 4.8 Å. in diameter and 9.1 Å. long. Stewart[16] has studied the X-ray diffraction pattern of liquid hydrocarbons at room temperature and reported 4.63 Å. as the distance of nearest approach. With either of these values, the area occupied by a *n*-heptane molecule with the long axis perpendicular to the solid surface would be approximately 20 sq. Å. If the molecule were oriented with the long axis parallel to the solid surface, the area would be 42.3 sq. Å. for the closest possible packing. This value would be greater for a less ordered arrangement.

From X-ray studies of the long-chain alcohols, Bernal[17] has concluded that their molecular di-

(10) Emmett and Brunauer, THIS JOURNAL, **59**, 1553 (1937).

(11) McBain and Bakr, *ibid.*, **48**, 690 (1926).

(12) This table was developed with the assistance of Prof. W. H. Zachariasen.

(13) Emmett and DeWitt, *Ind. Eng. Chem., Anal. Ed.*, **13**, 28 (1941).

(14) Ruhemann, *Z. Physik*, **76**, 368 (1932).

(15) Müller, *Trans. Faraday Soc.*, **29**, 990 (1933).

(16) Stewart, *Phys. Rev.*, **31**, 174 (1928).

(17) Bernal, *Proc. Roy. Soc. London*, **A113**, 117 (1926); Bernal and Crowfoot, *Trans. Faraday Soc.*, **29**, 1032 (1933); Bernal and Fowler, *J. Chem. Phys.*, **1**, 515 (1933); Bernal, *Proc. Phys. Soc. London*, **45**, 321 (1933); Bernal and Crowfoot, *Nature*, **133**, 794 (1934); Bernal, *Trans. Faraday Soc.*, **29**, 1039 (1933); Bernal and Crowfoot, *Z. Krist.*, **83**, 153 (1932).

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mensions are similar to those for hydrocarbons, except that the molecular length is increased by 1.0 Å. by the hydroxyl group. His data indicate that the *n*-propyl alcohol molecule is 4.9 Å. long and 4.8 Å. in diameter. Stewart and Morrow[18] found liquid *n*-propyl alcohol molecules to give a diffraction pattern corresponding to 4.3 Å. for the distance of closest approach and 5.1 Å. for the molecular length (4.8 Å. from a smooth curve). If the propyl alcohol molecule is considered to be a sphere 4.8 Å. in diameter, the section area will be 23.0 sq. Å. per molecule if square packing is assumed, and 19.9 sq. Å. per molecule for close packing. Film balance measurements can be used to determine the cross-sectional area of alcohol molecules oriented with the hydroxyl to the water surface. The extrapolation to zero pressure of the pressure–area curve for liquid films is considered to give the area of the alcohol group. The best available data are those of Copeland, Harkins and Boyd[19] for eicosyl alcohol at 24°, which give 22.4 sq. Å. molecule. It is not certain that this zero pressure value has much relation to the area of a propyl alcohol molecule which is on a solid surface under a surface pressure[9] of 60 dynes per cm.

Results.—On the basis of the considerations developed in the preceding paragraphs, values of σ have been chosen which will give satisfactory agreement among all the adsorption data. It was concluded that the section areas are in the ratio

$$N_2:H_2O:PrOH:Heptane = 15.4:10.6:20.0:55.0$$

The data supporting this conclusion are presented in Table IV. The high section area obtained for heptane indicates that the molecules are oriented with the long axis parallel to the solid surface, or at least that the molecules are spaced so that there is room for such a flat orientation.

The q_m values from the nitrogen isotherms were used for calculating the specific surface of the finely-divided solids, according to the method outlined by Emmett.[5] Equation (3) was used, with 15.4 sq. Å. taken as the section area of the nitrogen molecule, instead of 16.2 which Emmett prefers. This value of 15.4 coincides with the most frequent and also the average value reported by Jura and Harkins[20] on the basis of 60 isotherms. This value was obtained by reference to a sample of anatase the area of which had been measured by a calorimetric technique which was independent of cross-sectional area data for the adsorbed molecules.[21] This new technique offers an interesting method of checking section area values.

TABLE IV

COMPARISON OF SPECIFIC SURFACE AND SECTION AREA VALUES

Vapor	Value of σ used, Å.² per molecule	Specific surface, sq. m./g., corresponding to each value of σ TiO_2	SiO_2	$BaSO_4$	Graphite
Nitrogen	16.2	8.70	3.20	2.39	27.6
	15.4	8.27	3.05	2.27	26.2
Water	10.6	8.28	3.03	2.03	
Propyl alcohol	20.0	8.25	2.99	1.74	
Heptane	20.0	2.68	0.70	0.49	7.1
	43.6	5.85	2.42	1.70	24.7
	55.0	7.39	3.08	2.14	31.2

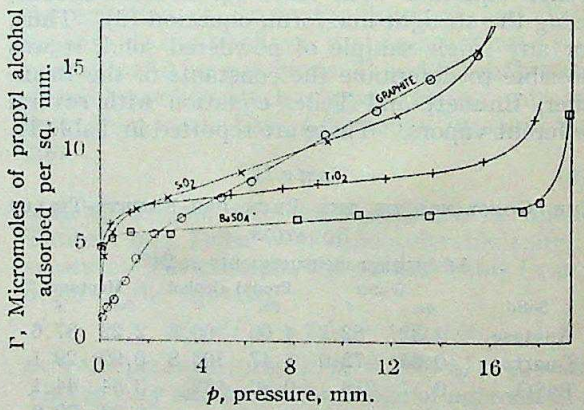

Fig. 2.—The adsorption of *n*-propyl alcohol by various solids (saturation pressure = 19.3 mm., temperature 24°).

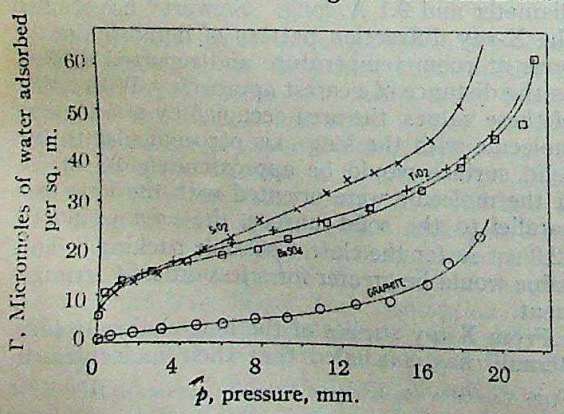

Fig. 1.—The adsorption of water by various solids (saturation pressure = 22.4 mm., temperature 24°).

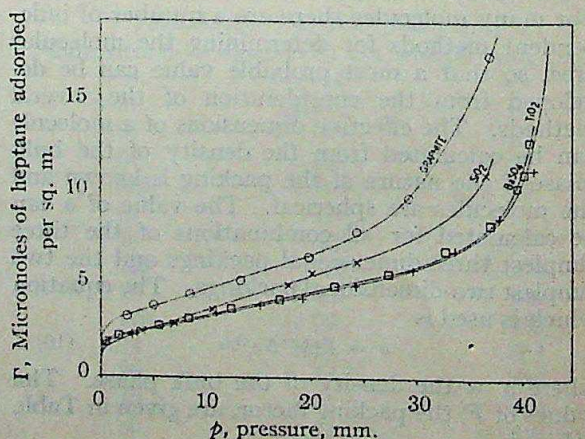

Fig. 3.—The adsorption of *n*-heptane by various solids (saturation pressure = 44.6 mm., temperature 24°).

(18) Stewart and Morrow, *Phys. Rev.*, **30**, 232 (1927).

(19) Copeland, Harkins, and Boyd, *J. Chem. Phys.*, **10**, 357 (1942).

(20) Jura and Harkins, *ibid.*, **11**, 431 (1943).

(21) Harkins and Jura, *ibid.*, **11**, 430 (1943).

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The specific surface of the solids (in sq. m. per g.) determined by this method were TiO_2, 8.27; SiO_2, 3.05; $BaSO_4$, 2.27; graphite, 26.2.

The adsorption isotherms presented in a previous publication[9] have been recalculated and transposed into a form which emphasizes the agreement between the various sets of data. These isotherms have been plotted in Figs. 1, 2 and 3. The ordinate for these plots is Γ, the molar adsorption per unit area, obtained from the equation

$$\Gamma = q/M\Sigma \qquad (11)$$

The Σ-value which was obtained from the nitrogen isotherms was used in every case. It will be seen that for quartz, anatase and barium sulfate, the break in the isotherms which corresponds to a complete monolayer[4] occurs at very nearly the same value of Γ.[22] For any vapor, the adsorbed molecules in the monolayer occupy the same area on each of these three solid surfaces. The isotherms for adsorption on graphite are not in agreement with the others. This may be due in part to impurities in the graphite sample (Dixon 0708) or to the extreme difficulty of outgassing graphite surfaces.[23]

The isotherm for heptane on graphite appears to be normal except for the higher Γ-value at the break of the curve. This suggests that heptane has a closer packing on the graphite surface than on quartz or the other solids. For heptane molecules on graphite, the section area is found to be 44 sq. Å., as compared to 55 sq. Å. for heptane on other surfaces (see Table IV). This value is very near the minimum area for the flat orientation (42.3). It is interesting that the section area value for heptane adsorbed on solids corresponds to an orientation with the long axis parallel to the solid surface. X-Ray studies of aliphatic molecules have consistently indicated an orientation with the long axis normal to the solid surface.[24]

Conclusions.—The modified McBain–Bakr adsorption technique which was described by Boyd and Livingston[9] has been used to determine isotherms for organic molecules and water. The technique can be used to study the cross-sectional area of organic molecules which are too volatile to be used in film balance work with insoluble monolayers on water.

It has been mentioned that a comparison between specific surface values obtained when different vapors were used with the same solid would make it possible to assemble a complete set of data regarding the section area of adsorbed molecules. All values would be relative; however, X-ray, density, and film balance measurements could be used to calculate area values for each molecule which should be interrelated with the relative values from adsorption data. There would be a degree of uncertainty because some molecules would pack more closely on one surface than on another. This seems to be the case for heptane on graphite, in the present study. Such differences could be recognized easily, as could differences in orientation. The final result of a series of such adsorption measurements would be a table presenting the area of molecules adsorbed as monolayers on solids, and would be analogous to the tabulated data which now exist for substances which form insoluble films on water.[2]

Acknowledgment.—The writer appreciates the interest and encouragement of Dr. G. E. Boyd, who was senior author of an earlier publication[9] based on the same experimental data used in the present work.

Summary

For four different finely-divided solids, adsorption isotherms have been measured both by the Brunauer–Emmett low temperature nitrogen adsorption technique and by the McBain–Bakr method, using vapors from substances which boil well above room temperature. By comparison of the various isotherms, the cross-sectional area values for the adsorbed molecules (in Å.^{2} per molecule) have been found to be H_2O, 10.6; PrOH, 20.0; heptane, 55.0, if nitrogen is taken to be 15.4. These areas are in every case in good agreement with the molecular areas of the molecules as determined from density, X-ray, or film balance measurements. The modified McBain-Bakr technique offers a method for measuring the section areas of adsorbed organic molecules of all types. It can also be used for determining the surface area of finely-divided solids from adsorption measurements at room temperature, using the vapors from ordinary volatile liquids.

SHARON HILL, PA. RECEIVED JANUARY 18, 1944

(22) Propyl alcohol on barium sulfate seems to be an exception.

(23) The outgassing procedure which was used was as follows: The adsorption chamber was evacuated to 250 mm., heated to 500–650° for two hours, then while still at this temperature evacuated with a mercury diffusion pump for twelve hours and finally with a charcoal trap at liquid air temperatures until a vacuum of 1μ had been indicated for one hour.

(24) Finch, *J. Chem. Soc.*, 1137 (1938).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF MICHIGAN]

An Electron Diffraction Investigation of the Monomers and Dimers of Formic, Acetic and Trifluoroacetic Acids and the Dimer of Deuterium Acetate[1]

BY J. KARLE[2] AND L. O. BROCKWAY

Introduction.—Recent spectroscopic studies[3,4] of the monomers and dimers of formic and acetic acids have indicated that the carbon to oxygen distances in the carboxyl group are not equal. Since an early electron diffraction study[5] on formic acid indicated equal carbon to oxygen distances, a repetition of the original study was suggested. In addition to this problem there arises the question concerning what changes, if any, occur in the monomers of the acids on association.

Robertson and Ubbelohde[6] studied the structure of deuterated oxalic acid dihydrate and observed an increase in length of the crystallographic unit cell in the direction of the hydrogen bridge. If the increase is located only in the bridge portion of the molecule, it would correspond to an expansion of the hydrogen bond of 0.044 Å. on substituting deuterium for hydrogen. Since an isotope effect in the dimer of acetic acid of 0.04 Å. might be detected by an electron diffraction investigation, the structure of the dimer of deuterium acetate was investigated.

Trifluoroacetic acid is a very strong acid whereas acetic acid is moderately weak. It was considered interesting therefore to attempt to observe a change in the acetic acid structure introduced by a trifluoromethyl group.

Experimental.—The method of obtaining electron diffraction photographs and a description of the apparatus have been given.[7]

Theoretical intensity curves were calculated using the formula

$$I(s) = \sum_i \sum_j Z_i Z_j (\sin s r_{ij})/s r_{ij}$$

where $s = 4\pi\sin(\theta/2)/\lambda$. The structural parameters determined were compared to those obtained from radial distribution curves calculated by the Walter and Beach[8] formula assuming a_k, the approximate half width of the maxima and minima, to be 0.7 s unit.

In order to study the monomers of the acids, an apparatus was required for photographing the equilibrium vapor at approximately 150°. This was accomplished by means of a 500-ml. glass container and a nozzle which could be heated independently to the desired temperature. In the nozzle, the copper tube through which the vapor flows was heated by a spiral winding of resistance wire insulated by a Pyrex tube with beads fused on for spacing the turns of wire. The large glass container was heated by means of an electric oven.

An interesting feature of this apparatus is the type of vacuum seal used. The glass to metal tapered joint, which is employed for room temperature studies, was not used because of the danger of breakage and leakage at the higher temperatures. Instead, the seal was produced by attaching the upper end of the container which consisted of a flat, well ground ring of glass, whose inner and outer radii differed by about 5 mm., to a flat metal surface on the bottom of the nozzle. Between the glass and metal surfaces a very useful high temperature vacuum grease was employed. This grease, made from aluminum stearate and SAE 50 motor oil, is described by Puddington.[9] It also was used to lubricate the stopcock on the container of vapor and a vacuum was conveniently maintained at 160°. No attempt was made to reach higher temperatures.

The degree of dissociation of the dimer at the elevated temperature was calculated from T_1 (the observed room temperature), p_1 (the total pressure at T_1), K_1 (the equilibrium constant at T_1), ΔH (the heat of dissociation assumed constant over the temperature range) and T_2 (the temperature of the diffraction measurements). The equilibrium constants and heats of dissociation for formic and acetic acids were taken from the work of Coolidge[10] and MacDougall[11]; the equilibrium constant for trifluoroacetic acid was determined from the vapor density measurements described below and its heat of dissociation was assumed to be the same as that for acetic acid. Table I gives the dissociation data for the three acids.

TABLE I

F = Formic, A = acetic and T = trifluoroacetic acids.

Acid	T_1, °K.	P_1, mm.	K_1, mm.	ΔH, kcal.	T_2, °K.	P_2, mm.	$K_2 \times 10^{-4}$, mm.	α
F	303	22.5	3.6	14	403	48	1.13	0.93
A	303	21.0	0.7	16	416	50	0.95	0.91
T	305	22.5	5.0	16	390	46	1.56	0.95

These calculations are necessarily approximate in character due to the assumptions involved in employing the formulas. However, the small contribution to the electron scattering of the long distances occurring in the dimer are negligible for the amounts of the dimers indicated above. Also, the degree of dissociation which appears in Table I is the one for the first exposure and the dissociation for successive photographs must continuously increase since the total pressure in the system is decreasing. An average of fifteen exposures were taken from a single sample in the container. Since no detectable difference was observed between the first and last photographs of any of the monomers, it is therefore concluded that the dimer makes a negligible contribution to the scattering in these high temperature experiments.

No dissociation data for the vapor of trifluoroacetic acid could be found in the literature. Experiments were therefore performed to obtain a value corresponding to the conditions of the diffraction study. Since the intensity curves are not sensitive to differences in dissociation of one or two per cent., no attempt was made to make very precise measurements. The apparatus used was a two-liter bulb which could be filled to a measured pressure with vapor from a weighing bottle. The temperature was room temperature and α, the degree of dissociation, was calcu-

(1) This paper is based upon the thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy to the Faculty of the Graduate School of the University of Michigan by J. Karle. For supplementary tables order Document 1807 from American Documentation Institute, 1719 N St., N. W., Washington, D. C., remitting 50¢ for microfilm or 60¢ for photoprints.

(2) Present address: University of Chicago, Chicago, Illinois.

(3) L. G. Bonner and R. Hofstadter, *J. Chem. Phys.*, **6**, 531 (1938).

(4) M. M. Davies and G. B. Sutherland, *ibid.*, **6**, 755 (1938).

(5) Pauling and Brockway, *Proc. Natl. Acad. Sci.*, **20**, 336 (1934).

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lated using the perfect gas law. The uncertainty is estimated to be within 20% of the average of the values obtained in Table II.

TABLE II

Expt.	P, mm.	V, ml.	T, °K.	w, g.	α
1	97.35	2128	300.5	2.3013	0.10
2	89.15	2128	299.0	2.1181	.10
3	100.40	2129	302.5	2.3215	.11
4	103.20	2128	302.5	2.3896	.11

The first two experiments were performed after a single vacuum distillation and the last two were performed on samples which were also pumped through phosphorus pentoxide.

Formic Acid Monomer.—The formic acid was prepared by passing hydrogen sulfide over the lead salt. It was further purified by the fractional vaporization method of Coolidge.[10] With regard to the question of possible decomposiion at the temperature of the experiment for the monomer, a set of photographs were taken and then the container was allowed to cool. About four hours later another series of photographs were taken at the high temperature. No change in patterns was observed indicating no significant decomposition.

A total of nineteen models were studied in which the longer carbon to oxygen distance (C—O) varied from 1.29 to 1.45 Å., the shorter carbon to oxygen distance (C=O) varied from 1.22 to 1.29 Å. and the enclosed angle (O—C=O) varied from 115 to 130°. Figure 1 represents a plot of C—O/C=O ratios *versus* the O—C=O angle, the range of uncertainty being enclosed within the dotted lines and the scale is fixed by setting C=O equal to 1.22 Å. in model K, equal to 1.24 Å. in models A, B, C, D, E, J, L and M, equal to 1.25 Å. in models I, N, O, Q and R, equal to 1.27 Å. in models P and S and equal to 1.29 Å. in models F, G and H. Figure 2 shows some of the corresponding intensity curves. All the curves except those marked with an *h* neglect the scattering due to the hydrogen distances in the molecule. In curves Ah and Bh, the C–H distance was assumed to be 1.09 Å. and the O–H distance to be 0.95 Å.

Curves A and B compare quite favorably with the observed features of the photographs. They contain an O—C=O angle of 117° and C—O/C=O ratios of 1.40/1.24 and 1.43/1.24, respectively. It is observed by comparison with curves Ah and Bh that the introduction of scattering terms due to the hydrogen distances does not alter the positions of the maxima and minima although there is a small effect on the qualitative features which must be taken into consideration.

Model I, which is unsatisfactory, is interesting since it occurs as the structural unit of the dimer possessing an O—C=O angle of 121° and a C—O/C=O ratio of 1.36/1.25.

Two significant peaks were obtained in the radial distribution curve in Fig. 3, one at 1.38 Å. composed of the unresolved C—O and C=O distances and the second at 2.27 Å. representing the distance between the oxygen atoms.

TABLE III

OBSERVED AND CALCULATED MAXIMA AND MINIMA OF FORMIC ACID MONOMER

Max.	Min.	I_k	S_0	S_A/S_0	S_B/S_0
2		15	6.23	0.979	0.970
	3	− 9	8.00	0.994	0.975
3		8	9.25	1.038	1.016
4		10	11.29	1.019	1.010
	5	− 6	13.10	1.008	1.008
5		4	14.46	1.024	1.007
	6		16.06	1.009	0.990
6		2	17.32	1.003	.993
	7		18.92	0.995	.990
7		3	20.38		
			Average	1.008	0.995
			Average deviation	±0.013	.013

On the basis of the quantitative agreement indicated in Table III, the following model is chosen for the monomer of formic acid: C—O = 1.42 ± 0.03 Å., C=O = 1.24 ± 0.03 Å., and ∠ O—C=O = 117 ± 2°. The average of the carbon to oxygen distances chosen is 1.33 Å. and the oxygen to oxygen distance is 2.27 Å.

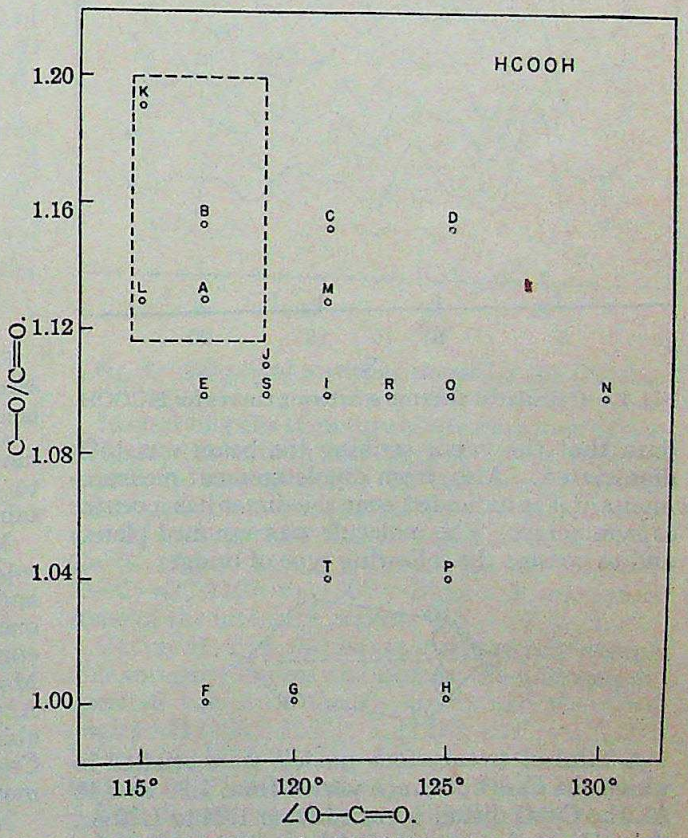

Fig. 1.—Models calculated for HCOOH. Dotted line encloses the models giving best agreement with the photographs.

Formic Acid Dimer.—In studying the dimer of formic acid it was assumed from vapor density

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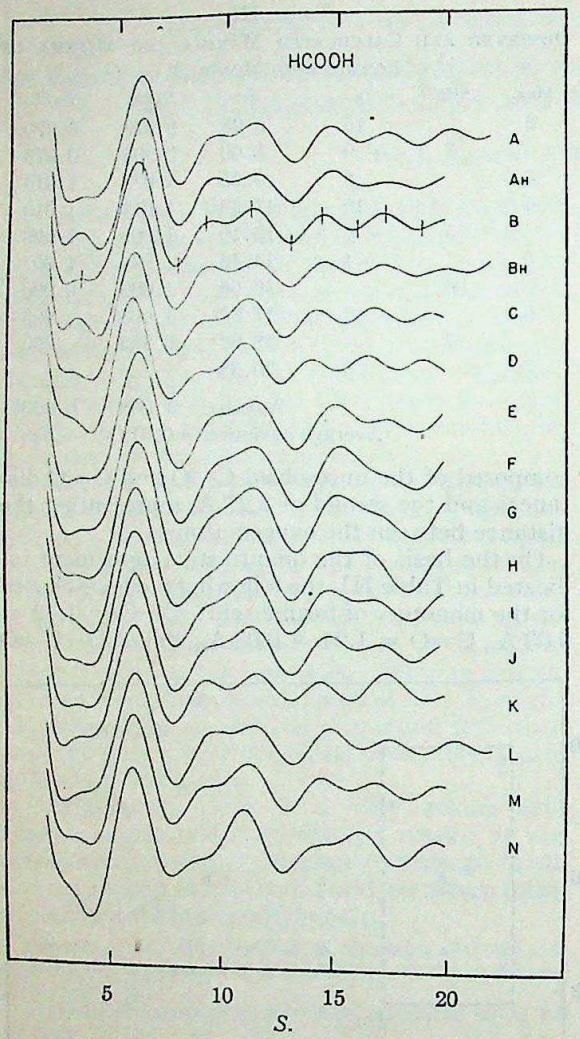


Fig. 2.—Calculated electron scattering curves for HCOOH.

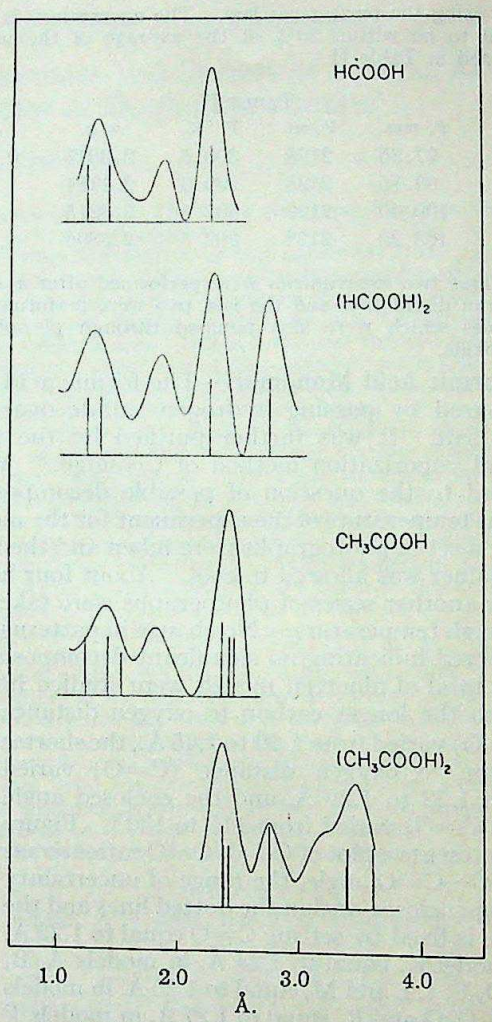
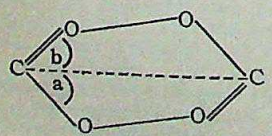


Fig. 3.—Radial distribution curves. The relative scattering powers associated with the interatomic distances are indicated by the heights of the vertical lines.

data that the vapor striking the beam was 15% dissociated. Also, from dipole moment measurements,[12] it is indicated that the dimer has a center of symmetry. The molecule was assumed planar and to possess the following type of bridge



A total of twenty-four models were studied in which the C—O distance varied from 1.29 to 1.43 Å., the C=O distance varied from 1.24 to 1.29 Å., the OH—O distance varied from 2.65 to 2.80 Å., the O—C=O angle varied from 117 to 130° and angle *b* varied from 54 to 62.5°. Some of the intensity curves are reproduced in Fig. 4. The great complexity of a five parameter problem makes a complete survey prohibitive. It is believed however that the models considered lead to reasonable conclusions and limits of uncertainty.

Models F and G which possess a C—O/C=O ratio of 1.36/1.25, angle O—C=O equal to 121° and angle *b* equal to 58°, are chosen as the best ones. Model F possesses an OH–O distance equal to 2.70 Å. whereas that of G is 2.76 Å. Models having equal carbon to oxygen distances, A, B and C, are unsatisfactory. Also unacceptable are models I and J which possess a C—O/C=O ratio comparable to that of the chosen monomer, 1.43/1.24.

Model B compares with the best model of Pauling and Brockway in which, however, they suggested 2.67 Å. instead of 2.65 Å. for the OH–O distance across the bridge. Better photographs and a study of a wider range of models account for a choice of structure different from that of model B.

The effect of a change of the OH–O distance to 2.65 Å., without changing the other parameters from their values in models F, is shown in curve

(12) I. E. Coop, N. R. Davidson and L. E. Sutton, *J. Chem. Phys.*, **6**, 905 (1938).

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E. Curves D and K show the effect of making angle O—C═O 119° and 123°, respectively, the only change. A decrease of five per cent. from the value of the C—O/C═O ratio used in model F produces an almost negligible change in curve H although the latter model contains an oxygen to oxygen separation differing a little more from the radial distribution peak than that of model F.

The shape of the intensity curves is very sensitive to changes in angles *a* and *b*. Model L differs from G by a 2° change in these angles and the difference in appearance is striking. In model M these angle changes are accompanied by a change in the C—O/C═O ratio to 1.40/1.24 and in the OH–O distance to 2.74 Å.

Attempts to obtain a suitable model of the dimer from a structural unit based on the chosen monomer were unsuccessful.

Model N is interesting since it is based on the most suitable model for the dimer of acetic acid which has an O—C═O angle of 130°. A comparison of curves N and Nh shows the negligible effect of including the scattering due to hydrogen distances in the theoretical intensity curves.

The significant maxima in the radial distribution curve in Fig. 3 occur at 1.30 Å. composed of the unresolved C—O and C═O distances, at 2.30 Å. representing the O–O distance and at 2.75 Å. representing the OH–O distance.

On the basis of the quantitative results in Table IV, the following model is chosen for the dimer of formic acid C—O = 1.36 ± 0.04 Å.; C═O = 1.25 ± 0.03 Å.; ∠ O—C═O = 121 ± 2°; O—H—O = 2.73 ± 0.05 Å.; ∠ b = 58 ± 1°. In the previous investigation[5] the two C–O distances were reported equal at 1.29 Å.

TABLE IV

OBSERVED AND CALCULATED MAXIMA AND MINIMA OF FORMIC ACID DIMER

Max.	Min.	I_k	S_0	S_F/S_0	S_G/S_0
	2	−15	4.84		
2		15	5.87	0.993	0.983
	3		(6.62)		
3			(7.22)		
	4	− 8	8.42	0.994	0.988
4		8	9.61	1.000	0.987
	5	− 4	10.29	1.005	0.997
5		9	11.32	1.000	0.996
	6	−10	13.12	1.021	1.016
6		4	14.56	1.013	1.000
	7	− 3	15.64	1.007	0.991
7		3	16.71	0.998	0.981
	8		18.39	0.998	0.995
			Average	1.003	0.993
			Average deviation	±0.006	.007

Acetic Acid Monomer.—The acetic acid was made by the General Chemical Company and assayed at 99.5%. A melting point determination verified this figure and so no further purification was attempted.

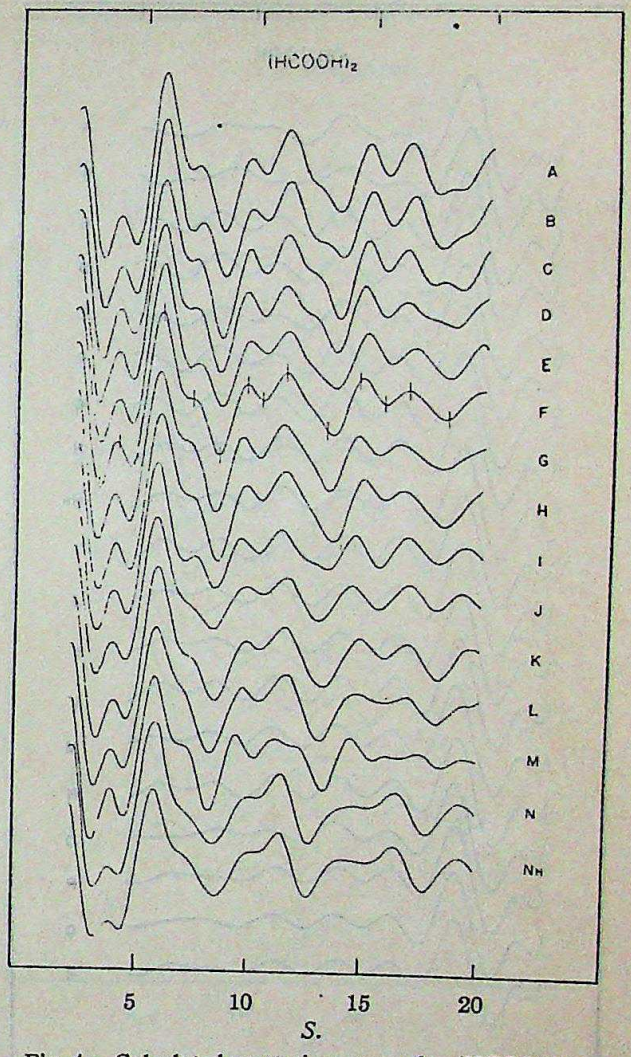

Fig. 4.—Calculated scattering curves for $(HCOOH)_2$.

In studying the structure of the monomer of acetic acid, the carbon and oxygen atoms were assumed to be coplanar. In the twenty models calculated the parameter ranges considered were: C—C, 1.48 to 1.54 Å.; C—O, 1.29 to 1.43 Å.; C═O, 1.22 to 1.29 Å.; O—C═O, 120° to 140°; C—C═O, 110° to 130°. Figure 5 reproduces some of the intensity curves.

Curves H, L, I and N are qualitatively acceptable intensity curves and possess the following respective values of the O—C═O and C—C═O angles: H (125°, 125°); L (127°, 123°); I (130°, 120°); N (135°, 115°). In each the C—O/C═O ratio is 1.43/1.24 and the C—C distance is 1.54 Å. A little less satisfactory are J (125°, 120°) and K (130°, 115°) with the bonded distances unchanged. and M (125°, 125°) with C—O/C═O equal to 1.40/1.24. No satisfactory intensity curve could be obtained with an O—C═O angle as low as 120°, illustrated by models A, B, P and Q. Curve R, the only one calculated with an O—C═O of 140°, is also unacceptable. Models C, D, E, F and G show the reversed intensities

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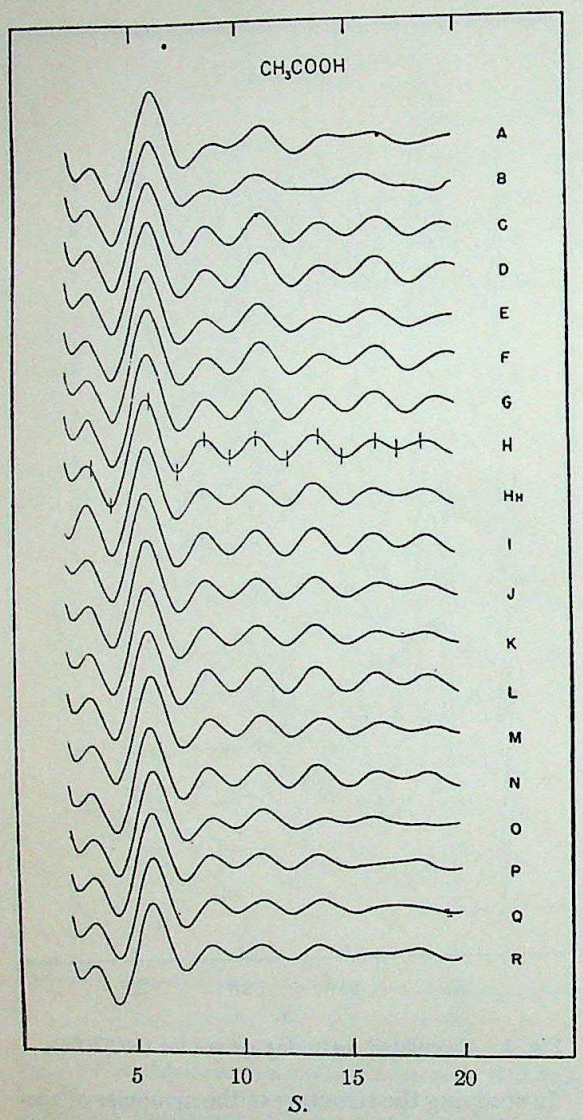

Fig. 5.—Calculated scattering curves for CH_3COOH.

produced by C—O/C=O ratios varying from 1.29/1.29 to 1.36/1.25 with the other parameters similar to those of the more acceptable curves. Model G, based on the structural unit of the dimer of acetic acid is also unsatisfactory because of the reversed relative intensities of some of the peaks.

A comparison of curves A and B shows the effect of changing the C—C distance from 1.48 to 1.54 Å. It is noted that the intensity curves are rather sensitive beyond the fourth maximum to changes in the C—C distance.

A comparison of curve H with Hh, which includes all of the hydrogen distances based on a structure with a tetrahedral arrangement of the CH_3 group, shows that the effect on the curves of neglecting the non-bonded hydrogen distances is negligible.

Since no sharp distinction is possible between the favorable curves, the values of the C—C=O and O—C=O angles must be considered very uncertain. In the acceptable range the monomer of acetic acid has its three longer distances arranged in an approximately equilateral triangle. Since, in calculating the intensity curves, two of the coefficients for the scattering terms are the same for these long distances and the third is only three halves larger, changes in the bond angles necessarily alter the resultant curves only very slightly.

The radial distribution curve for the monomer of acetic acid in Fig. 3 shows a rather broad peak at 1.41 Å. and thus the C—O, C=O and C—C distances are not resolved. Also unresolved are the longer carbon to oxygen distances and the oxygen to oxygen distance as shown by the largest peak which occurs at 2.43 Å. In this case the radial distribution curve is of no aid in fixing the structure of the molecule.

The following values are obtained for the structure of the monomer of acetic acid: C—O = 1.43 ± 0.03 Å.; C=O = 1.24 ± 0.03 Å.; ∠ O—C=O = 122–138°; C—C = 1.54 ± 0.04 Å.; ∠ C—C=O = 113–128°.

Table V shows that these values, based on the qualitatively acceptable curves, are in agreement with the quantitative results.

TABLE V

OBSERVED AND CALCULATED MAXIMA AND MINIMA OF ACETIC ACID MONOMER

Max.	Min.	I_k	S_0	S_H/S_0	S_I/S_0
2		15	5.96	0.978	0.973
	3	−10	7.29	1.000	1.000
3		9	8.57	1.000	0.991
	4	− 5	9.74	0.996	0.996
4		9	10.91	1.003	1.003
	5	− 6	12.45	0.994	0.994
5		5	13.82	0.986	0.984
	6		14.89	1.007	1.007
6		3	16.40	0.997	0.994
	7		17.36	1.010	1.010
7		3	18.46	1.010	1.010
			Average	0.998	0.997
			Average deviation ±	.007	.009

Acetic Acid Dimer.—The association of acetic acid is assumed to involve the same type of coupling of single molecules as occurs in formic acid. It was also assumed that all four carbon atoms were on the same axis, since in a test an angular displacement of the methyl group through 7° made only a small change in the calculated intensity curves (M and N). The vapor striking the beam was considered to be 9% dissociated.

In the seventeen models calculated the parameter ranges considered were: C—C, 1.48 to 1.54 Å.; C—O, 1.29 to 1.43 Å.; C=O, 1.22 to 1.29 Å.; OH—O, 2.67 to 2.82 Å.; O—C=O, 120° to 130°; b, 55 to 65°. Some of the intensity curves appear in Fig. 6.

Model H is chosen as the best one possessing an O—C=O angle of 130°, an angle b of 60°, an

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OH–O distance of 2.76 Å., a C–C distance of 1.54 Å. and a C—O/C=O ratio of 1.36/1.25. Models J and K with a ratio of 1.43/1.24 are unsatisfactory as are models A, B, C and D with equal carbon to oxygen distances and O—C=O angles ranging from 120 to 130°. Model G differs from H in possessing an OH–O distance 0.06 Å. smaller and model I possesses an OH–O distance 0.06 Å. larger. A comparison of curves F and G wherein the ratios are 1.32/1.27 and 1.36/1.25, respectively, shows only slight sensitivity to changes of the carbon to oxygen distances over this range.

Model E differs from F and model L differs from J in possessing an O—C=O angle of 125° instead of 130°. The difference in intensity curves produced is striking.

Model N is based on the most suitable model for the dimer of formic acid and is observed to produce a very unsatisfactory intensity curve.

The calculated models contain the bonded hydrogen distances whose lengths were assumed to be the same as applied to the monomer of formic acid. Curve Hh contains all the distances due to the hydrogen atoms and may be compared with curve H. A negligible difference is observed.

The radial distribution curve for the dimer of acetic acid in Fig. 3 contains only one useful peak. It is the relatively small one at 2.76 Å. corresponding to the OH—O separation across the bridge.

The structure chosen for the dimer of acetic acid in agreement with the quantitative results in Table VI is as follows: C—O = 1.36 ± 0.04 Å.; C=O 1.25 ± 0.03 Å.; ∠ O—C=O = 130 ± 3°; O—H—O = 2.76 ± 0.06 Å.; ∠ b = 60 ± 2°; C—C = 1.54 ± 0.04 Å.

TABLE VI

OBSERVED AND CALCULATED MAXIMA AND MINIMA OF THE DIMERS OF ACETIC ACID AND DEUTERIUM ACETATE

Max.	Min.	I_k	S_0(HAc)$_2$	S_H/S_0	S_0(DAc)$_2$
3		20	5.83	0.978	5.83
	4	− 7	7.05	1.010	7.05
4		7	8.26	1.017	8.23
5			9.30	0.997	9.25
	5	− 3	10.10	0.990	10.10
6		5	11.40	1.000	11.37
	6	− 5	12.56	1.000	12.60
7		4	13.93	0.995	13.89
	7	− 4	15.14	0.997	15.11
8		4	16.61	0.998	16.67
	8		17.85	1.000	
9			18.94	1.005	
			Average	0.999	
			Average deviation	± .006	

Deuterium Acetate Dimer.—No difference was observed in the qualitative appearance of the photographs of the dimer of deuterium acetate and those of acetic acid. Table VI shows that the molecules also cannot be distinguished quantitatively. It must be concluded then that any difference in structure that exists between the dimer of deuterium acetate and that of acetic acid is within the uncertainty of the determination of the structure of the latter compound.

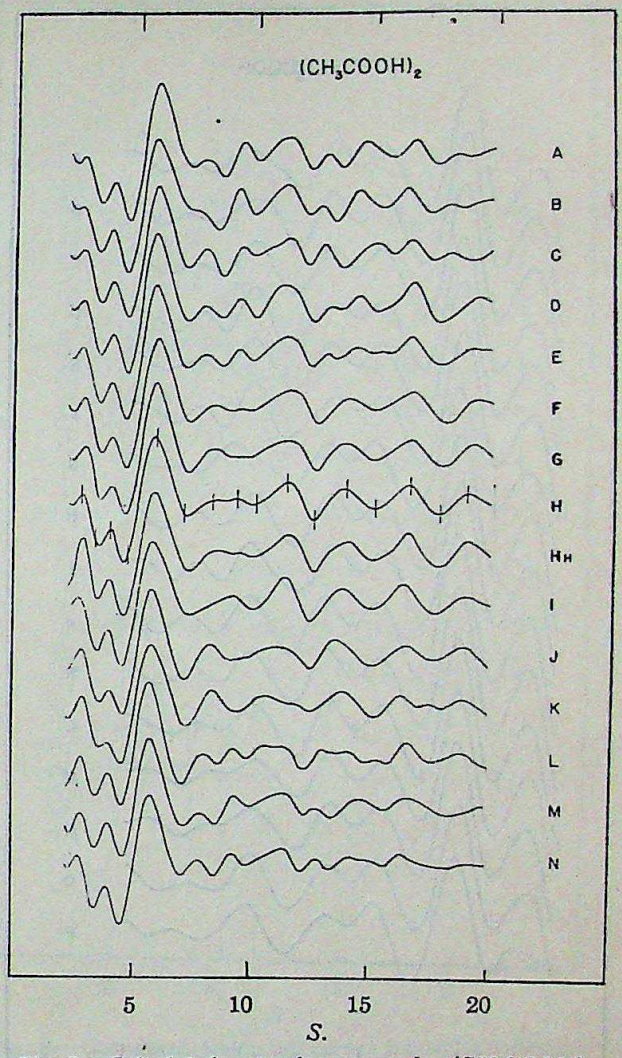

Fig. 6.—Calculated scattering curves for $(CH_3COOH)_2$.

The deuterium acetate used in these experiments was kindly supplied by Dr. Paul Gross of Duke University.

Trifluoroacetic Acid Monomer.—The trifluoroacetic acid used in the diffraction study and the vapor density study reported previously was kindly supplied by Dr. A. L. Henne of The Ohio State University.

In calculating the intensity curves, the CF_3 group was considered to be trigonally symmetric about the carbon to carbon axis, and the carbon and oxygen atoms were assumed to be coplanar. In the twenty-four models studied the parameter ranges considered were: C—C, 1.42 to 1.54 Å.; C—F, 1.33 to 1.36 Å.; C—O, 1.26 to 1.36 Å.; C=O, 1.25 to 1.36 Å.; F—C—F, 107.5° to 112°; O—C=O, 102° to 130°; C—C=O, 115° to 129°; orientation of the CF_3 group, fixed positions to a study of free rotation. Figure 7 shows some of

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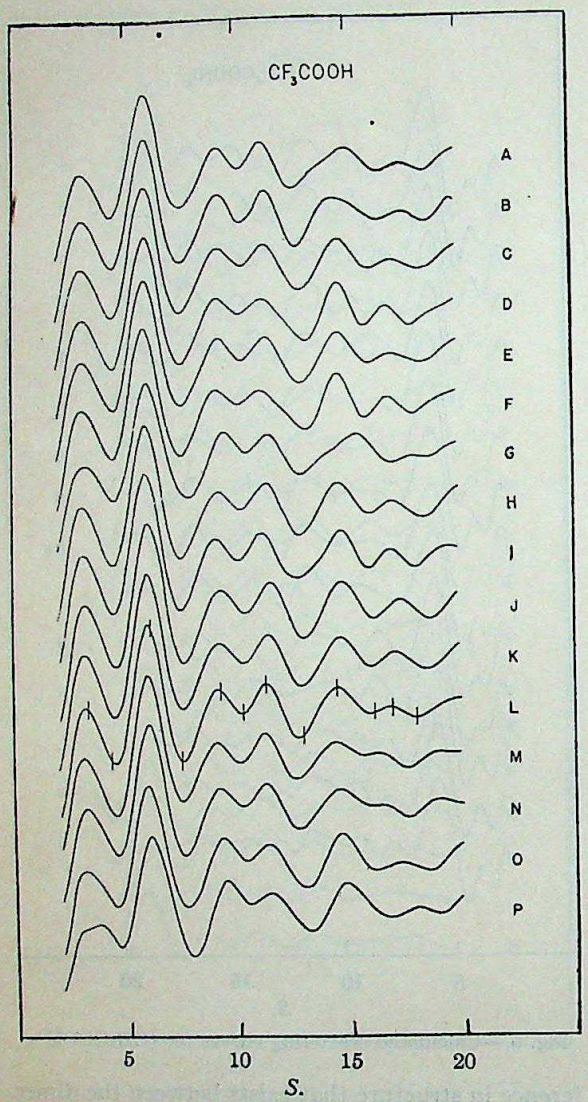

Fig. 7.—Calculated scattering curves for CF_3COOH.

the intensity curves. Although eight parameters present an exceedingly complex structure problem, a study of less than eight effective parameters was anticipated due to the possibility of a marked lack of sensitivity of the intensity curves to changes in some of the structural features.

A 15° orientation of a C—F bond out of the plane of the carboxyl group produces an intensity curve indistinguishable from one closely resembling a curve for free rotation within the range of variation of the shape of the carboxyl group considered in this paper. This is shown by a comparison of curve C possessing a 15° orientation with curve E composed of an average of twenty-four positions and is further substantiated by the similarity of curves D and F possessing C—O/C=O ratios of 1.29/1.29 and 1.36/1.25, respectively, and of models C and L wherein there occurs a change of 10° in the O—C=O angle in addition to a change in the C—O/C=O ratio. The models studied in which a C—F bond was placed in the plane of the carboxyl group were unsatisfactory as illustrated by curves B, A and G.

The relative intensities of the two maxima following the largest one in curves O and P do not agree with the visual interpretation of the photographs. These models possess O—C=O angles of 110° and 102°, respectively, and the qualitative effect may be ascribed to an increase in the oxygen to fluorine distances in the molecule.

It is possible to select eight more or less satisfactory intensity curves, curves D, F, C and H which have an O—C=O angle of about 120° and curves I, J, K and L with an O—C=O angle of 130°. All these curves possess a C–F distance of 1.36 Å. and a C–C distance of 1.48 Å. except J which has a C–C distance equal to 1.44 Å. However, it is noted that curve J is shifted with respect to the s_0 values, indicating some unusually small distances in the molecule. The orientation of the CF_3 group in these models is 15 and 30° with respect to the carboxyl group measured from the C—O side and the remaining parameters almost cover the maximum range of variation discussed above.

It is possible to draw definite conclusions only with regard to the structure of the CF_3 group in the monomer of trifluoroacetic acid: C—F = 1.36 ± 0.05 Å.; ∠ FCF = 110 ± 4°. As far as the orientation of the CF_3 group is concerned, there may be a preferred position excluding the one in which there is a C—F bond in the plane of the carboxyl group, there may be vibrations of rather large amplitude or there may be free rotation. No significant conclusions can be drawn about the C—O/C=O ratio and the C—C=O and O—C=O angles and it is not possible to fix with certainty the C—C distance since a change in the distance of 0.06 Å. is fairly well compensated for by a change in the F—C—F angle of 2°, as indicated by a comparison of curves M and N.

A radial distribution curve was not calculated because resolution of the many intramolecular

TABLE VII

OBSERVED AND CALCULATED MAXIMA AND MINIMA OF TRIFLUOROACETIC ACID MONOMER

Max.	Min.	S_0	S_L/S_0
2		6.15	0.984
	3	7.49	1.012
3		9.28	0.998
	4	10.30	1.000
4		11.34	1.005
	5	12.98	0.994
5		14.49	1.008
	6	16.15	0.994
6		16.96	1.000
	7	18.01	1.004
7		19.94	0.997
		Average	1.000
		Average deviation	±0.006

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distances was not expected from the number of maxima and minima available for the calculation.

Trifluoroacetic Acid Dimer.—In addition to the assumptions which applied to the study of the monomer, a center of symmetry is believed to exist for the carbon and oxygen atoms and the same type of bridge was assumed as occurs in the dimers of formic and acetic acids. The four carbon atoms were assumed to be on a straight line and on the basis of the experiments reported above the vapor striking the electron beam was considered to be 11% dissociated. Thus there is one parameter in the dimer in addition to the eight required to fix the structure of the monomer, the distance across the hydrogen bridge. Unlike the monomer, the number of parameters which have a negligible effect on the resultant intensity is too small to lead to a structure determination whose degree of uncertainty may be readily estimated. However, the large number of qualitative features in the patterns are advantageous in limiting the range of variation.

A total of fifteen models were studied in which the C—F was equal to 1.36 Å., the C=O distance varied from 1.25 to 1.33 Å., the OH—O distance varied from 2.67 to 2.76 Å., the O—C=O angle varied from 110 to 130° and the C—C=O angle[13] varied from 115 to 125°. The remaining parameters covered the same range as in the study of the monomer. Figure 8 contains some of the intensity curves.

Model B is the most acceptable model and is based on the structure for the dimer of acetic acid except that the C—C distance is shortened from 1.54 to 1.48 Å. It possesses in addition a tetrahedral CF_3 group in which the C–F distance is equal to 1.36 Å. and a 15° orientation of a C–F bond with respect to the plane of the carboxyl group. Models A and C are similar but possess orientations of 0 and 30°, respectively.

As pointed out above, a marked sensitivity to changes in several of the parameters can be observed. A comparison of models N and B shows the effect of changing the C–C distance to 1.54 Å. Model E produces a very poor intensity curve and it differs from B in possessing equal C—C=O and C—C—O angles and equal C—O and C=O distances whose average is about 0.04 Å. less than that of model B. Model F has the same structure in the carboxyl group as does E with a C–C distance smaller by 0.04 Å. and an OH–O separation smaller by 0.06 Å. A comparison of curve G with curve H shows the relatively small change arising from a difference of 0.08 Å. in the OH–O distance.

The series of models K, L and M have the same orientation relation as models A, B and C. This is also true for models H, I and J. Models K, L and M have a CF_3 group similar to that of A, B and C but the structure of the carboxyl group is modeled after the one which occurs in formic acid dimer. Models H, I and J differ slightly in possessing an O—C=O angle of 120°, equal carbon to oxygen distances of 1.29 Å. and equal C—C=O and C—C—O angles.

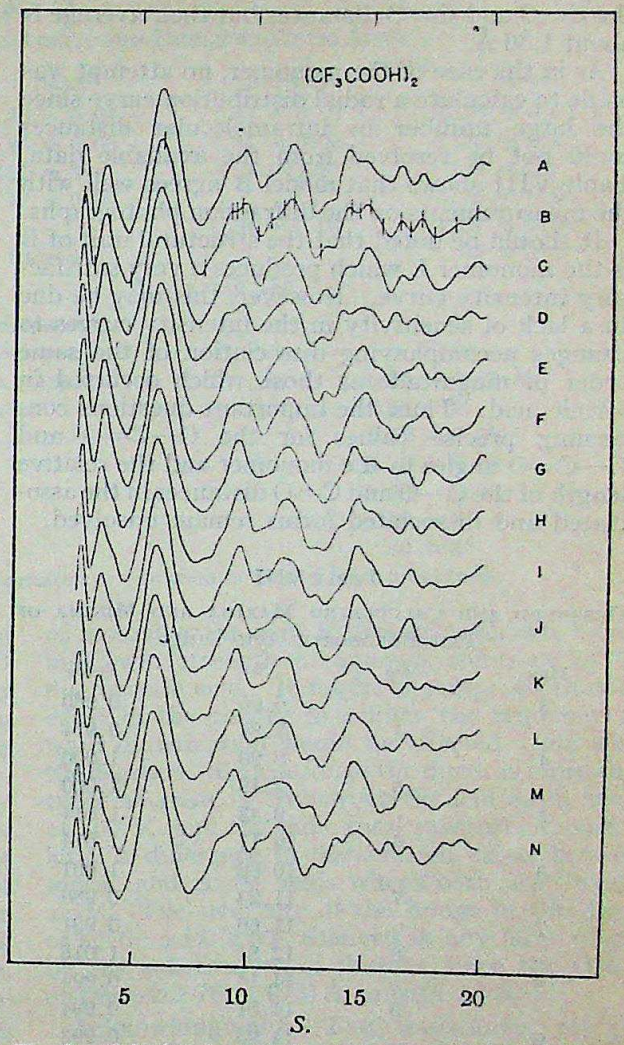

Fig. 8.—Calculated scattering curves for $(CF_3COOH)_2$.

From reasoning similar to that applied to the study of the monomer and the observation that the portion of the intensity curve of the dimer due to the scattering of the distances across the monomeric units is insensitive to changes in the orientation of the CF_3 group, a 15° orientation of a C—F bond out of the plane of the carboxyl group may be interpreted as producing an intensity curve which closely represents a curve of free rotation.

The following values are obtained for the parameters in the dimer of trifluoroacetic acid: C—F = 1.36 ± 0.03 Å.; ∠ FCF = 109 ± 2°; C—C = 1.48 ± 0.03 Å.; O—H—O = 2.76 ± 0.06 Å.; ∠ O—C=O = 130 ± 3°; ∠ b = 60 ± 3°. The CF_3 group probably rotates freely or vibrates in arcs of large amplitude. Nothing definite can be said about the relative length of

(13) On the assumption that all four carbon atoms are on a straight line, ∠C—C=O is the supplement of angle *b* used to fix the structures of the dimers previously discussed.

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the C—O and C=O distances but their average is about 1.30 Å.

As in the case of the monomer, no attempt was made to calculate a radial distribution curve since the large number of intramolecular distances could not be resolved from the available data. Table VIII shows that model B agrees well with the measurements on the diffraction photographs.

It should be noted that the structural unit of B is the monomer L which produces a very satisfactory intensity curve. However, this may be due to a lack of sensitivity in the intensity curves to changes accompanying dissociation of the same order of magnitude as those which occurred in formic acid. Thus, the important questions concerning precise values for the O—C=O and C—C=O angles in the monomer and the relative length of the C—O and C=O distances in the associated and dissociated forms remain unsolved.

TABLE VIII

OBSERVED AND CALCULATED MAXIMA AND MINIMA OF TRIFLUOROACETIC ACID DIMER

Max.	Min.	S_0	S_B/S_0
3		6.05	0.980
	4	7.84	0.974
4		8.99	1.000
	5	9.19	1.000
5		9.43	1.014
	6	10.11	1.014
6		10.69	1.001
	7	11.23	0.980
7		11.66	0.991
	8	12.81	1.015
8		14.14	0.994
	9	14.51	0.994
9		14.95	0.993
	10	15.49	1.020
10		16.26	1.004
	11	16.68	1.006
11		17.17	1.000
	12	17.70	1.006
12		18.59	1.008
13		19.49	1.006
		Average	1.000
		Average deviation	±0.009

Discussion

Several interesting structural features of the carboxyl group are shown by the foregoing results on formic and acetic acids. The two C–O distances in the unassociated carboxyl are distinctly different; indeed, the longer distance is the same as that observed in ether linkages while the shorter corresponds to the C—O linkage in ketones. It may be concluded from these results that the hydrogen atom is much closer to one oxygen than to the other. The attachment of the hydrogen to one of the two oxygens makes their attachments to the carbon as distinct from each other as an ordinary single and double bond. It is still expected that in the free carboxylate ion the two C–O links would be equivalent.

When the dimer is formed the longer C—O bond becomes about 0.06 Å. shorter than it was in both formic and acetic monomers, while the shorter C—O bond is unchanged. The difference between the two C—O bonds in the carboxyl is thereby reduced to about 0.1 Å. It appears, then, that although both of the carboxyl oxygens have an adjacent hydrogen in the dimer and are therefore more nearly alike than they were in the monomer, a considerable difference persists in the behavior of the two oxygens. The observed non-equivalence of the two C—O bonds requires a non-equivalence of the two O—H linkages; or in other words the diffraction results lead to the conclusion that the two hydrogen atoms in the carboxyl dimer are not located in the center positions in the respective OH—O bonds.

A further difference between the monomer and dimer is noted in formic acid in the O—C=O angle, which is 4° larger in the dimer. Since the O—O distance across the carboxyl is the same in both forms, it seems probable that the repulsion between the oxygen atoms prevents the decrease in their separation, which would have accompanied the shortening of the C—O distance if the O—C=O angle had remained unchanged.

The only significant difference between the results on formic and acetic acids is in the O—C=O angles. In the formic acid dimer this angle is 121° while in acetic acid dimer it is 130°. This angle happens to be indeterminate over a wide range (122–138°) in acetic acid monomer so that the monomer comparison cannot be made. The OH–O distance in the dimers is substantially the same, 2.73 and 2.76 Å.

Spectroscopic results on carboxylic acids are in general agreement with the above conclusions. Hofstadter[14] working on heavy formic acid and Herman and Hofstadter[15] on light and heavy acetic acids found an increase in the O–H and O–D distances from about 0.97 Å. in the monomers to about 1.07 Å. in the dimers. This increase would have to be up to 1.35 Å. if the hydrogen (or deuterium) atom were in the center of the OH—O dimer bond. Sutherland and Davies[4] report a somewhat smaller change in the O–H distance in the dimerization of acetic acid. They also report a difference of about 0.1 Å. between C—O and C=O although each distance is somewhat shorter than the diffraction values given in this paper.

Force constants of 5.4×10^5 dynes/cm. for the C—O and 11.8×10^5 dynes/cm. for the C=O in the formic acid monomer are reported by Hofstadter and Bonner.[3] The first value is close to that for an alcoholic C—O (4.5×10^5 dynes/cm.) while the second is essentially that for a carbonyl group. This comparison is consistent with the conclusions based on the diffraction results.

(14) R. Hofstadter, *J. Chem. Phys.*, **6**, 541 (1938).

(15) R. Hofstadter, *ibid.*, **6**, 534 (1938).

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TABLE IX

DIFFRACTION RESULTS ON FORMIC, ACETIC AND TRIFLUOROACETIC ACIDS

Parameter	Formic		Acetic	
	Monomer	Dimer	Monomer	Dimer
C—O	1.42 ± 0.03 Å.	1.36 ± 0.04 Å.	1.43 ± 0.03 Å.	1.36 ± 0.04 Å.
C=O	1.24 ± 0.03	1.25 ± 0.03	1.24 ± 0.03	1.25 ± 0.03
O—C=O	117 ± 2°	121 ± 2°	122 – 138°	130 ± 3°
OH—O		2.73 ± 0.05		2.76 ± 0.06
C—C			1.54 ± 0.04	1.54 ± 0.04
b		58 ± 1°		60 ± 2°
C—C=O			113–128°	

Parameter	Trifluoroacetic	
	Monomer	Dimer
C—F	1.36 ± 0.05 Å.	1.36 ± 0.03 Å.
F—C—F	110 ± 4°	109 ± 2°
C—C		1.47 ± 0.03
OH—O		2.76 ± 0.06
Av. of C—O & C=O		1.30 ± 0.03
O—C=O		130 ± 3°
b		60 ± 3°
$-CF_3$	Free rotation or vibration in arcs of large amplitude.	

The isotope effect (increase in distance between associated carboxyl groups on substitution of D for H) found by Robertson and Ubbelohde in oxalic acid dihydrate was also studied by them in phthalic acid, α-resorcinol, β-resorcinol, sodium bicarbonate and in succinic and benzoic acids. No such effect was detected in phthalic acid or β-resorcinol while the other substances all show effects smaller than in oxalic acid. Our hope of checking on this effect in acetic acid vapor was not realized since the uncertainty of the determination of the OH–O distance is as large as the magnitude of the effect observed in oxalic acid dihydrate. The similarity of the electron diffraction photographs of light and heavy acetic acids does not exclude the possibility of an isotope effect as large as that occurring in some of the above-mentioned compounds.

In trifluoroacetic acid the structure of the carboxyl group could not be determined as completely as in the other acids because of the relatively high scattering power of the CF_3 group. In the dimer the average value of the C—O and C=O distances is 1.30 Å. as in the other acid dimers, but the individual values are indeterminate. The CF_3 group in both the monomer and dimer has about the same structure found in other compounds containing this group, *i. e.*, the C–F distance is 1.36 Å., and the F—C—F angle is near the regular tetrahedral value. The group is free to rotate or at least to oscilllate with large amplitude about the C—C axis.

In the dimer with a CF_3 group at each end some additional distances were determined. The C–C distance is only 1.48 Å., or 0.06 Å. shorter than in acetic acid. The effect of shortening the bond to the attached atom when fluorine is substituted for the hydrogen in a methyl group occurs in many other compounds as well, but here the fluorine substitution has the further interesting effect of loosening the acid hydrogen as shown by the high acid strength of aqueous solutions of trifluoroacetic acid. It might be supposed that because of the change in acidity the tendency toward dimerization would be affected; but while the degree of dissociation of the dimer is more than twice as great in trifluoroacetic acid as in acetic at 300°K. and the same total pressure, almost as large a difference in dissociation exists between formic and acetic acids where both are "weak" acids. The structure of the bridge in the dimer of acetic acid is not changed in any large degree by the substitution of fluorine since the OH–O distance is 2.76 ± 0.06 Å. in both acids.

Acknowledgment.—The assistance of the Board of Governors of the Horace H. Rackham School for Graduate Studies and of the Midgley Foundation in providing funds for the construction of the diffraction apparatus is gratefully acknowledged. We also wish to thank Mrs. J. Karle for tracing the theoretical intensity curves.

Summary

The structures of the monomeric and dimeric forms of formic, acetic and trifluoroacetic acids in the vapor state have been investigated by the electron diffraction method with the results summarized in Table IX. The two C—O bonds in the carboxyl group differ in both the monomer and the dimer. The OH–O distance across the bridge is substantially the same in all three dimers, while in the acetic acid the C—C bond is 0.06 Å. longer than in the fluorine substituted acid.

Acetic acid and the deuterated acid, $(CH_3COOD)_2$, show no detectable difference in their diffraction photographs.

Measurements were made on the vapor density and the dissociation constants of the dimeric trifluoroacetic acid.

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A high temperature nozzle for introducing samples into the gas diffraction camera over the range from room temperature up to 160° is described.

ANN ARBOR, MICHIGAN RECEIVED JANUARY 14, 1944

[A CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY]

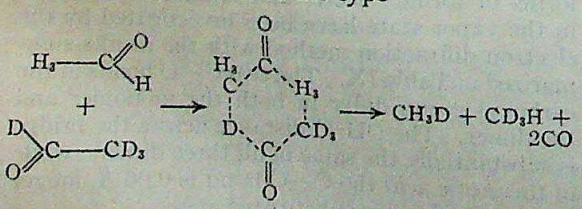
The Thermal Decomposition of Acetaldehyde

BY J. CARRELL MORRIS

Recent studies on the mechanism of the thermal decomposition of acetaldehyde into carbon monoxide and methane have indicated that the reaction proceeds, at least in part, by means of a reaction chain involving free radicals. Thus Burton, Ricci and Davis[1] were able to demonstrate that radio-lead was transported in a Paneth-type experiment in which acetaldehyde was decomposed under normal conditions. This undoubtedly showed the presence of free radicals in their experiments. Rice and Polly[2] and later, in a more extensive fashion, Smith and Hinshelwood[3] found that the normal thermal decomposition was inhibited by the addition of propylene to the gaseous acetaldehyde in the reaction vessel. These studies on inhibition, generally considered a very reliable test for the detection of radical chain reactions, led to an estimate that a minimum of about $^2/_3$ of the reaction occurred by means of free-radical chains.

In an attempt to confirm this conclusion and perhaps to check on more detailed phases of the mechanism of the reaction a somewhat different approach to the problem was devised. Mixtures of ordinary acetaldehyde and acetaldehyde-d_4 were allowed to decompose together and the resulting products were analyzed as to the isotopic composition of the methanes formed.

Such a determination might be expected to give a rather intimate knowledge of actual processes occurring in the reaction. For, if the decomposition were an intramolecular one, then the CH_3CHO could give just CH_4 and CO, while CD_3CDO would yield only CD_4 and CO. Consequently, if this mechanism were operative, the analysis should show none of the partially deuterated methanes. If the decomposition were a bimolecular one, then reactions of the type



should occur, yielding CD_3H and CH_3D as well as CH_4 and CD_4. One would not anticipate finding CH_2D_2, however. In the third plausible case, if the reaction took place by a chain mechanism, processes of the type

$$CH_3 + CD_3CDO = CH_3D + CD_3 + CO$$
$$CD_3 + CH_3CHO = CD_3H + CH_3 + CO$$

would be expected to produce CD_3H and CH_3D and perhaps also CH_2D_2, if the reactions were more complicated than those illustrated.

So, while it might not be possible by this method to distinguish between the latter two possibilities, such an analysis should certainly provide evidence differentiating the first possibility from the other two.

Benedict, Morikawa, Barnes and Taylor[4] have shown that such mixtures of the isotopic methanes may be analyzed readily by means of their infrared spectra. In particular, the absorption in the range 1000–1500 cm.$^{-1}$ is very characteristic of the particular isotopic methanes present in a mixture and their relative proportions. In the present study this method of analysis was followed by measuring the infrared absorption over the range 1000–1500 cm.$^{-1}$ of the samples of gas obtained from the decomposition of the mixtures of acetaldehyde and acetaldehyde-d_4. The results obtained led to the conclusion that the thermal decomposition of such mixtures produced CH_4 and CD_4 almost exclusively.[5] This is definite evidence that, contrary to the findings of previous authors,[1,2,3] the decomposition of acetaldehyde proceeds mainly by a unimolecular mechanism.

Confirmation for this point of view was obtained by an analysis of data on the absolute rate of the thermal decomposition of acetaldehyde. During the course of the present research it was noted that the rate of decomposition of "pure" acetaldehyde was materially decreased if the aldehyde were treated with hydroquinone and freshly distilled from it before use. The rates found after such treatment were considerably lower than the "normal" rates of Smith[6] or of Smith and Hinshelwood[3] and approached the "inhibited" rates found by the latter authors. A reasonable conclusion is that the positive indications of a chain reaction found in this decomposition were caused by a superimposed induced process initiated by an impurity.

(1) M. Burton, J. E. Ricci and T. W. Davis, THIS JOURNAL, 62, 265 (1940).

(2) F. O. Rice and O. L. Polly, *J. Chem. Phys.*, 6, 273 (1938).

(3) J. R. E. Smith and C. N. Hinshelwood, *Proc. Roy. Soc.* (London), A180, 237 (1942).

(4) W. S. Benedict, K. Morikawa, R. B. Barnes and H. S. Taylor *J. Chem. Phys.*, 5, 1 (1937).

(5) J. C. Morris, THIS JOURNAL, 63, 2535 (1941).

(6) R. E. Smith, *Trans. Faraday Soc.*, 35, 1328 (1939).

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Experimental.—The acetaldehyde was an Eastman Kodak Co. product which was purified further by several distillations in the vacuum system from baths at 0° to baths at −80°. During the series of distillations the acetaldehyde was several times outgassed by causing ebullition while the bulb containing the liquid was connected directly to the vacuum pump. In addition the aldehyde was twice frozen in liquid air and pumped out to 10^{-5} mm. to remove any final traces of oxygen, which is known to accelerate the reaction.[7] Attempts to purify the acetaldehyde by distillation from a dry-ice bath to a liquid-air bath were unsuccessful because of the formation of the white, solid polymer which has been observed before under the same conditions.[8] The vapor pressure of the final material at 0° checked that given in the literature[9] within a few mm. and remained substantially constant during the use of 80% of the liquid. This material is called the "untreated" sample.

A portion of the above sample was further purified by distilling it into a bulb containing some solid hydroquinone crystals and allowing it to remain there for several days. It was then distilled off from the hydroquinone in small samples just before use. This latter is called the "treated" sample and gave a rate of decomposition only one-half to one-third as great as the previous material.

The deuteroacetaldehyde came from two sources. First runs were made on a sample prepared from C_2D_2 and D_2O by slight modification of the method of Zanetti and Sickman,[10] while later a quantity of 99.5% deuteroacetaldehyde was purchased from Norsk Hydro. Each was subjected to the same purification procedure as the CH_3CHO, the final samples having a vapor pressure at 0° which checked that given by Zanetti and Sickman.[10] Both samples were shown to contain better than 99% C—D bonds by means of their infrared absorption spectra.[11]

With the deuteroacetaldehyde also subsequent treatment with hydroquinone was found to give a sample which decomposed more slowly than the untreated sample, but the decrease in this case was not nearly as marked, and additional treatments failed to lower the rate any further.

The decompositions were carried out in a cylindrical Pyrex vessel of approximately 300-ml. capacity, which had an outside diameter of about 5 cm. and was mounted snugly in a cavity bored in an aluminum block of 10-cm. diameter. The block was wound with insulated resistance wire and was surrounded by several inches of magnesia insulation. To maintain the block at 500° a current of about 3 amperes was required. The reaction vessel was connected by means of capillary tubing to a three-way stopcock and to a variable-level mercury manometer, which gave a total dead space amounting to less than 1 ml.

By passing the heating current through a voltage controller such a uniform heating was obtained that temperatures constant within 0.5° could be maintained indefinitely and no additional temperature regulation was necessary. The temperature was measured with a two-junction thermocouple inserted in a well of 8-mm. glass tubing which ran into the center of the reaction vessel. The thermocouple was standardized against boiling sulfur and by comparison with a Bureau of Standards platinum resistance thermometer at several temperatures.

For the infrared analyses the reacted mixture of gases was allowed to expand into a 300-ml. bulb which had its lower end chilled in dry-ice to condense any unreacted acetaldehyde. Usually, however, this was an unnecessary precaution, for the mixtures were generally allowed to react completely before withdrawing them from the reaction vessel. It was not necessary to eliminate the carbon monoxide since it does not absorb in the portion of the spectrum used. The sample of methanes and carbon monoxide was then transferred by means of a Töpler pump to the infrared absorption cell, which was 30 cm. in length and 2.5 cm. in diameter with plane rock salt ends cemented on with Apiezon wax. This was attached to the apparatus by a ground glass joint so that it could be transferred easily to the spectrograph. Ordinarily the cell was filled with 200 mm. of the carbon monoxide–methanes, corresponding to 100-mm. pressure for the methanes present. This pressure was found empirically to give the most suitable amount of absorption for the significant frequencies.

The spectrograph used was the one described by Gershinowitz and Wilson.[12] It was necessary to use only the rock salt prism to obtain the 1000–1500 $cm.^{-1}$ spectra with sufficient precision. The technique of measurement and recording of the spectra was the same as that outlined in the Gershinowitz and Wilson paper.

I am grateful to Prof. E. Bright Wilson for permission to use the spectrograph for these analyses.

Results of Infrared Analyses.—A number of preliminary spectra were determined to ascertain the exact results to be expected from various possibilities. First, the spectrum for the case of no mixing of the methanes was measured by mixing 100 mm. of $CD_4 + CO$ from the decomposition of CD_3CDO alone with 100 mm. of $CH_4 + CO$ from the decomposition of CH_3CHO and determining the infrared spectrum for the mixture. The absorption spectrum obtained is shown as curve I of Fig. 1. The significant features of this curve are the double absorption maximum caused by the CD_4 at 990 and 1035 $cm.^{-1}$, the double maximum caused by CH_4 at 1305 and 1350 $cm.^{-1}$ and the absence of appreciable absorption in between. If there were partially substituted

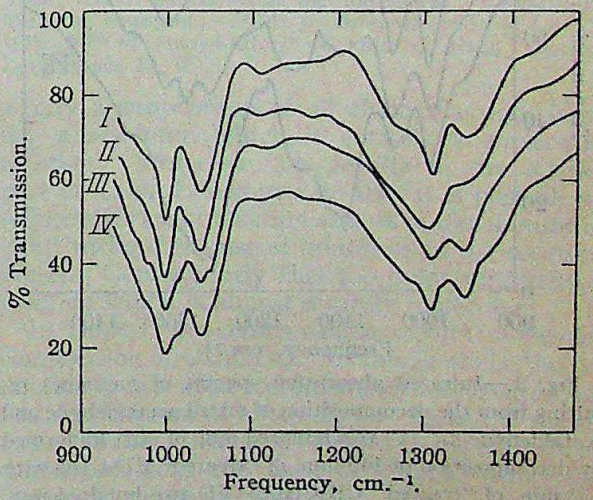

Fig. 1.—Infrared absorption spectra of methanes resulting from the decomposition of acetaldehyde and acetaldehyde-d_4: (I) prepared mixture of 100 mm. of $CH_4 + CO$ and 100 mm. of $CD_4 + CO$; (II) two hundred mm. of 1:1 mixture of $CH_4 + CO$ with $CD_4 + CO$ which has been heated for five days at 500° (scale is displaced downward 10%); (III) two hundred mm. of mixture formed by decomposition of 215 mm. of CH_3CHO in presence of 400 mm. of $CD_4 + CO$ (scale is displaced by 20%); (IV) two hundred mm. of mixture formed by decomposition of 183 mm. of CD_3CDO in presence of 370 mm. of $CH_4 + CO$ (scale is displaced by 30%).

(7) M. Letort, *Compt. rend.*, **197**, 1042 (1933).
(8) M. Letort, *ibid.*, **202**, 767 (1936).
(9) R. Gilmour, *J. Soc. Chem. Ind.*, **41**, 293 (1922).
(10) J. E. Zanetti and D. V. Sickman, THIS JOURNAL, **58**, 2034 (1936).
(11) J. C. Morris, *J. Chem. Phys.*, **4**, 300 (1948).
(12) H. S. Gershinowitz and E. B. Wilson, *ibid.*, **6**, 197 (1938).

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deuteromethanes present, there should be additional maxima of absorption at 1160 cm.$^{-1}$ for CH_3D, at 1090 and 1235 cm.$^{-1}$ for CH_2D_2 and at 1290 cm.$^{-1}$ for CHD_3.[4]

Since it is known that traces of oxygen will induce a chain reaction in the decomposition of acetaldehyde,[13] it was concluded that a representation of the absorption curve to be expected if the thermal reaction occurred by a chain mechanism might be obtained by analyzing the sample obtained from decomposing a mixture of the aldehydes in the presence of a trace of oxygen. Accordingly, 148 mm. of CD_3CDO, 150 mm. of CH_3CHO and 0.05 mm. of oxygen were mixed and allowed to react overnight at a temperature of 435°. The temperature was chosen low enough to make the ordinary thermal reaction negligible. When a sample of the products was subjected to infra-red analysis, curve VII in Fig. 2 was obtained. The expected maxima listed above are all apparent, some of them occurring with great intensity. The appearance of the maximum at 1090 cm.$^{-1}$ for CH_2D_2 means that the chain processes are more complicated than the simple ones listed in the introduction to the paper.

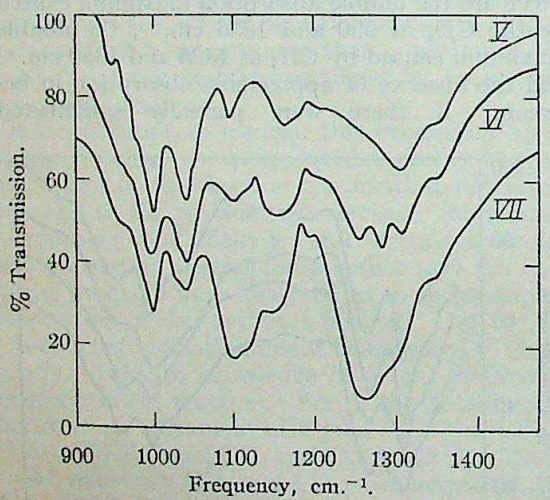

Fig. 2.—Infrared absorption spectra of methanes resulting from the decomposition of mixed acetaldehyde and acetaldehyde-d_4: (V) two hundred mm. of mixture formed by decomposition of 145 mm. of "treated" CD_3CDO with 152 mm. of "treated" CH_3CHO; (VI) two hundred mm. of mixture formed by decomposition of 209 mm. of "untreated" CD_3CDO with 239 mm. of "untreated" CH_3CHO (scale displaced by 10%); (VII) two hundred mm. of mixture formed by decomposition of 150 mm. of CH_3CHO, 148 mm. of CD_3CDO and 0.05 mm. of O_2 (scale displaced by 30%).

A run was now made to make sure that if mixed deuteromethanes were found in the later experiments, they had resulted from processes taking place in the actual decomposition of the acetaldehydes and not from side exchange reactions. A sample consisting of 206 mm. of CH_4 + CO and 203 mm. of CD_4 + CO was heated in the reaction vessel at 500° for five days to test whether the methanes would exchange among themselves at this temperature. The spectrum of a sample taken at the end of this time is shown as curve II of Fig. 1. The increased absorption between 1200 and 1300 cm.$^{-1}$ indicates the formation of a small amount of CHD_3, but the exchange has been very slight, as indicated by the general similarity of the curve with curve I.

It was still possible, however, that exchange might take place between molecules of acetaldehyde and of methane. Or, if there were methyl radicals present as a result of chain processes, the reactions

$$CH_3 + CD_4 = CH_3D + CD_3$$
$$CD_3 + CH_4 = CD_3H + CH_3$$

might have complicated the conclusions. Therefore, two additional preliminary runs were carried out. In the first, 215 mm. of CH_3CHO was allowed to decompose completely at 480° in the presence of 400 mm. of CD_4 + CO, obtained from the previous decomposition of 201 mm. of CD_3CDO. In the second the process was reversed and 183 mm. of CD_3CDO was allowed to decompose completely at the same temperature in the presence of 370 mm. of CH_4 + CO, obtained from the decomposition of 189 mm. of CH_3CHO. The absorption spectra of samples taken from these runs are shown in curves III and IV, respectively. Both indicate only slight exchange and therefore reactions of the type shown above will not affect the conclusions to be drawn from the mixed decomposition experiments.

Curves V and VI in Fig. 2 show the results of the spectroscopic analysis of the methanes resulting from the decomposition of mixtures of CH_3CHO and CD_3CDO. For curve VI a mixture of 209 mm. of "untreated" CD_3CDO and 239 mm. of "untreated" CH_3CHO was allowed to react for two days at 480°, after which it was transferred to the absorption cell and analyzed. A marked increase in absorption in the 1100–1300 cm.$^{-1}$ range over that shown in curves I–IV is noted. Pronounced maxima are found at 1100, 1160, 1260 and 1290 cm.,$^{-1}$ showing the presence of all of the partially deuterated methanes and indicating that chain processes had been instrumental in the decomposition in this instance.[14] However, none of the maxima for the intermediate deuteromethanes are as strong as those obtained in curve VII for the reaction induced by oxygen. Hence, it is probable that only a portion of the reaction proceeded by means of the chain mechanism. This is in accord with the results of other

(13) M. Letort, *J. Chim. Phys.*, **34**, 428 (1937).

(14) This result offers some experimental verification for the proposition that the reaction CH_3 + CH_3CHO is a much faster process than CH_3 + CH_4, since the reactions which yielded the samples for curves III and IV, which showed no exchange, were also carried out with the "untreated" aldehydes. (See "The Aliphatic Free Radicals," F. O. Rice and O. K. Rice, Johns Hopkins Press, 1935, for an

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workers on the nature of the "normal" decomposition of acetaldehyde.[1,2,3]

In contrast curve V shows the absorption spectrum of the sample resulting from the reaction together of 145 mm. of "treated" CD_3CDO and 152 mm. of "treated" CH_3CHO at 542°. The temperature is not of major importance, for an almost identical curve was obtained from a similar mixture decomposed at about 480°. It can be seen that the absorption between 1100 and 1300 cm.$^{-1}$, while greater than that for curves I–IV, is nevertheless much less than that for curve VI, indicating a much smaller amount of chain reaction in this case. By a comparison of curve V with curve VII, assuming that the latter represents 100% chain reaction, it may be concluded that not more than 10–20% of the reaction with the "treated" aldehydes proceeded by means of a chain mechanism. Because of the difficulty in obtaining perfectly pure acetaldehyde, even by means of the treatment with hydroquinone, it seems likely that the residual 10% of chain reaction may have resulted from a slight remainder of induced chain reaction, and that the decomposition of acetaldehyde itself is completely a molecular reaction.

Results on the Rate of Decomposition of Acetaldehyde.—Table I presents a summary of experiments on the absolute rate of decomposition of CH_3CHO, both before and after treatment with hydroquinone, along with a comparative tabulation of the results of other researches.[3,6,13,15] For the "untreated" acetaldehyde the rates check the values calculated from the results of Smith for the "normal" decomposition of acetaldehyde. It was for samples like these that the infrared experiments showed a considerable amount of chain reaction, perhaps 50%, and the inhibition experiments of Smith and Hinshelwood[3] pointed to 60–70% of chain reaction. However, the second part of Table I shows that these rates can be considerably decreased by further purification. The absolute rates after treatment with hydroquinone are equal to about half the values for the "normal" reaction of Smith and are reduced almost to the values recorded by Smith and Hinshelwood for the completely inhibited reaction. The results of Letort, who used a very rigid purification procedure, are also lower than those of Smith or of the present untreated samples, although they are not as low as the rates for the "treated" samples in the present study. However, they constitute additional evidence that thoroughly purified acetaldehyde decomposes at a slower rate than previously supposed. The implication is that the more rapid rates are caused by traces of impurity which initiate a chain reaction.

In addition there is evidence here that the slower rates represent a molecular reaction in agreement with the infrared analyses. For, the inhibited rates of Smith and Hinshelwood presumably

(15) M. Letort, *J. Chim. Phys.*, **34**, 265 (1937).

TABLE I

THE RATE OF THERMAL DECOMPOSITION OF ACETALDEHYDE

Temp., °C.	Orig. pres., mm.	Initial rates of decomposition, mm./min. This study	Smith and Hinshelwood Normal[a]	Smith and Hinshelwood Inhibited[b]	Letort[c]
	(a)	Before treatment with hydroquinone			
445	309	2.1	1.7	0.65	1.1
477	67	0.9	0.57	0.21	0.42
478	118	1.6	1.46	.54	1.05
478	240	5.6	4.85	1.8	3.07
478	309	7.0	7.2	2.8	4.50
478	479	13.3	15.0	5.9	8.60
494	302	12.0	14.3	5.4	8.5
	(b)	After treatment with hydroquinone			
484	107	1.1	1.6	0.6	1.2
484	186	2.1	4.0	1.5	2.7
484	328	5.2	10.2	3.9	6.3
542	313	40	97	35	49

[a] These figures were calculated from the results of R. E. Smith (ref. 6) by the following procedure. Since the values tabulated by Smith were found to conform to the relation $-dx/dt = kx^{1.6}$, the half-life times were converted to initial rates by the equation: initial rate, $R = 1.15t_{50}/p_0$. Then large-scale plots of log R against $1/T$ were constructed and values of R at the required temperatures for a number of different pressures were read off from the straight line relationships. These values of R were used to evaluate k at each temperature in the table, and from these latter the rates at the specific pressures in the table were computed from the first equation above. It is estimated that errors of calculation should be certainly less than 10%. [b] The values in this column were calculated from the data of J. R. E. Smith and C. N. Hinshelwood (ref. 3) by the same method as (a). [c] Computed from the equation $-dx/dt = kx^{1.5}$, where $k = 4.44 \times 10^{12}e^{-46,000/RT}$ (moles/liter)$^{-1/2}$ min.$^{-1}$, given by M. Letort (refs. 13, 15).

signify a suppression of all chain reaction, leaving a residuum which is entirely a molecular reaction. Moreover, the results in the second part of Table I demonstrate that it is possible to reduce the rate of reaction almost to this minimum point without the use of inhibitors in the reaction vessel. Consequently this too must represent a reaction which is almost entirely molecular.

In Table II are shown similar results on the decomposition of CD_3CDO. In this instance the reduction in rate after treatment with hydroquinone was a maximum of about 20%. As in the previous table the "untreated" results agree with those calculated from the data of Smith, while the "treated" values are lower.

It is of interest to speculate on the nature of the impurity which causes the acceleration in these decompositions. Some qualitative observations have been made. It was found that in a series of duplicate runs the rates of successive runs would gradually tend to increase as more and more of the liquid acetaldehyde in the storage reservoir was used up. This pointed toward an accelerant which was less volatile than the acetaldehyde and therefore could not have been gaseous oxygen. It was also noted that even following the treatment with hydroquinone to remove the impurity, the rate of decomposition of samples of the acetaldehyde was

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TABLE II

RATE OF THERMAL DECOMPOSITION OF ACETALDEHYDE-d_4

Temp., °C.	Orig. press., mm.	Initial rates of reaction, mm./min. This study	Smith[a]
	(a) Before treatment with hydroquinone		
478	188	0.90	1.2
478	316	3.0	2.8
478	334	3.3	3.1
478	387	4.2	3.9
483	94	0.60	0.46
483	214	1.5	1.8
483	277	3.0	2.8
483	298	3.5	3.1
	(b) After treatment with hydroquinone		
484	293	3.1	3.1
493	295	4.3	4.8
509	193	4.7	5.0
542	70	3.4	3.8
542	122	7.9	9.4
542	210	18.7	22.7
542	302	33.6	40.2

[a] Calculated by same method as values in Table I from paper of R. E. Smith (ref. 6).

again accelerated when the liquid acetaldehyde was allowed to stand after distillation from the hydroquinone. The formation of either an autoxidation product or a polymerization product of the acetaldehyde as the substance responsible for the accelerating chain reaction would account for this result. The cause of the effectiveness of hydroquinone in removing the impurity was not discovered, though it may be connected with its reducing power.

The amount of impurity necessary to produce such an acceleration is very small. Chain lengths of 4000 have been reported by Letort[13] in the oxygen accelerated reaction at this temperature. If the same chain length held in the induced reaction under consideration, then less than 0.1% of impurity would be needed to triple the rate of reaction. Few physical tests can detect the presence of this quantity of material.

The fact that the rate of decomposition of deuteroacetaldehyde was not subject to the same rapid acceleration as the ordinary acetaldehyde may be accounted for in a number of ways. One would be that the rate of formation of impurity is considerably smaller in CD_3CDO than in CH_3CHO so that there was a lesser quantity of the impurity present to cause acceleration. Or, the quantity of accelerant may have been about the same, but the rate of the induced reaction compared to the rate of the molecular reaction may have been smaller for the heavier isotope.

Discussion.—Both approaches to the problem of the mechanism of the thermal decomposition of pure acetaldehyde lead to the same conclusion that the reaction takes place substantially through a molecular process. However, a further conclusion may be drawn from the infrared analyses. The meager formation of intermediate deuteromethanes in the reaction of the pure mixed aldehydes provides definite evidence for the first of the possible reaction mechanisms mentioned earlier—the decomposition of individual particles of acetaldehyde to give methane and carbon monoxide in a single act. This means that the reaction must be truly unimolecular.

One might picture the operation of such a mechanism as an amplification of the normal bending vibration frequency of acetaldehyde in which the aldehyde hydrogen and the methyl group vibrate toward one another by means of a decrease in the C–C–H angle, while the carbonyl group recedes sufficiently to maintain the balance of the system. In discussing the spectrum of acetaldehyde this frequency has been called the "H-wagging frequency,"[11] since the hydrogen atom contributes most of the motion because of its lightness.

The dependence of the rate of reaction on concentration, however, is intermediate between a first-order and a second-order relation. This is another example of the common phenomenon that the kinetic order of a chemical reaction may not tell us its fundamental mechanism. A probable reason for such a difference in this case is that the rate of activation of acetaldehyde molecules by collision is not sufficiently rapid to maintain an equilibrium concentration of the activated species as it decomposes. This implies that the decomposition of the activated acetaldehyde molecules must be fast enough so that a sizable fraction will have decomposed before they have a chance to become deactivated by subsequent collision. The rate of activation of the molecules by collision then becomes a rate-determining step of comparable magnitude to the rate of decomposition of the activated molecules. If this is the case experiments with purified acetaldehyde at very high pressures should show a first-order relation and at very low pressures the reaction should become more nearly second order.

Insufficient experiments were performed in these researches to determine a kinetic equation for the decomposition of the completely purified acetaldehyde with any certainty.

Although the absolute rate is smaller, the dependence on concentration and the activation energy seem to be quite similar to those of previous kinetic studies. Consequently, one might obtain a satisfactory equation either by multiplying the constant factor in the equation of Letort[15] by 0.75 or by adopting the equation given by Smith and Hinshelwood[3] for the completely inhibited reaction as that for the decomposition of pure acetaldehyde.

The present data give a different value for the relative rates of decomposition of light and heavy acetaldehyde from that recorded by Smith.[6] Over a wide set of conditions he found a ratio for the rate of reaction of CH_3CHO to that of CD_3CDO of about 2.4. However, since the rate of

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reaction of the CH_3CHO was decreased by treatment much more than that of the CD_3CDO, it means that the true ratio must be lower. As in the case of the kinetic equation, no accurate evaluation of this ratio is possible because of the lack of sufficiently extensive figures, but they indicate that the value over the temperature range of the present experiments is 1.3–1.4.

Summary

1. The thermal decomposition of mixtures of acetaldehyde and acetaldehyde-d_4 has been carried out and the resulting methanes have been analyzed by means of their infrared absorption spectra. The results indicate that the thermal decomposition of acetaldehyde is a true unimolecular reaction and that chain processes play a very minor part, if any.

2. This conclusion has been confirmed by studies on the absolute rate of the thermal decomposition of acetaldehyde, which show the true rates to be only half as great as those previously observed.

3. The relative rate of thermal decomposition of acetaldehyde to that of acetaldehyde-d_4 is approximately 1.3–1.4.

CAMBRIDGE, MASS. RECEIVED DECEMBER 3, 1943

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

Quinoidation of Triaryl Compounds—Hydroxyphenylbiphenylcarbinols

BY LEIGH C. ANDERSON AND W. A. FISHER[1]

Previous papers from this Laboratory[2] have presented data on the absorption spectra of several hydroxytriarylcarbinols and the corresponding fuchsones. A comparison of the absorption spectra of colored carbinols, of triphenylmethyl salts[3] and of triphenylmethyl[4] with those of quinone and the fuchsones indicated the existence of quinonoid structures for all these substances. Quinone, the free radical in ether solutions and the quinonoid carbinols have quinonoid bands which are low when compared to the corresponding bands in the fuchsones, the free radical in sulfur dioxide, and the triphenylmethyl salts. No attempt has yet been made to give an interpretation for the difference. This investigation presents data on triarylcarbinols wherein *p*-biphenyl groups have replaced one or both of the unsubstituted phenyl groups of *p*-hydroxytriphenylcarbinol. The absorption spectra obtained from these carbinols appear to offer an explanation for the variation in height of the quinonoid bands.

Two biphenylhydroxyphenylcarbinols have been studied: 4-hydroxy-4′-phenyltriphenylcarbinol and 4-hydroxy-4′,4″-diphenyltriphenylcarbinol. They were made by the condensation between phenol and *p*-biphenyldichlorophenylmethane and di-*p*-biphenyldichloromethane, respectively. Unless the correct conditions are adhered to, this condensation produces diphenoxymethane and tetraphenylmethane derivatives as chief products. The carbinols were also made by the aluminum chloride demethylation of the methoxy derivatives which were prepared by the reaction between *p*-anisylmagnesium bromide and 4-phenylbenzophenone and 4,4′-diphenylbenzophenone, respectively. The monobiphenylcarbinol was isolated in two forms: an intensely colored yellow form and a colorless modification. The dibiphenylcarbinol was isolated in two yellow modifications: one intensely colored and one which was considerably lighter in color. The fuchsone of each carbinol was prepared also.

The ultraviolet absorption spectra of ether solutions of these compounds show that a broad high band replaces the double band in the benzenoid portion of the spectrum when a *p*-biphenyl group is substituted for one of the phenyl groups of 4-hydroxytriphenylcarbinol (Fig. 1). This band is very similar to the one obtained from an hexane solution of biphenyl and is due, undoubtedly, to the biphenyl group in the carbinol. That its maximum is about 0.3 unit higher and its position about 200 mm.$^{-1}$ further toward the visible are effects easily attributable to the presence of the carbinol substitutent on the biphenyl. A second *p*-biphenyl group substituted in the carbinol merely increases the height of this band, emphasizing its source in the biphenyl groups.

The change in benzenoid absorption when a phenyl group in 4-hydroxytriphenylcarbinol is replaced by a biphenyl group seems to indicate that the biphenyl group acts as a unit in producing absorption and not as two phenyl groups. The absorption spectra of molecules containing both phenyl and biphenyl groups show that the phenyl absorption is completely blotted out beneath the biphenyl band (Figs. 1 and 2). The fact that the only appreciable change in this biphenyl band upon the introduction of more biphenyl groups into the molecule is in its height (Figs. 1 and 2) shows that each biphenyl group is acting more or less independently in producing the absorption

(1) The material presented in this and the following paper constitutes a portion of a dissertation submitted by Willis Allan Fisher to the Horace H. Rackham School of Graduate Studies of the University of Michigan in partial fulfillment of the requirements of the Ph.D. degree, February, 1940.

(2) Anderson and Gomberg, THIS JOURNAL, 50, 204 (1928); Anderson, *ibid.*, 51, 1889 (1929); Anderson and Geiger, *ibid.*, 54, 3058 (1932).

(3) Anderson, *ibid.*, 52, 4567 (1930).

(4) Anderson, *ibid.*, 57, 1673 (1935).

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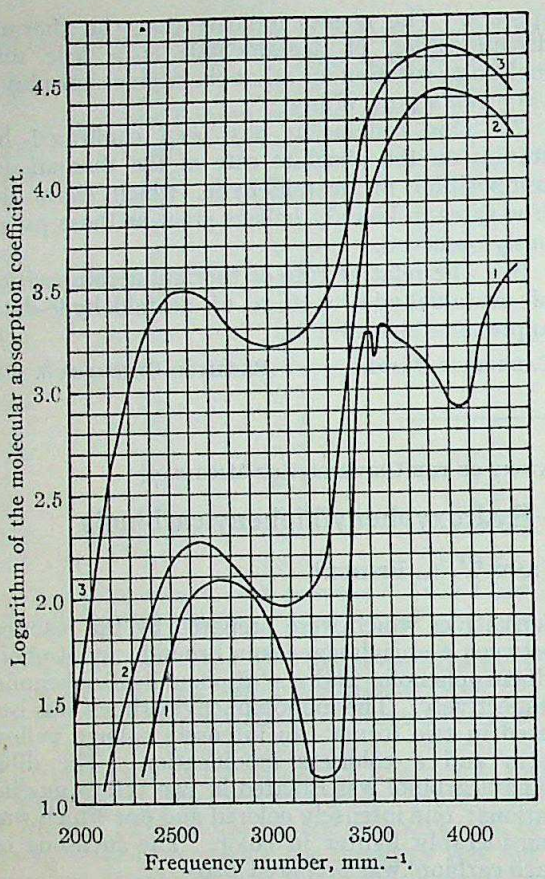

Fig. 1.—Absorption in ether solution of the quinonoid forms of: 1, 4-hydroxytriphenylcarbinol; 2, 4-hydroxy-4′-phenyltriphenylcarbinol; 3, 4-hydroxy-4′,4″-diphenyltriphenylcarbinol.

band. There is no great interaction with the rest of the molecule even in the quinonoid forms of the carbinols where a double bond is on the carbon next to the biphenyl group.

When a comparison is made of the absorption in ether of the three fuchsones: diphenylquinomethane, *p*-biphenylphenylquinomethane and di-*p*-biphenylquinomethane (Fig. 3), a regular shift of the two bands toward the visible is observed when the biphenyl groups are introduced. This is accompanied, as far as the band nearest the visible is concerned, by a slight regular increase in height. The higher frequency band in the fuchsones does not appear at the position where the biphenyl group absorbs in the carbinols nor does it have the shape of the biphenyl band.[5] Since the characteristic biphenyl band does not show up in this series of compounds, the electronic structure of the biphenyl group in the fuchsones is changed in some manner which does not occur with the carbinols. Resonance may occur with

(5) A similar change has been observed in the absorption spectra of all the fuchsones from hydroxytriphenylcarbinols which have been made in previous work. Each of them has had a second band which was different in both shape and position from the benzenoid bands found in the corresponding methanes and carbinols.

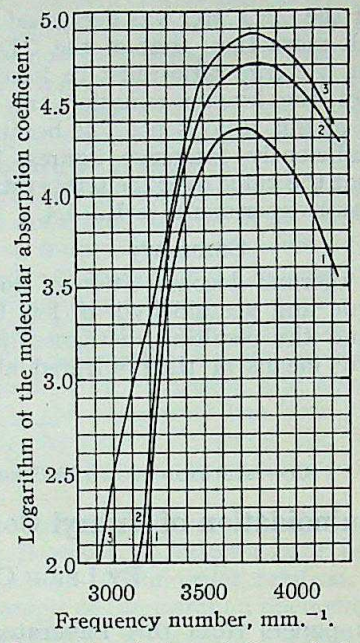

Fig. 2.—Absorption of ether solutions of: 1, 4-(*p*-anisyl)-triphenylcarbinol; 2, 4-(*p*-anisyl)-4′-phenyltriphenylcarbinol; 3, 4-(*p*-anisyl)-4′,4″-diphenyltriphenylcarbinol.

the fuchsones by a simple change in the nature of the double bond to the oxygen but the same type of resonance cannot occur with the hydroxycarbinols since there is no double bonded oxygen present. For example, the fuchsone of *p*-hydroxytriphenylcarbinol may be represented by

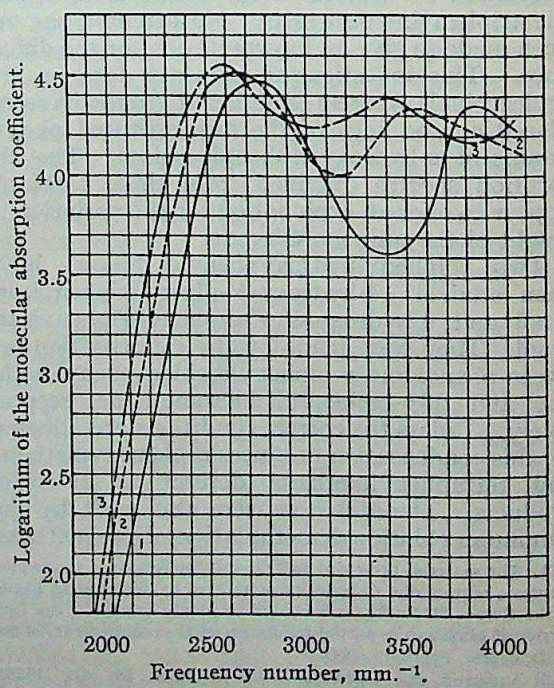

Fig. 3.—Absorption of ether solutions of: 1, diphenylquinomethane; 2, phenyl-*p*-biphenylquinomethane; 3, di-*p*-biphenylquinomethane.

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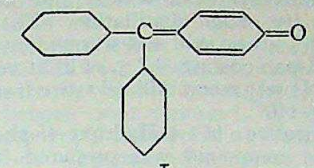
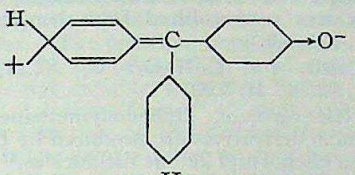
the conventional structure (I) in resonance with electronically isomeric structures such as II

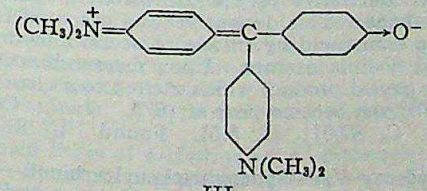


I

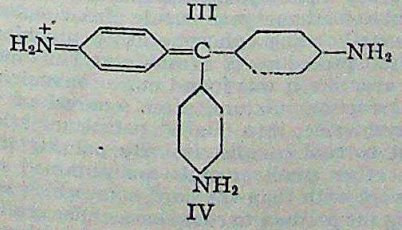


II

Because of this resonance in the fuchsones, the structure of the benzenoid groups is now altered while in the hydroxycarbinols any biphenyl group exercises its own absorption. A preferred position for the positive charge in II cannot be indicated. The introduction of biphenyl groups with the corresponding increase of possible resonance structures should increase the probability of occurrence of the phenolic ring structure. That any structure containing a biphenoquinone nucleus does not play a major part in the total makeup of the molecule is indicated because there is no abrupt change in the nature of the absorption in this series. It will be shown in the paper which follows that the absorption of 4-methoxy-*p*-biphenyldiarylmethyl cations is very different from *p*-methoxyphenyldiarylmethyl cations and that this marked change in absorption may be accounted for by a quinoidation which involves the biphenyl group. The above concept of resonance in the fuchsone molecules is in harmony with data obtained by Hantzsch from 4,4′-tetramethyldiaminofuchsone.[6] He found the absorption of this compound to be strikingly similar to that of a water solution of *p*-fuchsine, a salt, and not at all like that of fuchsone. This can be attributed to the presence of a resonance structure III like those in the salt cation IV



III



IV

According to this conception, there should be a similar relationship between the absorption of diphenylquinomethane and the triphenylmethyl ion. The curves for the latter two compounds do have almost identical absorption between 2000 and 3000 mm.$^{-1}$.

The light absorption of these fuchsones does not, then, occur in a manner which would be expected of the classical formula, but instead indicates that the molecule is the result of several resonance structures which may be similar to those indicated. Since, according to this hypothesis, the absorption of the fuchsones in the quinonoid region of the spectrum cannot be attributed to the carbonyl containing ring only, no surprise can be evidenced at the great increase in intensity of fuchsone absorption over that of quinone, whose absorption bands in this region are very low. Furthermore, the low intensity of the quinonoid carbinols may be explained by their lack of the resonance present in the fuchsone molecule and consequent dependence on the quinone ring only for absorption in this region.

The absorption curves for the quinonoid forms of these carbinols are from samples produced under similar conditions. The quinonoid forms were secured by crystallizing the carbinols from 60–70% acetic acid solutions. Since these carbinols undoubtedly exist as the corresponding cations in acetic acid solutions, the crystallization of the quinonoid variety from such solutions lends support to the idea that the hydroxy containing ring is quinonoid in the cations.

The benzenoid forms were made by precipitating the hydroxycarbinols from dilute sodium hydroxide solution by means of carbon dioxide and recrystallizing the products from aqueous alcohol containing a trace of ammonia. In an alkaline solution the phenolic character of the hydroxy containing ring is stressed and this results in the occurrence of the benzenoid form. If a very weak acid such as carbon dioxide is used to convert the salt of the phenol to the hydroxy compound and recrystallization is carried out in a slightly alkaline medium, there is little chance for conversion to the quinonoid cation and the solid benzenoid form is obtained.

In general, the conditions for producing the benzenoid forms of the carbinols which have been studied in previous investigations gave samples whose absorption in the quinonoid region was entirely removed or at least reduced in intensity to well below 1 unit. This is not true, however, in the case of 4,4′-diphenyl-4″-hydroxytriphenylcarbinol which was prepared under conditions which yield the benzenoid variety with other hydroxycarbinols. Though the height of the quinonoid band for this sample was almost 1.5 units less than in the case of the quinonoid variety, yet its peak was still at 2.1. Such a decrease with most of the other carbinols which have been studied would have meant the complete disappearance of the band. Other investigators have shown gradations in the ability of various hydroxytriarylcarbinols to exist in both the

(6) Hantzsch, *Ber.*, **52**, 509 (1919).

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benzenoid and quinonoid forms. Gomberg and Lange reported that 4-hydroxydiphenyl-α-naphthylcarbinol was not stable in the benzenoid form.[7] It may be pointed out that an α-naphthyl group or two *p*-biphenyl groups present on each of the ethane carbon atoms in a hexaarylethane strongly favor dissociation of the ethane[8]; apparently they are equally effective in inhibiting the formation of the benzenoid carbinols under discussion.

The fuchsones, *p*-biphenylphenylquinomethane and di-*p*-biphenylquinomethane, were made by heating the corresponding carbinols under reduced pressure until the vigorous evolution of water vapor had ceased and were then recrystallized from benzene.

Experimental

4-Hydroxy-4′-phenyltriphenylcarbinol.—A mixture of 10 g. of dichloro-*p*-biphenylphenylmethane[9] and 10.5 g. of phenol was allowed to react for fifteen hours at room temperature with exclusion of moisture. The excess phenol was then removed from the mixture by steam distillation. The residue was cooled, crushed, and extracted with 2.5% sodium hydroxide solution. The insoluble 4-phenylbenzophenone was removed by filtration. Some ketone is held in the alkaline solution and it cannot be satisfactorily removed by ether extraction as can be done in the case of 4-hydroxytriphenylcarbinol.[10] The alkaline solution was acidified with dilute acetic acid and the precipitated hydroxycarbinol was recrystallized from 60–70% acetic acid giving a light yellow material melting around 120° with evolution of water. The principal impurity in this crude carbinol is the ketone with a small amount of 4,4′-dihydroxy-4″-phenyltetraphenylmethane. The pure carbinol is best prepared by hydrolysis of pure phenyl-*p*-biphenylquinomethane.

Phenyl-*p*-biphenylquinomethane.—A sample of 4-hydroxy-4′-phenyltriphenylcarbinol was dehydrated by placing it in an evacuated flask heated by means of an oil-bath to 130–140°. The sample was maintained at this temperature until the vigorous evolution of water vapor had ceased. The product crystallizes from benzene–ether in orange needles, m. p. 166–167°. Its solubility in ether is 4 g. per liter. *Anal.* Calcd. for $C_{25}H_{18}O$: C, 89.79; H, 5.43. Found: C, 89.88; H, 5.54.

Quinonoid Form of 4-Hydroxy-4′-phenyltriphenylcarbinol.—Four grams of phenyl-*p*-biphenylquinomethane was dissolved in 100 cc. of warm 70% acetic acid and the solution allowed to cool. Water was added to the cold solution until a permanent cloudiness had appeared, and the material was allowed to crystallize. The resulting acid concentration was 60–65%. The precipitate was dried in a vacuum desiccator over soda-lime, m. p. 139–140°.

Benzenoid Form of 4-Hydroxy-4′-phenyltriphenylcarbinol.—To prepare the benzenoid form, either the pure quinonoid variety or the fuchsone was dissolved in 2.5% sodium hydroxide solution and the resulting solution acidified by passing in a stream of carbon dioxide. The precipitate was removed by filtration and dissolved in alcohol containing a trace of ammonia. Upon the gradual addition of water the carbinol crystallized with only a slight color, m. p. 155–157°.

4-Hydroxy-4′-phenyltriphenylcarbinol from 4-Methoxy-4′-phenyltriphenylcarbinol.—Six grams of anhydrous aluminum chloride was added to a hot solution of 4 g. of 4-methoxy-4′-phenyltriphenylcarbinol[11] in 100 cc. of benzene. This mixture was refluxed with exclusion of moisture for thirty minutes. The product was decomposed with ice and dilute hydrochloric acid, and the benzene was then removed by steam distillation. The residue was dissolved in 70% acetic acid and warmed on a steam-bath for an hour. Upon cooling, 3.7 g. of light yellow material was secured. It was recrystallized twice from 75% acetic acid, m. p. 134–140°.

Acetyl Derivative of 4-Hydroxy-4′-phenyltriphenylcarbinol.—This compound was prepared from the carbinol by means of acetic anhydride and anhydrous sodium acetate. It was recrystallized from benzene–petroleum ether, m. p. 134–136°.

Anal. Calcd. for $C_{27}H_{22}O_3$: C, 82.21; H, 5.62. Found: C, 82.26; H, 5.69.

Besides the carbinol, diphenoxymethane and tetraphenylmethane derivatives are produced by the condensation between phenol and ketone dichlorides.[12] The conditions under which the reaction is carried out determine the major product. These derivatives were made both in this case, the condensation between phenol and dichloro-*p*-biphenylphenylmethane, and in the subsequently described condensation between phenol and di-*p*-biphenyldichloromethane in order to determine their properties and thus facilitate their removal from the carbinols.

Phenyl-*p*-biphenyldiphenoxymethane.—Thirteen grams of dichloro-*p*-biphenylphenylmethane was added to a boiling solution of 14 g. of phenol in 250 cc. of anhydrous benzene. The mixture was refluxed with exclusion of moisture for one hour. At the end of this time hydrogen chloride evolution had ceased. The solution was then concentrated to one-half its original volume and 100 cc. of 60–75° petroleum ether was added to the residue. When the mixture had cooled, 12 g. of product precipitated. Upon recrystallization from alcohol, small white needles were obtained, m. p. 149–150°.

Anal. Calcd. for $C_{31}H_{24}O_2$: C, 86.89; H, 5.65. Found: C, 87.06; H, 5.70.

4,4′-Dihydroxy-4″-phenyltetraphenylmethane.—A mixture of 13 g. of dichloro-*p*-biphenylphenylmethane and 20 g. of phenol was heated on a steam-bath for five days. Moisture was excluded during this time. The excess phenol was then removed by steam distillation and the solid residue was extracted with 2.5% sodium hydroxide solution. After the insoluble material had been removed by filtration, the alkaline solution was acidified with carbon dioxide. The product became colorless after three recrystallizations from benzene–petroleum ether. A 55% yield of material which begins to soften at 157° and melts at 163–165° was secured.

Anal. Calcd. for $C_{31}H_{24}O_2$: C, 86.89; H, 5.65. Found: C, 86.65; H, 5.95.

Diacetyl Derivative of 4,4′-Dihydroxy-4″-phenyltetraphenylmethane.—This derivative was prepared from the dihydroxy compound by means of acetic anhydride and anhydrous sodium acetate. Upon recrystallization from alcohol it gave a product which melted to a cloudy liquid at 168–170° and became clear at 187°. *Anal.* Calcd. for $C_{35}H_{28}O_4$: C, 82.01; H, 5.51. Found: C, 81.82; H, 5.57.

4-Hydroxy-4′,4″-diphenyltriphenylcarbinol.—Di-*p*-biphenyldichloromethane was made from 4,4′-diphenylbenzophenone[13] using phosphorus pentachloride and following the procedure of Straus and Dutzmann.[14] In this latter reaction it was found more convenient to pour the warm reaction mixture, after removal of the phosphorus oxychloride, into 60–75° petroleum ether before allowing it to cool completely. By pouring it into the petroleum ether small crystals are obtained which are easier to work with than the hard mass which is obtained by allowing the product to cool alone. The crude dichloro compound (m. p. 130–135°) was used without further

(7) Gomberg and Lange, THIS JOURNAL, **42**, 1879 (1920).

(8) Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1938, p. 504.

(9) Schlenk and Bergmann, *Ann.*, **463**, 120 (1928).

(10) Gomberg and Jickling, THIS JOURNAL, **37**, 2580 (1915).

(11) Anderson and Fisher, *ibid.*, **66**, 690 (1944).

(12) Gomberg and Snow, *ibid.*, **47**, 198 (1925); Gomberg and Anderson, *ibid.*, **47**, 2022 (1925).

(13) Bachmann, *ibid.*, **55**, 770 (1933).

(14) Straus and Dutzmann, *J. prakt. Chem.*, [2] **103**, 1 (1921).

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purification; 25 g. of this material was mixed with 20 g. of phenol and the resulting reaction allowed to continue for fifteen hours at room temperature with exclusion of moisture. The excess phenol was then removed from the mixture by steam distillation. After the residue had been dried and crushed, it was digested with 200 cc. of cold alcohol and the mixture was left overnight; 6 g. of 4,4′-diphenylbenzophenone was removed by filtration. The residue after removal of the alcohol was recrystallized from 70% acetic acid. Crystallization occurs only with difficulty. The compound can be secured in a solid form by quickly pouring the dilute acetic acid solution into a large excess of water. The principal impurities are the ketone, which in spite of its insolubility in alcohol and dilute acetic acid is not entirely separated by the above procedure, and 4,4′-dihydroxy-4″,4‴-diphenyltetraphenylmethane. Preparation of the carbinol from the corresponding fuchsone gives a purer product but the method is not as easy as was found with 4-hydroxy-4′-phenyltriphenylcarbinol since separation of this fuchsone and ketone is not so readily carried out. The tetra compound is slightly more soluble in most solvents than the ketone or the fuchsone. The carbinol is readily soluble in ether, alcohol and benzene and is only slightly soluble in dilute alkali. *Anal.* Calcd. for $C_{31}H_{24}O_2$: C, 86.89; H, 5.65. Found: C, 86.59; H, 5.87.

Di-*p*-biphenylquinomethane.—A sample of 4-hydroxy-4′,4″-diphenyltriphenylcarbinol was placed in an evacuated flask heated by means of an oil-bath to 130–140°. It was maintained at this temperature until the vigorous evolution of water vapor had ceased. The product crystallizes from benzene in orange needles. If it is heated gradually it melts over a range 140–155°. If it is placed in a melting point-bath at 150° and then heated, it melts at 159–161.5°. This compound is soluble in ether to the extent of about 2 g. per liter. *Anal.* Calcd. for $C_{31}H_{22}O$: C, 90.70; H, 5.40. Found: C, 90.49; H, 5.60.

Di-*p*-biphenylquinomethane from 4-Methoxy-4′,4″-diphenyltriphenylcarbinol.—Two grams of anhydrous aluminum chloride was added to a boiling solution of 2.2 g. of 4-methoxy-4′,4″-diphenyltriphenylcarbinol[11] in 50 cc. of benzene and the mixture was refluxed with exclusion of moisture for fifteen minutes. The product was decomposed with ice and dilute hydrochloric acid. The benzene solution was separated, dried, and evaporated to dryness. The resulting solid was dehydrated at 130–140° in an evacuated flask until water evolution had ceased. Recrystallization of the product from benzene yielded 0.5 g. of orange needles, m. p. 155–157°. The melting point of a mixture of this material with that prepared by dehydration of the hydroxycarbinol indicated the identity of the two products.

Quinonoid Form of 4-Hydroxy-4′,4″-diphenyltriphenylcarbinol.—3.5 g. of di-*p*-biphenylquinomethane was dissolved in 300 cc. of 70% acetic acid by heating on a steam-bath for two hours. Sufficient water was then added to reduce the concentration of the acetic acid to 60–65% and the solution allowed to stand. Crystallization occurred after long standing. The product was red-orange in color, m. p. 106–107.5°.

Benzenoid Form of 4-Hydroxy-4′,4″-diphenyltriphenylcarbinol.—Attempts to prepare the benzenoid form of this carbinol resulted in a product lighter in color than the quinonoid variety but by no means colorless. Though the solubility of this carbinol in dilute sodium hydroxide is not great, some solution will take place. An alkaline solution of a sample of the quinonoid variety was filtered and then acidified with carbon dioxide. Recrystallization of the precipitate from aqueous alcohol containing a trace of ammonia gave a yellow-orange product, m. p. 124–126°.

Acetyl Derivative of 4-Hydroxy-4′,4″-diphenyltriphenylcarbinol.—This compound was prepared from the carbinol by means of acetic anhydride and anhydrous sodium acetate. It was recrystallized twice from benzene–petroleum ether mixtures, m. p. 149–152°. *Anal.* Calcd. for $C_{33}H_{26}O_3$: C, 84.23; H, 5.57. Found: C, 83.90; H, 5.76.

Di-*p*-biphenyldiphenoxymethane.—Fifteen grams of di-*p*-biphenyldichloromethane was added to a boiling solution of 10 g. of phenol and 5 g. of pyridine in 100 cc. of anhydrous benzene. This mixture was refluxed with exclusion of moisture for four hours. The product was extracted with water several times to remove pyridine hydrochloride, pyridine and phenol. The volume of the benzene solution was then reduced to 75 cc. and an equal volume of 60–75° petroleum ether was added. The ketone which precipitated was removed by filtration and the filtrate evaporated nearly to dryness. The product was crystallized from petroleum ether, yield 10 g., m. p. 118–120°. This compound is very soluble in benzene, high boiling petroleum ether and slightly soluble in alcohol. *Anal.* Calcd. for $C_{37}H_{28}O_2$: C, 88.06; H, 5.59. Found: C, 87.87; H, 5.86.

4,4′-Dihydroxy-4″,4‴-diphenyltetraphenylmethane.—A mixture of 20 g. of phenol and 12 g. of di-*p*-biphenyldichloromethane was heated on a steam-bath for five days with the exclusion of moisture. Water was then added and the excess phenol was removed by steam distillation. The residue crystallized slowly from a mixture of benzene and 60–75° petroleum ether giving 10 g. of material. Recrystallized from alcohol, m. p. 253–255.5°. This compound dissolves in hot 2.5% sodium hydroxide solution. It is moderately soluble in ether and in benzene and slightly soluble in alcohol.

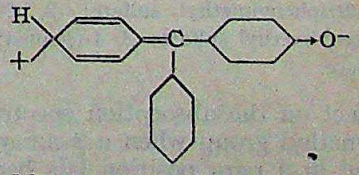
Diacetyl Derivative of 4,4′-Dihydroxy-4″,4‴-diphenyltetraphenylmethane.—This substance was prepared from the dihydroxy compound by means of acetic anhydride and anhydrous sodium acetate; recrystallized from benzene and 60–75° petroleum ether, m. p. 256–258°. *Anal.* Calcd. for $C_{41}H_{32}O_4$: C, 83.65; H, 5.48. Found: C, 83.20; H, 5.54.

Summary

1. 4-Hydroxy-4′-phenyltriphenylcarbinol and 4-hydroxy-4′,4″-diphenyltriphenylcarbinol have been made. Each carbinol has been isolated in the benzenoid and quinonoid forms and various derivatives are described.

2. The ultraviolet absorption spectra of these carbinols and certain derivatives have been determined. The *p*-biphenyl group in these carbinols acts almost as an isolated unit in absorption, producing a characteristic, high, broad absorption band near 3800 mm.$^{-1}$ which resembles the band others have reported for biphenyl itself.

3. A study of the ultraviolet absorption for the fuchsones of the above carbinols indicates that resonance structures of the following type appear to be an important factor in the absorption of ether solutions of fuchsones



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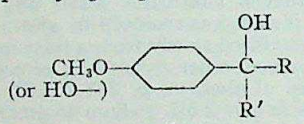
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

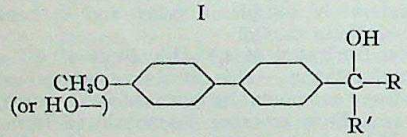
Quinoidation of Triaryl Compounds—Hydroxybiphenyldiarylmethyl Cations

BY LEIGH C. ANDERSON AND W. A. FISHER

Data have been presented from this Laboratory on the preparation and absorption spectra of *p*-hydroxyphenylbiphenylcarbinols.[1] This paper discusses investigations which have been made on biphenylcarbinols in which a hydroxyl or methoxyl group has been substituted on the terminal carbon of the biphenyl group in order to obtain data on the biphenoquinone type of structure. Two types of carbinols were used in this investigation: methoxy or hydroxyphenyldiarylcarbinols illustrated by I and methoxy or hydroxybiphenyldiarylcarbinols illustrated by II where the aryl groups R and R′ are either phenyl or *para*-biphenyl groups. The absorption spectra



I



II

of the cations produced by solutions of these carbinols in acid have been ascertained.

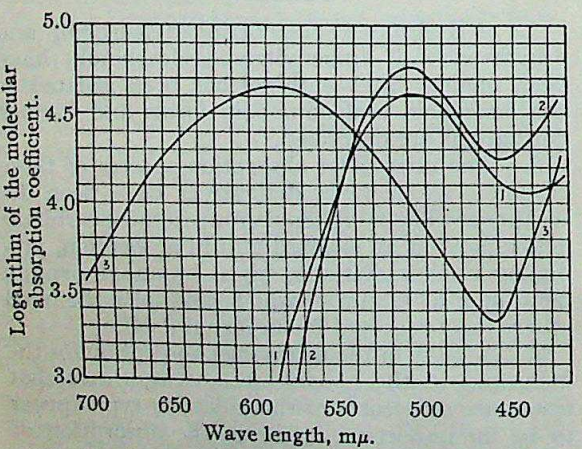


Fig. 1.—Absorption of acetic–sulfuric acid solutions of: 1, 4-phenyltriphenylmethyl sulfate; 2, 4-methoxy-4′-phenyltriphenylmethyl sulfate; 3, 4-(*p*-anisyl)-triphenylmethyl sulfate.

The effect on the absorption spectrum of the triphenylmethyl group when a *p*-anisyl group is substituted in a para position has been investigated for the first time. The chemical investigation of 4-(*p*-hydroxyphenyl)-triphenylcarbinol gave no evidence that the substance would become quinonoid through the biphenyl group. A study of the absorption curves gives evidence that the cations derivable from this compound and others containing the 4-hydroxybiphenyl or 4-methoxybiphenyl group contain predominating electronic structures which include quinoidation of the biphenyl group in a manner similar to that shown for fuchsones in the preceding paper. Considering the ions: 4-phenyltriphenylmethyl, 4-methoxy-4′-phenyltriphenylmethyl, and 4-(*p*-anisyl)-triphenylmethyl, the absorption of the first two is found to be similar while that of the third is markedly different (Fig. 1). It absorbs over a much broader region of the spectrum and has its absorption maximum much further toward the infrared. The structural change between the second and third ion is only in the position of the methoxy group; in the second it is on a phenyl group and in the third case it is on a biphenyl. The striking difference in absorption of the third ion as compared to that of the second is most logically explained by assuming that a predominating electronic structure for the third ion is that in which the biphenyl group has become quinonoid. A study of the absorption of the ions: 4,4′-diphenyltriphenylmethyl, 4-methoxy-4′4″-diphenyltriphenylmethyl, and 4-(*p*-anisyl)-4′-phenyltriphenylmethyl leads one to similar conclusions (Fig. 2).

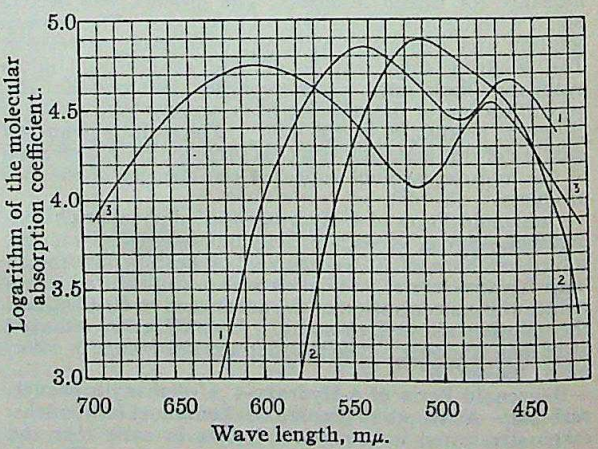


Fig. 2.—Absorption of acetic–sulfuric acid solutions of: 1, 4,4′-diphenyltriphenylmethyl sulfate; 2, 4-methoxy-4′,4″-diphenyltriphenylmethyl sulfate; 3, 4-(*p*-anisyl)-4′-phenyltriphenylmethyl sulfate.

If the methoxy group can fix the positive charge out at the end of the biphenyl group as the evidence indicates, there is no reason for assuming that the methoxy situated on the phenyl group has any less effect in causing the phenyl group to become quinonoid. This determines the predominating electronic structure of the 4-methoxy-

(1) Anderson and Fisher, THIS JOURNAL, 66, 780 (1944).

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4′-phenyltriphenylmethyl ion. A preferred position for the location of the charge on the 4-phenyltriphenylmethyl ion is not indicated by these data although the lack of similarity of its absorption to that of the substituted biphenyl compound makes it improbable that the charge is on the end of the biphenyl group.

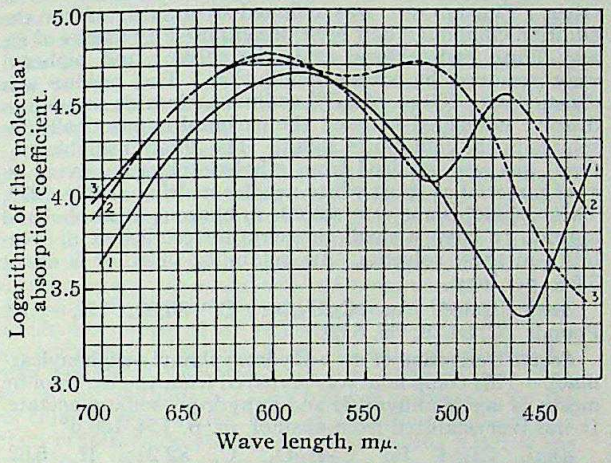


Fig. 3.—Absorption of acetic–sulfuric acid solutions of: 1, 4-(*p*-anisyl)-triphenylmethyl sulfate; 2, 4-(*p*-anisyl)-4′-phenyltriphenylmethyl sulfate; 3, 4-(*p*-anisyl)-4′,4″-diphenyltriphenylmethyl sulfate.

A para-anisyl group substituted in a para position of the triphenylmethyl ion is more strongly bathochromic than that of any other single substituent which has been reported (Fig. 3). This is consistent with data of Morton and Emerson, who found the maximum absorption of the 4,4′,4″-tri-(*p*-anisyl)-triphenylmethyl ion at 638 mμ.[2] These data appear to rule out conclusively any structural theory relating color to the central carbon atom. It is not reasonable to assume that replacing the methoxyphenyl group in a carbinol by a methoxybiphenyl group and thus increasing the distance between the substituted methoxy group and the central carbon atom would increase the effect of the methoxy on this atom. Dilthey and Harenberg[3] have claimed that groups far away from the central carbon atom have only a slight influence on the color. This is undoubtedly correct in the case of the methoxy groups in the 4,4′,4″-tri-(*p*-methoxyphenoxy)-triphenylmethyl ion they were investigating. They concluded that this was evidence against the quinonoid theory on the assumption that the diphenylether group might be expected to become quinonoid by having a tetracovalent ether oxygen. There is no evidence for this since tetravalent oxygen has usually been assumed to possess three covalences, the fourth being an ionic valence.

That the hydroxy or methoxy group is strongly concerned in attracting the charge is further evidenced by the absorption of corresponding pairs of

(2) Morton and Emerson, THIS JOURNAL, 59, 1947 (1937); 60, 284 (1938).

(3) Dilthey and Harenberg, *J. prakt. Chem.*, [2] 138, 49 (1933).

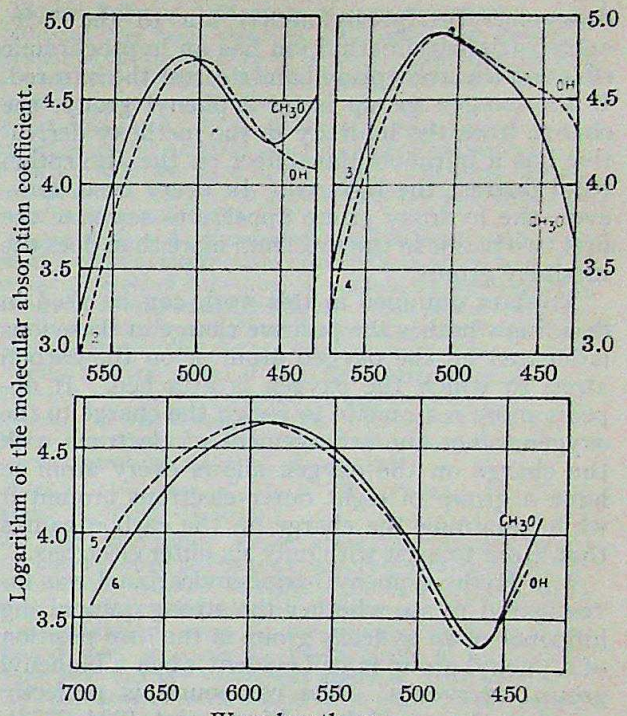
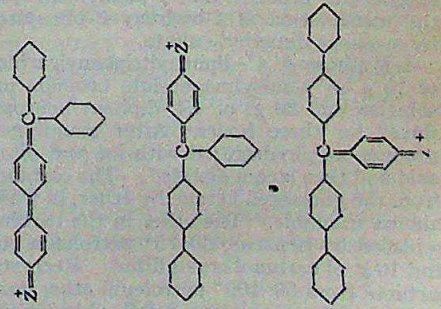


Fig. 4.—Comparison of the absorption of methylated and unmethylated hydroxytriarylmethyl sulfates: 1, 4-methoxy-4′-phenyltriphenylmethyl sulfate; 2, 4-hydroxy-4′-phenyltriphenylmethyl sulfate; 3, 4-methoxy-4′,4″-diphenyltriphenylmethyl sulfate; 4, 4-hydroxy-4′,4″-diphenyltriphenylmethyl sulfate; 5, 4-(*p*-hydroxyphenyl)-triphenylmethyl sulfate; 6, 4-(*p*-anisyl)-triphenylmethyl sulfate.

these compounds, one containing a hydroxy group and the other a methoxy. The absorption curves of ether solutions of 4-(*p*-hydroxyphenyl)-triphenylcarbinol and the corresponding methoxy compound cannot be distinguished from one another. On the other hand, the change from hydroxy to methoxy groups in the case of the ions causes a displacement of the absorption bands. The direction of the displacement depends upon whether a phenyl or a biphenyl group is substituted (Fig. 4). The change from the 4-(*p*-hy-

TABLE I

POSITIONS OF THE ABSORPTION MAXIMA OF THE QUINONOID BANDS OF OH—CH_3O PAIRS OF COMPOUNDS (mμ)



HO-	592	502	508
CH_3O-	587	508	512

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droxyphenyl)-triphenylmethyl ion to the 4-(*p*-anisyl)-triphenylmethyl ion has an hypsochromic effect on the absorption band nearest the infrared. If the oxygen group is on a phenyl group, the change from the hydroxy to the methoxy derivative has a bathochromic effect on the absorption band nearest the infrared. In every case, however, the hydroxy group appears to separate the first two bands in the spectrum more than does the methoxy group.

No data obtained in this work can be used in deciding whether the positive charge in these ions is located on the oxygen atom or on the carbon atom to which the oxygen is attached. It appears more reasonable to assign the charge to the oxygen, since the arrangement of electrons with the charge on the oxygen allows every atom to have a group of eight outer electrons around it while retaining the charge on the carbon causes that atom to exist with only six outer electrons.

4-(*p*-Hydroxyphenyl)-triphenylcarbinol was investigated to see whether the strong quinonizing influence of an hydroxy group in the *para* position of a phenyl group is still evident when a biphenyl group intervenes. The compound is perfectly colorless, has a high melting point (224–227°), and shows no tendency whatsoever to exist in a quinonoid form in the solid state. If it is maintained above its melting point, it decomposes quite rapidly with the evolution of gas. The product, however, could not be obtained crystalline and it did not have an intense color as should be characteristic of such a compound as diphenylbiphenoquinomethane. The color, though a deep purple-brown, seemed to be possessed by only a small amount of the material even when the copious gas evolution had ceased. It is thought likely that any evolution of water took place between molecules resulting in condensation rather than intramolecularly leading to a quinonoid biphenyl group. An attempt to make diphenylbiphenoquinomethane by the reaction between biphenoquinone and diphenylketene was also unsuccessful.

Experimental

4-Methoxy-4′-phenyltriphenylcarbinol.—This carbinol was described by Bowden, Harris and Roberts[4] while this investigation was being carried on. We prepared it by two procedures: (1) the reaction between *p*-anisylmagnesium bromide and *p*-phenylbenzophenone, and (2) the methylation of 4-hydroxy-4′-phenyltriphenylcarbinol by means of dimethyl sulfate.

4-Methoxy-4′,4″-diphenyltriphenylcarbinol.—A mixture of 15 g. of *p*-anisylmagnesium bromide in ether–benzene solution and 20 g. of 4,4′-diphenylbenzophenone was refluxed for three hours. After standing overnight, the product was hydrolyzed with ice and dilute hydrochloric acid and then steam distilled. The carbinol was extracted from the unreacted ketone by ether, in which the ketone is almost insoluble. The ether in the carbinol solution was replaced by benzene, 60–75° petroleum ether was added, and 10 g. of carbinol crystallized. Recrystallization of the carbinol from 90–100° petroleum ether containing a small amount of benzene gave small white needles, m. p. 144–146°. In contrast to 4-methoxytriphenylcarbinol and 4-methoxy-4′-phenyltriphenylcarbinol, this compound crystallizes readily and is less soluble in the common solvents.

Anal. Calcd. for $C_{32}H_{26}O_2$: C, 86.85; H, 5.92. Found: C, 87.08; H, 6.14.

4-(*p*-Hydroxyphenyl)-triphenylcarbinol.—Thirty grams of 4-hydroxy-4′-benzoylbiphenyl dissolved in 200 cc. of benzene was added to the Grignard reagent made from 55 g. of bromobenzene, 7.9 g. of magnesium and 100 cc. of ether. The mixture was refluxed overnight. After the addition compound had been decomposed by means of ice and dilute hydrochloric acid, the solvent and biphenyl were removed by steam distillation. The residue was digested with 500 cc. of 2.5% sodium hydroxide solution to dissolve unreacted ketone; the carbinol is practically insoluble in the cold dilute alkali. The alkali insoluble material was recrystallized from ethylene chloride giving 30 g. of material as short white needles melting at 224–227°. This carbinol is not very soluble in benzene or alcohol and appears to have a small temperature coefficient of solubility in these solvents. Its solubility in ether is about 3.5 g. per liter.

Anal. Calcd. for $C_{25}H_{20}O_2$: C, 85.20; H, 5.72. Found: C, 84.79; H, 5.99.

Acetyl Derivative of 4-(*p*-Hydroxyphenyl)-triphenylcarbinol.—This compound was prepared from the carbinol by means of acetic anhydride and anhydrous sodium acetate. It was recrystallized from alcohol, m. p. 154–156.5°.

Anal. Calcd. for $C_{27}H_{22}O_3$: C, 82.21; H, 5.62. Found: C, 82.13; H, 5.73.

4-(*p*-Anisyl)-triphenylcarbinol.—4-Methoxy-4′-benzoylbiphenyl was prepared from 4-methoxybiphenyl according to the method of Fieser and Bradsher.[5] This ketone was treated with a large excess of phenylmagnesium bromide. After the addition compound had been hydrolyzed with ice and ammonium chloride, the solvent and biphenyl were removed by steam distillation. The carbinol was recrystallized four times from 90–100° petroleum ether, m. p. 108–109°.

Anal. Calcd. for $C_{26}H_{22}O_2$: C, 85.22; H, 6.05. Found: C, 85.08; H, 6.14.

4-(*p*-Hydroxyphenyl)-triphenylcarbinol from 4-(*p*-Anisyl)-triphenylcarbinol.—Aluminum chloride was more satisfactory than acetic–sulfuric acid and acetic–hydrobromic acid mixtures in our attempts to demethylate 4-(*p*-anisyl)-triphenylcarbinol. A partial demethylation occurred when a mixture of two parts by weight of anhydrous aluminum chloride and one of the methoxy carbinol dissolved in benzene was refluxed for one hour. The product was decomposed with ice and dilute hydrochloric acid and the benzene layer was washed with water and dried. The hydroxycarbinol crystallized from the solution prior to the methoxycarbinol upon the addition of petroleum ether. The hydroxycarbinol was recrystallized several times from benzene–petroleum ether. Experiments showed it to be the same as the previously described 4-(*p*-hydroxyphenyl)-triphenylcarbinol.

Attempts to Make Diphenylbiphenoquinomethane.—Two methods were employed in attempting to make this compound: (1) the dehydration of 4-(*p*-hydroxyphenyl)-triphenylcarbinol, and (2) the reaction between diphenylketene and biphenoquinone. The dehydration procedure was tried by heating the carbinol in inert solvents for extended periods of time, and by heating the solid carbinol under reduced pressure in inert atmospheres. For example, a sample of carbinol was placed in a flask immersed in a sulfuric acid bath; the flask was evacuated and a small amount of carbon dioxide introduced. When the sample was heated at 220–230°, a vigorous evolution of water occurred. After heating for thirty minutes, the product was a purple gum which could not be crystallized. It did not have the intense color which diphenylbiphenoquinomethane might be expected to have, and the purple color seemed to be a property of only part of the material.

(4) Bowden, Harris and Roberts, *J. Chem. Soc.*, 802 (1939).

(5) Fieser and Bradsher, THIS JOURNAL, 58, 2337 (1936).

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It is thought likely that the decomposition which occurred took place by evolution of water between molecules rather than intramolecularly.

The biphenoquinone necessary for the other attempted preparation was made according to the directions of Willstätter and Kalb[6] by the oxidation of 4,4′-dihydroxybiphenyl which was prepared from benzidine as described by Hirsch.[7] This dihydroxy compound is much less soluble in water than Hirsch indicated. Recrystallization of the material from water using a soxhlet extractor gave a better product than recrystallization from glacial acetic acid as suggested by Bratz and von Niementowski.[8]

The formation of fuchsones from diphenylketene and quinones has been investigated by Staudinger and by Staudinger and Bereza.[9] In contrast to the quinones used previously, biphenoquinone is quite insoluble in most solvents. For this reason the reaction was run in nitrobenzene in which it is somewhat soluble. A suspension of biphenoquinone in nitrobenzene containing diphenylketene was stirred under a carbon dioxide atmosphere for forty-eight hours. No diphenylbiphenoquinomethane was isolated from the yellow gum which precipitated when petroleum ether was added to the filtered product.

4-(*p*-Anisyl)-4′-phenylbenzophenone.—4-Phenylbenzoyl chloride was prepared by refluxing a mixture of 20 g. of 4-phenylbenzoic acid and 50 cc. of thionyl chloride for thirty minutes. The excess thionyl chloride was then removed by distillation under reduced pressure. To the acid chloride were added 19 g. of 4-methoxybiphenyl and 400 cc. of tetrachloroethane, and the resulting solution was cooled to −10°; 16 g. of anhydrous aluminum chloride was added and the mixture allowed to warm to room temperature while being stirred vigorously. After standing overnight, the product was decomposed with ice and dilute hydrochloric acid and the tetrachloroethane was removed by steam distillation. The solid residue was dried and then digested with 600 cc. of ether. The ether insoluble 4-(*p*-anisyl)-4′-phenylbenzophenone was recrystallized from *o*-dichlorobenzene giving plates which melted at 246–248°. *Anal.* Calcd. for $C_{26}H_{20}O_2$: C, 85.69; H, 5.53. Found: C, 85.30; H, 5.61.

2-Methoxy-4′,5-diphenylbenzophenone.—This compound is the ether soluble fraction from the above reaction. The ether was evaporated and the residue recrystallized from methyl alcohol giving white needles, m. p. 127–130°. The assignment of the formulas for these two compounds was made on the basis of their melting points and the analogy between this reaction and that occurring between benzoyl chloride and 4-methoxybiphenyl. The total yield in this reaction was 75%; 50–65% of this was 4-(*p*-anisyl)-4′-phenylbenzophenone. *Anal.* Calcd. for $C_{26}H_{20}O_2$: C, 85.69; H, 5.53. Found: C, 85.48; H, 5.57.

4-(*p*-Anisyl)-4′-phenyltriphenylcarbinol.—A solution of 4 g. of 4-(*p*-anisyl)-4′-phenylbenzophenone dissolved in 75 cc. of ether was added to the Grignard reagent prepared from 5.4 g. of bromobenzene and 0.8 g. of magnesium. The mixture was refluxed for two hours and allowed to stand. After the addition compound had been hydrolyzed with ice and dilute hydrochloric acid, the solvent and biphenyl were removed by steam distillation. The residue was twice recrystallized from benzene–petroleum ether giving 4 g. of material, m. p. 141–143°.

Anal. Calcd. for $C_{32}H_{26}O_2$: C, 86.85; H, 5.92. Found: C, 86.94; H, 6.08.

4-Methoxy-4′-carboxybiphenyl.—This compound was made by the oxidation of 4-methoxy-4′-acetylbiphenyl. Fieser and Bradsher have prepared this acid by alkaline permanganate oxidation of the acetyl compound.[10] In the present work the oxidation was carried out with permanganate and with sodium hypoiodite.

Methyl Ester of 4-Methoxy-4′-carboxybiphenyl.—This compound has been reported by Fieser and Bradsher. Because of the insolubility of both the ester and the acid in methanol, it was found convenient to carry out the esterification of large quantities of the acid by the use of a soxhlet apparatus; 20 g. of the acid was placed in the soxhlet extractor and 600 cc. of methanol containing 5 cc. of sulfuric acid was used in the flask. The ester crystallized from the solution in plates with the previously reported melting point, 172–173°.

4-(*p*-Anisyl)-4′,4″-diphenyltriphenylcarbinol.—An excess of *p*-biphenylmagnesium bromide was added to 5 g. of the methyl ester of 4-methoxy-4′-carboxybiphenyl and the mixture was refluxed for five hours. The product was decomposed with ice and dilute hydrochloric acid and then steam distilled. The residue was extracted with one liter of ether leaving most of the tetraphenyl undissolved. The ether solvent was replaced by benzene and 6 g. of the carbinol was precipitated by the addition of petroleum ether. The product was recrystallized several times from benzene–petroleum ether, m. p. 130–132°.

Anal. Calcd. for $C_{38}H_{30}O_2$: C, 88.00; H, 5.83. Found: C, 87.63; H, 6.06.

All the compounds whose absorption spectra were determined showed no change in absorption after recrystallization from suitable solvents. Curve 1, Fig. 2, was taken from the published work of Burawoy.[11]

The absorption curves for the triarylmethyl ions were obtained from solutions of the carbinols in an acetic–sulfuric acid mixture which was prepared by dissolving 5 cc. of concentrated sulfuric acid in 95 cc. of glacial acetic acid. Increasing the amount of sulfuric acid in the solvent had no effect on the absorption. The absorption of 4-(*p*-hydroxyphenyl)-triphenylcarbinol was also determined in a solution of *p*-toluenesulfonic acid in glacial acetic acid and found to be identical with that of the acetic–sulfuric acid solution except for intensity. Using 10 g. of *p*-toluenesulfonic acid in 100 cc. of glacial acetic acid gave an absorption maximum of 4.3 units as compared to 4.65 units for the acetic–sulfuric acid solution. By using 25 g. of the sulfonic acid in 100 cc. of acetic acid, this maximum was raised to 4.55 units. The acetic–sulfuric acid solutions of these carbinols were stable for weeks.

Summary

1. 4-(*p*-Hydroxyphenyl)-triphenylcarbinol and the corresponding methoxy compound have been made, as well as the series of related compounds secured by replacing one and then both of the phenyl groups in the methoxy compound by *p*-biphenyl groups.

2. A comparison of the visible absorption of the 4-phenyltriphenylmethyl, 4-methoxy-4′-phenyltriphenylmethyl and 4-(*p*-anisyl)-triphenylmethyl ions and the corresponding ions containing an additional 4-phenyl substituent indicates that the biphenyl group is quinonoid in the 4-(*p*-anisyl) compounds.

3. Replacing an hydroxyl group by a methoxy group in these ions causes a shift in the absorption maximum of the principal band, which is different in direction depending on whether the substituted group is on a phenyl or biphenyl group.

4. 4-(*p*-Hydroxyphenyl)-triphenylcarbinol shows no tendency to exist in a quinonoid form in the solid state and attempts to prepare diphenylbiphenoquinomethane from it by dehydration failed.

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(6) Willstätter and Kalb, *Ber.*, **38**, 1233 (1905).
(7) Hirsch, *ibid.*, **22**, 335 (1889).
(8) Bratz and von Niementowski, *ibid.*, **52**, 192 (1919).
(9) Staudinger, *ibid.*, **41**, 1359 (1908); Staudinger and Bereza, *Ann.*, **380**, 258 (1911).
(10) Fieser and Bradsher, THIS JOURNAL, **58**, 1738 (1936).
(11) Burawoy, *Ber.*, **64**, 1640 (1931).

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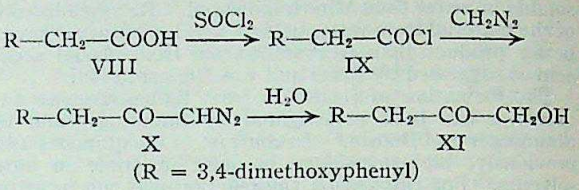
[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

Studies on Lignin and Related Compounds. LXXIX. Synthesis and Properties of 3-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone[1]

BY HERBERT E. FISHER, MARSHALL KULKA AND HAROLD HIBBERT

In a previous communication[2] the allylic and dismutation rearrangements attendant upon the conversion of the two halides, 1-bromo-1-(3,4-dimethoxyphenyl)-2-propanone and 3-chloro-1-(3,-4-dimethoxyphenyl)-2-propanone, to the corresponding alcohols, acetates and ethyl ethers were reported, and the bearing of these transformations on the relative validity of the Freudenberg and Hibbert theories of lignin structure was discussed.

During the course of that investigation, the synthesis of seventeen of the eighteen possible compounds formed by substitution of bromine, acetyl, hydroxyl and ethoxyl groups in the side chains of 1-(3,4-dimethoxyphenyl)-2-propanone (I) and 1-(3,4-dimethoxyphenyl)-1-propanone (II) was completed and the properties of these derivatives summarized. This communication deals with the synthesis and properties of the eighteenth member of this series (A(iii), Table I), namely, 3-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone, the veratryl analog of the keto form of β-oxyconiferyl alcohol. Its properties provide further support for the mechanism[2,3,4] suggested to account for the presence of the ethyl ethers of the benzoins, 1-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-2-propanone[5] and 2-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone[6] in the ethanolysis products of spruce wood.



(R = 3,4-dimethoxyphenyl)

Synthesis of the homoveratric acid (VIII) involved considerable investigation. Among methods investigated were those of Hahn, Stiehl and Schultz,[7] Julian and Sturgis[8] and Arndt and Eistert.[9] A modification of the last-named procedure was finally adopted. This involved rearrangement of the diazoketone (VI) to the methyl ester (VII) followed by saponification of the latter to homoveratric acid (VIII), rather than conversion of (VI) to homoveratric amide and subsequent hydrolysis as employed in the original procedure. This rapid modified Arndt–Eistert synthesis yielded easily purifiable intermediate products in a higher yield (60% based on veratric aldehyde (III)) than by other methods. Conversion of the homoacid (VIII) to homoveratroyl chloride (IX) with thionyl chloride, thence to homoveratroyl diazomethane (X) using diazomethane in ether was effected by the procedure used by Haworth and Atkinson[10] for the synthesis of 3-chloro-1-(3,4-dimethoxyphenyl)-2-propanone. Hydrolysis

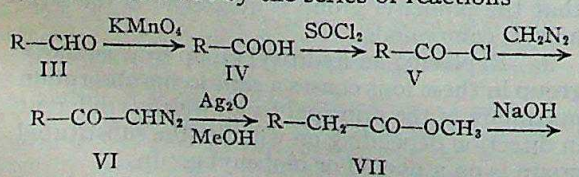
TABLE I

REFERENCE COMPOUNDS OF THE VERATRYL PROPANONE SERIES

	R—CH2—CO—CH3, I		R—CO—CH2—CH3, II	
	A	B	C	D
(i)	R—CH2—CO—CH2Br	R—CHBr—CO—CH3	R—CO—CHBr—CH3	R—CO—CH2—CH2Br
(ii)	R—CH2—CO—CH2OAc	R—CHOAc—CO—CH3	R—CO—CHOAc—CH3	R—CO—CH2—CH2OAc
(iii)	R—CH2—CO—CH2OH	R—CHOH—CO—CH3	R—CO—CHOH—CH3	R—CO—CH2—CH2OH
(iv)	R—CH2—CO—CH2OEt	R—CHOEt—CO—CH3	R—CO—CHOEt—CH3	R—CO—CH2—CH2OEt

(R = 3,4-dimethoxyphenyl)

The synthesis of the new ketol, 3-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone (A(iii), Table I), was carried out by the series of reactions



of the diazoketone was carried out by Wolff's method[11] using water at 100°, as in his conversion of diazoacetophenone to benzoyl carbinol. The ketol (A(iii), Table I) obtained (56% yield based on homoveratric acid) analyzed correctly, and differed in physical properties from the three other isomers (B(iii), C(iii) and D(iii), Table I). Its refractive index, $n^{25}D$ 1.5485, differed considerably from that of 2-hydroxy-1-(3,4-dimethoxyphenyl)-1-propanone (C(iii), Table I) $n^{25}D$ 1.5590 while 1-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone (B(iii), Table I) and 3-hydroxy-1-(3,4-dimethoxyphenyl)-1-propanone (D(iii), Table I) are

(1) From a thesis submitted to the Graduate Faculty of McGill University by Herbert E. Fisher in partial fulfillment of the requirements for the degree of Doctor of Philosophy, October, 1943.

(2) Eastham, Fisher, Kulka and Hibbert, THIS JOURNAL, 66, 26 (1944).

(3) Hibbert, *Paper Trade J.*, 113, No. 4, 35 (1941).

(4) Hibbert, *Ann. Rev. Biochem.*, 11, 183 (1942).

(5) West, MacInnes and Hibbert, THIS JOURNAL, 65, 1187 (1943).

(6) Cramer, Hunter and Hibbert, *ibid.*, 61, 509 (1939).

(7) Hahn, Stiehl and Schultz, *Ber.*, 72, 1291 (1939).

(8) Julian and Sturgis, THIS JOURNAL, 57, 1126 (1935).

(9) Arndt and Eistert, *Ber.*, 68, 200 (1935).

(10) Haworth and Atkinson, *J. Chem. Soc.*, 797 (1938).

(11) Wolff, *Ann.*, 394, 23 (1912).

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known solids, m. p. 77–78° and 83–84°, respectively. Moreover the semicarbazone of the new ketol, m. p. 123–124°, differed from those of the known ketols. Final conclusive evidence for its structure was obtained by acetylation with acetyl chloride and pyridine.[12] The reaction product was identified as 3-acetoxy-1-(3,4-dimethoxyphenyl)-2-propanone (A(ii), Table I) by melting point and mixed melting point determinations with an authentic sample.[2]

The behavior of 3-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone (XI) toward acidic and basic reagents was studied. On heating with dilute (5%) sulfuric acid at 100° it yielded a relatively small amount (20%) of amorphous polymer, but more concentrated acid (72%), under the conditions of the Klason lignin procedure, brought about polymerization to the extent of over 60%. Strong bases, even in high dilution, caused marked polymerization particularly in aqueous media. Thus treatment with aqueous 1% sodium hydroxide at 100° for twenty-four hours gave more than 50% of a polymer, while 3% aqueous sodium hydroxide, even at room temperature, polymerized it to the extent of 80% in three days. With 3% aqueous-ethanolic (1:1) sodium hydroxide, under the former conditions, only 17% of polymer was formed.

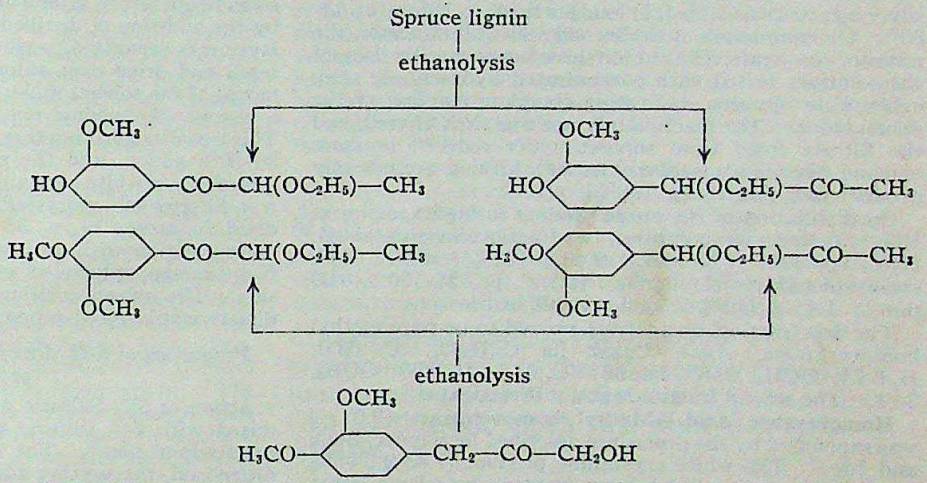
On treatment of (XI) with 5% aqueous potassium acetate under the same conditions which brought about rearrangement[2] of (B(iii)) to (C(iii)), no change was apparent, the ketol (XI) (75%), identified as its semicarbazone, being recovered unchanged.

Treatment of (XI) with ethanolic hydrogen chloride (2%) under the same conditions used for the ethanolysis of wood[5] yielded a bisulfite insoluble fraction containing a mixture of 2-ethoxy-1-(3,4-dimethoxyphenyl)-1-propanone (C(iv), Table I) and the corresponding isomer, 1-ethoxy-1-(3,4-dimethoxyphenyl)-2-propanone (B(iv), Table I) in a ratio of 3 to 7, the combined yield being 80%. The very small bisulfite soluble fraction apparently contained no 1,2-diketone.

These results, taken in conjunction with those obtained previously[2] on the hydrolysis of the corresponding halides and acetates ($R—CH_2—CO—CH_2X$; X = Br, Cl, $OCOCH_3$) supply strong experimental support for the theory that formation of the two isomeric ethyl ethers takes place by the following series of reactions[2]

$$R—CH_2—CO—CH_2OH \rightleftarrows R—CH=C(OH)—CH_2OH \rightleftarrows R—CHOH—C(OH)=CH_2 \rightleftarrows$$
$$R—CHOH—CO—CH_3 \rightleftarrows R—C(OH)=C(OH)—CH_3 \rightleftarrows R—CO—CHOH—CH_3$$
$$\downarrow EtOH,HCl \qquad\qquad \downarrow EtOH,HCl$$
$$R—CH(OC_2H_5)—CO—CH_3 \qquad R—CO—CH(OC_2H_5)—CH_3$$

The connection of these products with the postulated lignin progenitor, β-oxyconiferyl alcohol (keto-form), is shown below.



The occurrence of the guaiacyl analogs among the ethanolysis products of spruce and maple wood thus finds a satisfactory explanation in the assumption of their presence as stabilized end-products arising from a more reactive native lignin building unit, namely, β-oxyconiferyl alcohol or its keto-isomer[2,4] and provides further support in favor of the validity of Hibbert's and the non-validity of Freudenberg's theory of lignin structure.[2,4,13]

Experimental

Synthesis of Homoveratric Acid: Modified Arndt–Eistert Method

Veratric Acid.—Veratric aldehyde (25 g.) was oxidized to the corresponding acid with aqueous potassium permanganate according to the directions of Shriner and Kleiderer[14]; yield, 24.7 g. (90%). Recrystallized from absolute ethanol, m. p. 180–181°, the product gave no depression in melting point when mixed with an authentic sample of veratric acid.

Veratroyl Chloride.—Veratric acid (15.0 g.) was converted to the chloride with freshly purified[15] thionyl chloride, according to the procedure of Arndt and Eistert[9]; yield of crude product, 16.7 g. (100%). A small amount, purified by distillation, melted at 70–71°. The melting point of veratroyl chloride is 70° according to Mayer.[16]

Veratroyl Diazomethane.—Crude veratroyl chloride (16.7 g.) was treated with a solution of diazomethane in ether by the procedure of Arndt and Eistert,[9] yielding a yellow solid (17.0 g. (100%)) which, after recrystallization from benzene–petroleum ether (b. p. 30–50°), gave fine

(12) Smith and Bryant, This Journal, 57, 61 (1935).
(13) MacGregor, Evans and Hibbert, *ibid.*, 66, 41 (1944).
(14) Shriner and Kleiderer, *Org. Syntheses*, 10, 82 (1930).
(15) Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., N. Y., 2nd ed., 1941, p. 381.
(16) Meyer, *Monatsh.*, 22, 428 (1879).

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yellow needles, m. p. 76–77° (Arndt and Eistert, m. p. 75°).

Methyl Homoveratrate.—Recrystallized veratroyl diazomethane (12.4 g., m. p. 76–77°) was dissolved in absolute methanol (200 cc.) and warmed to 55–60° in a three-necked flask equipped with reflux condenser, stirrer and thermometer. At ten-minute intervals four portions of a slurry of freshly prepared silver oxide (from 2.5 g. of silver nitrate in 35 cc. methanol) were added to the rapidly stirred solution, which was maintained under an atmosphere of carbon dioxide throughout the reaction period, and the solution then refluxed for four hours.

The sludge of metallic silver and silver oxide was removed by filtration, and fresh silver oxide (from 2 g. of silver nitrate) was added, in four portions, as before, at 55–60°. On completion of the second series of additions, the mixture was again refluxed for three hours, until a drop of the solution, tested with concentrated hydrochloric acid, evolved no nitrogen, indicating complete reaction of the diazoketone. The reaction mixture was then filtered, and the filtrate freed from solvent under reduced pressure (carbon dioxide atmosphere) at 50°, leaving a crude oily product weighing 12.4 g. (98%).

On distillation of the crude product in high vacuum at 135–145° (bath temperature), two fractions were obtained: (I) b. 110–113° (0.03 mm.); 9.10 g. (72%); $n^{25}D$ 1.5300; straw-colored mobile liquid. (II) b. p. 128–130° (0.03 mm.); 1.48 g. (12%); semi-crystalline.

The first fraction, on analysis, proved to be pure methyl homoveratrate. *Anal.* Calcd. for $C_{11}H_{14}O_4$: C, 63.0; H, 6.74; OCH_3, 29.6. Found: C, 63.1; H, 6.90; OCH_3, 29.4. The second fraction was not investigated.

Homoveratric Acid.—Methyl homoveratrate (9.0 g.) was saponified by the procedure described by Snyder, Buck and Ide.[17] The white crystalline product (7.85 g., 95% yield) was recrystallized from benzene–petroleum ether (60–70°); white plates, m. p. 98–99°. A mixed melting point with homoveratric acid showed no depression.

Synthesis of 3-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone

Homoveratroyl Chloride.—Homoveratric acid (10.0 g.) was refluxed gently for forty-five minutes with freshly purified[15] thionyl chloride (20 cc.) in an all-glass apparatus under an atmosphere of carbon dioxide. Four portions (25 cc.) of benzene were successively added and removed by distillation under reduced pressure (carbon dioxide) in order to free the acid chloride from excess thionyl chloride. The dark red oil (10.9 g., 100% yield) was treated, without purification, as follows:

Homoveratroyl Diazomethane.—The homoveratroyl chloride (10.9 g.) was dissolved in benzene (50 cc.) and added slowly, with stirring, at 0° to a solution of diazomethane (from 40 g. nitrosomethyl urea) in ether (400 cc.). The solution was allowed to warm slowly to room temperature and react overnight. On removal of the solvents under reduced pressure (carbon dioxide) at room temperature, a red oily product weighing 11.2 g. (100%) was obtained.

3-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone.—The homoveratroyldiazomethane (11.2 g.) was dissolved in absolute ethanol (90 cc.) and added, over a period of thirty minutes, to water (500 cc.) heated to 70°, with stirring. After addition of the diazoketone was complete, the reaction mixture was refluxed for three hours, cooled, and concentrated at room temperature under reduced pressure (carbon dioxide) to remove ethanol. The aqueous solution was then extracted five times with chloroform, the extract concentrated to a small volume (50 cc.) under reduced pressure (carbon dioxide) and precipitated three times successively in a thin stream from this solvent into rapidly stirred petroleum ether (b. p. 30–50°). The latter solvent was then removed and the residual oil distilled at 150–160° (bath temperature) and 0.05 mm., yielding a pale yellow oil, $n^{25}D$ 1.5485, weighing 6.0 g. (56%). *Anal.* Calcd. for $C_{11}H_{14}O_4$: C, 63.0; H, 6.74; OCH_3, 29.6. Found: C, 62.8; H, 6.78; OCH_3, 29.6.

Semicarbazone of 3-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone.—White microscopic needles from water, m. p. 123–124°. *Anal.* Calcd. for $C_{12}H_{17}O_4N_3$: C, 53.9; H, 6.42; OCH_3, 23.2. Found: C, 53.7; H, 6.83; OCH_3, 23.1.

Characterization of 3-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone

Acetylation.—Oily 3-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone (0.505 g.) was acetylated with acetyl chloride (4 g.) in toluene (30 cc.) to which pyridine (6 cc.) had been added. The mixture was allowed to react for eleven hours at room temperature, after which the complex was decomposed by the addition of distilled water (500 cc.). The toluene layer was separated, washed three times with water, filtered and dried over anhydrous sodium sulfate. On removal of the solvent under reduced pressure (CO_2) at 35°, a viscous oily product remained weighing 0.450 g. (75%). This was dissolved in ether, filtered, petroleum ether (b. p. 30–50°) added, and the solution chilled to −15°. On scratching, a white crystalline product was obtained which was filtered off, recrystallized from dilute ethanol, and dried *in vacuo;* m. p. 55–56°. A mixed melting point determination with an authentic sample of 3-acetoxy-1-(3,4-dimethoxyphenyl)-2-propanone[2] showed no depression. The mixed melting point with 2-acetoxy-1-(3,4-dimethoxyphenyl)-1-propanone was 45°.

Properties of 3-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone

Action of 5% Sulfuric Acid.—The ketol (0.529 g.) was mixed with 5% sulfuric acid (50 cc.) and refluxed for twenty-four hours. The amorphous black residue was filtered off, the portion adhering to the flask dissolved in chloroform, the main product added, and the solution evaporated to dryness; yield, 0.103 g. (19.5%).

Action of 72% Sulfuric Acid.—The ketol (0.505 g.) was treated with 72% sulfuric acid (4 cc.) at room temperature for two hours. The dark solution was then diluted to 150 cc. with distilled water, refluxed for four hours, cooled, and the amorphous dark brown lignin-like product filtered, washed with water, and dried in an Abderhalden drier at 61°; product, 0.101 g. The filtrate from the amorphous precipitate was extracted three times with chloroform, the extract concentrated, under reduced pressure, to a small volume (7 cc.) and precipitated into rapidly-stirred low-boiling petroleum ether (75 cc.). An additional quantity of amorphous product, dry weight 0.215 g., was thus obtained; total yield 0.316 g. (62.5%).

Action of 1% Sodium Hydroxide at 100°.—The ketol (0.514 g.) was refluxed with dilute (1%) aqueous sodium hydroxide (50 cc.) for twenty-four hours. After neutralization (congo red) of the mixture with dilute sulfuric acid, the product was filtered, the amorphous residue dissolved in chloroform, evaporated to dryness, and the residue dried similarly and weighed; yield of amorphous product, 0.276 g. (54%).

Action of 3% Aqueous Sodium Hydroxide at Room Temperature.—The ketol (0.250 g.) was allowed to stand at room temperature for seventy-two hours with 3% aqueous sodium hydroxide. After neutralization of the mixture with 10% hydrochloric acid (4 cc.) the polymer was filtered off, washed with water, and dried; yield of amorphous brown product, 0.200 g. (80%).

Action of 3% Ethanolic Sodium Hydroxide at Room Temperature.—The ketol (0.120 g.) was dissolved in ethanol (5 cc.) and 6% aqueous sodium hydroxide (5 cc.) added. After standing at room temperature for three days, chloroform (5 cc.) was added, and carbon dioxide allowed to bubble through the solution for three days. After extraction of the reaction mixture with six portions of chloroform, the extract was washed with water, dried over anhydrous sodium sulfate, concentrated to a small volume (3 cc.) and precipitated, in a fine stream, into rapidly-stirred petroleum ether (b. p. 30–50°). The flaky white polymer was filtered and dried; wt., 0.020 g. (17%).

(17) Snyder, Buck and Ide, "Organic Syntheses," 15, 31 (1935).

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Action of 5% Aqueous Potassium Acetate.—The ketol (1.02 g., $n^{25}D$ 1.5490) was refluxed with 5% aqueous potassium acetate (100 cc.) for twelve hours in an atmosphere of carbon dioxide. The resulting solution was extracted four times with chloroform, the extract dried as above and the solvent removed at room temperature under reduced pressure (CO_2). Distillation of the residual oil at 150–160° bath temperature and 0.015 mm. pressure yielded a pale yellow oil weighing 0.75 g. (75%); $n^{25}D$ 1.5485.

Seeding a small portion of the product with the isomeric ketol, 1-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone produced no effect, and its relatively low refractive index (1.5485) indicated absence of the isomeric 2-hydroxy-1-(3,4-dimethoxyphenyl)-1-propanone ($n^{25}D$ 1.5610). The semicarbazone of the product was prepared and recrystallized from water; m. p. 122–123°. A mixed melting point determination with an authentic sample of the semicarbazone of 3-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone showed no depression. Thus so far as could be ascertained, treatment of 3-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone with 5% aqueous potassium acetate did not induce rearrangement of the ketol.

Action of 2% Ethanolic Hydrogen Chloride.—3-Hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone (2.85 g.) was refluxed for forty-eight hours under an atmosphere of carbon dioxide in an all-glass apparatus with 2% ethanolic hydrogen chloride (300 cc.).[5] At the conclusion of the reaction period the solution was cooled, water (5 cc.) added, and the solution neutralized (congo red) by the addition of small portions of solid sodium bicarbonate. After filtration, the solution was evaporated to dryness under reduced pressure (carbon dioxide) at room temperature. The residue was dissolved in benzene, the solution filtered, then extracted three times with 10% sodium bisulfite solution. After the bisulfite extract had been back-extracted twice with benzene, the combined benzene solutions were washed once with water, treated with decolorizing charcoal, and dried over anhydrous sodium sulfate (Extract I).

The bisulfite extract, after neutralization (congo red) with dilute sulfuric acid, was freed from sulfur dioxide under reduced pressure (carbon dioxide) and extracted three times with benzene. The benzene extract was washed with water, 1% aqueous sodium bicarbonate, again with water, and dried over anhydrous sodium sulfate (Extract II).

Extract I.—After removal of the solvent under reduced pressure (carbon dioxide) the residual oil was distilled at 125–135° (bath temperature) and 0.01 mm. pressure, yielding a pale yellow distillate, weighing 2.304 g., which slowly crystallized to a semi-solid yellow mass on cooling. The undistilled residue (polymerized by heat) weighed 0.276 g. The total bisulfite-insoluble fraction weighed 2.580 g. (80% of the theoretical ethylated product). The semi-solid product was washed with warm petroleum ether (10 cc.), then filtered on a glass nail and dried *in vacuo*; weight of crystalline product, 0.640 g. (28%). Recrystallization from dilute ethanol yielded a white crystalline material, m. p. 82–83°. A mixed melting point determination with an authentic sample of 2-ethoxy-1-(3,4-dimethoxyphenyl)-1-propanone showed no depression.

The 2,4-dinitrophenylhydrazone of the non-crystalline material ($n^{25}D$ 1.5220) recovered from the petroleum ether washings, after recrystallization from absolute ethanol, melted at 139–141°. A mixed melting point determination with an authentic sample of 1-ethoxy-1-(3,4-dimethoxyphenyl)-2-propanone 2,4-dinitrophenylhydrazone gave no depression.

Extract II.—Removal of the solvent under reduced pressure (carbon dioxide) left a crystalline residue weighing 0.350 g. The residue was washed with diethyl ether, this removing a portion of the material, and then with absolute ethanol, which dissolved the remainder. Addition of petroleum ether to this ethanol solution and chilling to 0° for several days resulted in the formation of a very small amount of long, light red, rod-like crystals; m. p. 138–139°. (A possible product of the reaction, 1-(3,4-dimethoxyphenyl)-1,2-propanedione, m. p. 68–69°, was thus eliminated.) The product was not identified.

No result was observed on addition of petroleum ether to the ether washings, and chilling to 0°. The combined ethanol and ether washings were evaporated to dryness, and tested for the presence of the diketone (1-(3,4-dimethoxyphenyl)-1,2-propanedione) by dissolving the residue in ethanol (10 cc.), adding water (50 cc.), hydroxylamine sulfate (0.2 g.), sodium acetate (1.0 g.) and 5% aqueous nickel chloride (1.5 cc.) and refluxing the solution gently under an atmosphere of carbon dioxide for twenty-four hours. Only a small amount (0.02 g.) of amorphous brown precipitate was formed; the characteristic red crystalline nickel glyoxime of the diketone was not obtained.

The action of 2% ethanolic hydrogen chloride on 3-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone thus produced the allylic rearrangement product, 1-ethoxy-1-(3,4-dimethoxyphenyl)-2-propanone, and its dismutation isomer 2-ethoxy-1-(3,4-dimethoxyphenyl)-1-propanone, in yields of 56 and 24%, respectively, together with a small amount of unidentified bisulfite soluble material.

Acknowledgment.—The authors wish to express their thanks to the Gottesman Foundation fund for the award of a scholarship to one of them (H. F.) through which this work was rendered possible.

Summary

1. The synthesis of 3-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone has been carried out, the process involving a modification of the Arndt–Eistert synthesis for the preparation of the intermediary homoveratric acid.

2. Acids, and to a greater degree alkalies, readily convert the ketol into a lignin-like product in high yield.

3. When subjected to the ethanolysis procedure, as used for the extraction of lignin from wood, 3-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone gives a mixture of 1-ethoxy-1-(3,4-dimethoxyphenyl)-2-propanone and 2-ethoxy-1-(3,4-dimethoxyphenyl)-1-propanone in a combined yield of 80%.

4. The formation of these products undoubtedly takes place through the medium of an allyl shift followed by dismutation changes. Such transformations are regarded as providing valuable support for Hibbert's postulation of their presence (as guaiacyl derivatives) in the ethanolysis mixture from spruce wood as the result of similar reactions involving a β-oxyconiferyl type of lignin building unit present in spruce native lignin.

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[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

Studies on Lignin and Related Compounds. LXXX. The Ethanolysis of 1-Acetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone and its Relation to Lignin Structure[1]

BY LEONARD MITCHELL[2] AND HAROLD HIBBERT

In recent communications of this series[3,4] ample experimental evidence has been provided in confirmation of the theory[3,5] that the water-soluble spruce lignin ethanolysis products 2-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone (I)[6] and 1-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-2-propanone (II)[7] obtained by the action of ethanol containing 2% hydrogen chloride represent stabilized end-products originating from an oxyconiferyl alcohol type of lignin building unit present in the spruce native lignin. Experimental evidence supporting this theory and also proving that the two remaining propyl phenol ethanolysis units, namely, the diketone, 1-(4-hydroxy-3-methoxyphenyl)-1,2-propanedione (III)[8,9] and the desoxybenzoin, 1-(4-hydroxy-3-methoxyphenyl)-2-propanone (IV)[10] belong in the same category is provided in the present communication.

The authors find that ethanolysis of 1-acetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (V) under the identical conditions used in the ethanolysis of wood[7] gives a mixture containing I, II, III and IV in yields of 54.6, 16.7, 7.3 and 1.3%, respectively, together with a petroleum–ether (b. p. 30–50°) insoluble polymer (10%). Inasmuch as the acetyl groups are readily removed under the experimental conditions, the four products may be regarded as formed from the corresponding free dihydroxy derivative, namely, 1-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-2-propanone (VI). This latter, however, in the form of its phenolic methyl ether, is readily obtained[4] under the same experimental conditions from the phenolic methyl ether of β-oxyconiferyl alcohol, (3-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone) as the result of an allylic shift

$$RCH_2COCH_2OH \rightleftharpoons RCH{=}C(OH)CH_2OH \rightleftharpoons RCHOHC(OH){=}CH_2 \rightleftharpoons RCHOHCOCH_3$$

(R = veratryl)

so that all four ethanolysis products may be envisaged as originating from β-oxyconiferyl alcohol (β,γ-dioxyisoeugenol). As stated previously,[3] it is probable the four products originate from a simple lignin building unit rather than from a higher lignin polymer. The value of the present discovery is much enhanced by the isolation for the first time in any synthetic ethanolysis mixture of the 1,2-diketone (III) and the desoxybenzoin (IV). Their relation to spruce lignin and the probable mechanism for the formation of all four products are both illustrated in the chart.

The results are thus in startling agreement with the earlier suggestion of Erdtman,[11] and accepted by the senior author (H. H.),[5] that the ethanolysis derivatives from spruce wood are stabilized end-products from a more reactive lignin progenitor, postulated by Hibbert as β-oxyconiferyl alcohol.

Experimental

The starting material for this investigation, 1-acetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone was prepared from 1-bromo-1-(4-acetoxy-3-methoxyphenyl)-2-propanone[12] by the action of silver acetate in aqueous dioxane solution at room temperature. The conditions of ethanolysis and the procedure for isolation of the ethanolysis products were identical with those used previously in connection with the isolation of the ethanolysis products from wood.[7]

Synthesis of 1-Acetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone.—1-Bromo-1-(4-acetoxy-3-methoxyphenyl)-2-propanone[12] (15 g.) was dissolved in aqueous dioxane (1:1) (180 cc.), freshly-precipitated silver acetate (13 g.) added, and the mixture stirred at room temperature for thirty-six hours. The silver bromide was removed by filtration, the liquor extracted thoroughly with chloroform, and the solvent removed under reduced pressure (15 mm.) leaving a very light yellow oil which solidified on standing. The crude crystalline product (13.5 g.) was recrystallized from dilute methanol; yield 11.0 g. (80%); m. p. 95–96°. By repeated recrystallization from dilute methanol, or ether-petroleum ether (b. p. 30–50°), the melting point was raised to 97–98°. *Anal.* Calcd. for $C_{14}H_{16}O_6$: C, 60.0; H, 5.85; OCH_3, 11.05. Found: C, 60.2; H, 5.58; OCH_3, 10.95.

Ethanolysis of 1-Acetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone.—1-Acetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (11.0 g.) was refluxed with 2% ethanolic hydrogen chloride (500 cc.) for forty-eight hours in an atmosphere of carbon dioxide. The reaction mixture was neutralized with the calculated amount of sodium bicarbonate, concentrated to 50 cc., filtered free of sodium chloride and the filtrate poured in a fine stream, and with vigorous stirring, into petroleum ether (b. p. 30–50°) (1000 cc.). The precipitated dark tarry oil (probably a condensation polymer) was allowed to settle overnight and then separated by decantation. Removal of solvent from it, *in vacuo*, left a dark brittle resin (0.87 g.).

Concentration of the petroleum ether–ethanol solution, followed by removal of the last traces of solvent under reduced pressure, left an orange-red oil (8.1 g.). This was dissolved in benzene (100 cc.), extracted with five 15-cc. portions of aqueous sodium bisulfite (20%) and the bisulfite extract back-extracted with three 15-cc. portions of benzene which were then combined with the main benzene solution. This treatment resulted in a rough separation of the ethanolysis oil into a bisulfite-soluble (A) and a so-called "phenol" fraction[7] (B).

(1) Extract from the thesis work of Leonard Mitchell to be presented in partial fulfillment of the requirements for the degree of Doctor of Philosophy, McGill University.

(2) Holder of a National Research Council of Canada Studentship, 1942–1943.

(3) Eastham, Fisher, Kulka and Hibbert, THIS JOURNAL, **66**, 26 (1944).

(4) Fisher, Kulka and Hibbert, *ibid.*, **66**, 598 (1944).

(5) Hibbert, *Ann. Rev. Biochem.*, **11**, 183 (1942).

(6) Cramer, Hunter and Hibbert, THIS JOURNAL, **61**, 509 (1939).

(7) West, MacInnes and Hibbert, *ibid.*, **65**, 1187 (1943).

(8) Brickman, Hawkins and Hibbert, *ibid.*, **62**, 986 (1940).

(9) Kulka, Hawkins and Hibbert, *ibid.*, **63**, 2371 (1941).

(10) Kulka and Hibbert, *ibid.*, **65**, 1180 (1943).

(11) Erdtman, *Svensk Papperstidn.*, **44**, 243 (1941).

(12) Mitchell, Eyans and Hibbert, THIS JOURNAL, **66**, 604 (1944).

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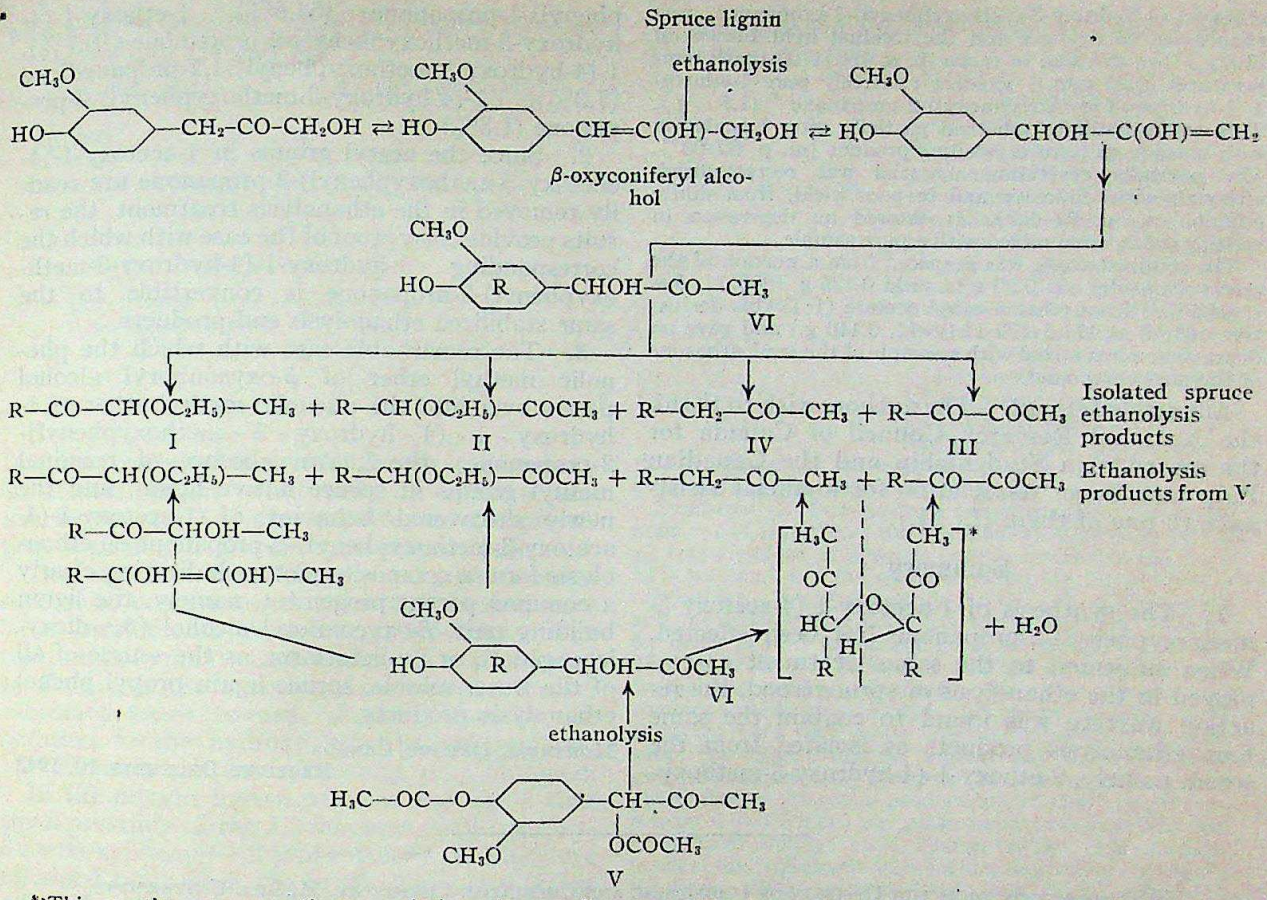

*This reaction may actually proceed *via* an intermediary, unstable six-membered ring, as indicated in the following communication, this Series, Pt. LXXXI.

Investigation of the Bisulfite-soluble Fraction (A).—The bisulfite solution (A) was acidified (congo red) with dilute sulfuric acid, the sulfur dioxide expelled (using a carbon dioxide bubbler under reduced pressure) and then extracted with eight 15-cc. portions of benzene. The united benzene extracts were dried with sodium sulfate and the solvent removed under reduced pressure. Distillation of the residual oil between 140–160° (bath temperature) (0.10 mm.) yielded a clear yellow oil (0.90 g.) from which the diketone, 1-(4-hydroxy-3-methoxyphenyl)-1,2-propanedione, and the desoxybenzoin, 1-(4-hydroxy-3-methoxyphenyl)-2-propanone, were isolated as follows:

(a) **Isolation of 1-(4-Hydroxy-3-methoxyphenyl)-1,2-propanedione.**—The above oil (0.90 g.), nickel chloride (5 cc. of 5% solution), hydroxylamine sulfate (0.75 g.) and sodium acetate (5.0 g.) were dissolved in water (200 cc.) and treated in the manner described previously[9] for the quantitative isolation of the nickel glyoxime salt of the diketone; yield of the latter (0.66 g.), equivalent to 0.60 g. diketone.

Distillation of the crude diketone obtained on hydrolysis[9] of the nickel glyoxime salt gave an oil (0.39 g.) which solidified on standing. After recrystallization from dilute ethanol the product melted at 69–70° and showed no melting point depression when mixed with an authentic sample of 1-(4-hydroxy-3-methoxyphenyl)-1,2-propanedione.

(b) **Isolation of 1-(4-Hydroxy-3-methoxyphenyl)-2-propanone.**—The aqueous filtrate left after separation of the insoluble nickel glyoxime salt was extracted continuously with benzene for twenty-four hours. Evaporation of the solvent and hydrolysis[10] of the residual oxime yielded an orange-yellow oil (0.12 g.). The crude semicarbazone (0.10 g.) of this melted at 155–156° and, after recrystallization from ethanol, at 156–158°; no depression when mixed with an authentic sample of the semicarbazone of 1-(4-hydroxy-3-methoxyphenyl)-2-propanone.

Investigation of the "Phenol" Fraction.—The original benzene solution (B) left after extraction with bisulfite and containing the "phenol" fraction mentioned previously was dried and evaporated to dryness under reduced pressure leaving a yellow oil (8.0 g.) which was dissolved in anhydrous ether (200 cc.).

(a) **Isolation of 2-Ethoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone.**—Dry ammonia gas was passed through the ether solution in the manner described for the separation of this component of the spruce wood ethanolysis "phenol" fraction.[7] The yellow ammonium salt (C) was filtered, washed with anhydrous ether and dried; weight, 5.1 g., equivalent to 4.9 g. of 2-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone.

Preparation of the Methyl Ether.—The ammonium salt (C) (5.1 g.), dissolved in sodium hydroxide (30 cc. of 5% solution), was methylated at room temperature in an atmosphere of nitrogen by the slow simultaneous addition, over a period of one-half hour, of dimethyl sulfate (15 cc.) and strong sodium hydroxide (15 cc. of 30% solution), the reaction mixture being stirred throughout, and then for a further period of two hours. The oily mixture was extracted thoroughly with benzene and the benzene solution back-extracted with dilute sodium hydroxide (5% solution). Removal of the benzene left a brownish oil which on distillation yielded an oil boiling constantly at 150–155° (bath temp.) (0.05 mm.), yield, 4.5 g. The oil solidified immediately and completely in the receiver; m. p. 80–81°. Recrystallization from dilute ethanol raised the m. p. to 82–83°; no depression when mixed with an authentic sample of 2-ethoxy-1-(3,4-dimethoxyphenyl)-1-propanone.

(b) **Isolation of 1-Ethoxy-1-(4-hydroxy-3-methoxyphenyl)-2-propanone.**—The ethereal solution remaining after separation of the insoluble ammonium salt (C) of 2-

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ethoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone was evaporated to dryness and the residual light brown oil (1.8 g.) then distilled *in vacuo* (b. p. 150–170° (bath temperature) (0.25 mm.)) yielding relatively pure 1-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-2-propanone (1.5 g.). This crude distillate solidified partially after inoculation with a trace of pure crystalline product (m. p. 62–63°). The partially crystalline material was recrystallized, although with difficulty and in poor yield, from dilute ethanol (m. p. 61–62°). It showed no depression in melting point when mixed with a pure sample.

The semicarbazone was prepared from a portion of the crude semi-solid oil (0.20 g.); yield 0.125 g. (60%). Recrystallized from ethanol–ethyl acetate (1:1) this derivative melted at 171.5–172.5° (yield, 0.110 g.) and gave no depression when mixed with a sample of the semicarbazone of the pure compound.

Acknowledgment.—The authors wish to thank the National Research Council of Canada for the award of a Studentship and the Canadian Pulp and Paper Association for financial assistance to one of them (L. M.).

Summary

1. The synthesis of 1-acetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone has been effected. When subjected to the same treatment as employed in the ethanolysis of spruce wood, the reaction mixture was found to contain the same four ethanolysis products as isolated from the wood, namely, 2-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone (54.6%), 1-ethoxy-1-(4-hydroxy-3-methoxyphenyl)-2-propanone (16.7%), 1-(4-hydroxy-3-methoxyphenyl)-1,2-propanedione (7.3%), 1-(4-hydroxy-3-methoxyphenyl)-2-propanone (1.3%).

2. Since the acetyl groups in 1-acetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone are readily removed in the ethanolysis treatment, the results provide clear proof of the ease with which the corresponding 1-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-2-propanone is convertible to the same stabilized ethanolysis end-products.

3. The remarkable ease with which the phenolic methyl ether of β-oxyconiferyl alcohol passes over into the phenolic methyl ether of 1-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-2-propanone; the known absence of terminal methyl groups in spruce native lignin, and the newly discovered behavior of 1-acetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone on ethanolysis form a composite picture indicating clearly a common parent progenitor, namely, the lignin building unit, β-oxyconiferyl alcohol (β,γ-dioxyisoeugenol), or its keto form, as the source of all of the water-soluble, spruce lignin propyl phenol ethanolysis products.

MONTREAL, QUEBEC, CANADA
RECEIVED DECEMBER 10, 1943

[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

Studies on Lignin and Related Compounds. LXXXI. Properties of 1-Bromo-1-(4-acetoxy-3-methoxyphenyl)-2-propanone and Relation to Lignin Structure[1]

BY LEONARD MITCHELL,[2] T. H. EVANS AND HAROLD HIBBERT

In the preceding communication[3] it was shown experimentally that 1-acetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (I), on ethanolysis under the identical conditions used for the extraction of spruce lignin from wood, gave a reaction product containing each of the four propyl phenol units found in the spruce wood ethanolysis mixture.

In the present paper additional confirmatory evidence for the β-oxyconiferyl alcohol theory of lignin structure is provided in the action of aqueous silver sulfate on 1-bromo-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (II). In aqueous solution at room temperature interaction takes place readily with precipitation of the theoretical quantity of silver bromide. The aqueous solution on analysis was shown to contain a distillable mixture (60% of original material) of 1-(4-acetoxy-3-methoxyphenyl)-1,2-propanedione (III) and 1-(4-acetoxy-3-methoxyphenyl)-2-propanone (IV) together with a non-distillable product (35%), presumably a polymer of 1-hydroxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (V). The amounts of III and IV present in the distillable mixture were found to be 44 and 27%, respectively, equivalent to 24 and 16% when calculated on the original bromo derivative (II). The low value for IV is to be regarded as a minimum due to the extensive losses involved in its isolation.

The formation of the theoretical quantity of silver bromide in this reaction indicates (1) absence of any secondary type of oxidation change; and (2) formation of 1-hydroxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (V) as the primary product of the reaction. Inasmuch as the veratryl analog[4] of V is stable to even *hot* dilute sulfuric acid, it is very improbable the formation of III and IV proceeds directly (intramolecularly) through V.

It is possible a bimolecular reaction takes place between the bromo product (II) and the hydroxy derivative (V) to give silver bromide, sulfuric

(1) Extract from the thesis work of Leonard Mitchell to be presented in partial fulfillment of the requirements for the degree of Doctor of Philosophy, McGill University.

(2) Holder of a National Research Council of Canada Studentship 1942–1943.

(3) Mitchell and Hibbert, THIS JOURNAL, 66, 602 (1944).

(4) Eastham, Fisher, Kulka and Hibbert, *ibid.*, 66, 26 (1944).

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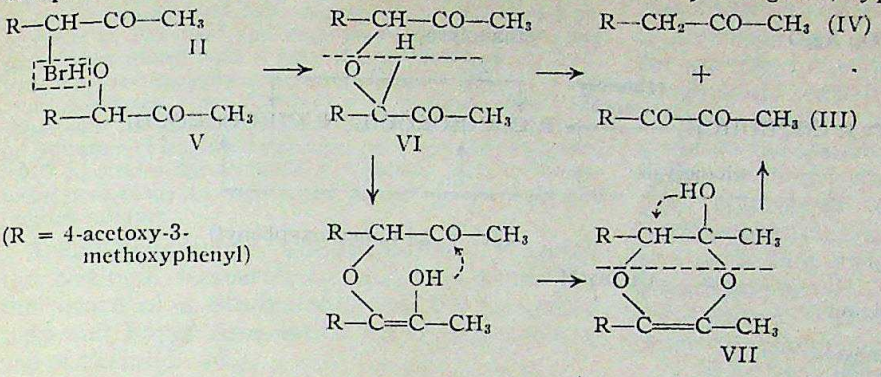
acid and an unstable ether (VI) which then decomposes into III and IV.



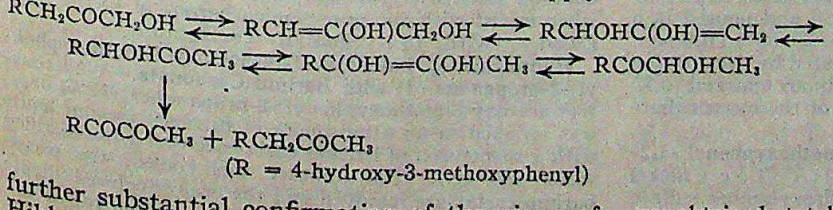
It is also conceivable that VI, by an intramolecular rearrangement could yield an unstable six-membered ring VII also capable, on decomposition, of giving III and IV in the manner indicated.

The fact that these changes take place under such mild conditions, *at room temperature*, may have considerable biological significance. The reaction is, in many ways, analogous to that found by Kohler[5] in the behavior of a series of aromatic α-bromoketones toward alkalies, whereby, in addition to the hydroxy substitution products, 1,2-diketones and desoxybenzoins were obtained.

In the present investigation it was found that small amounts of the 1,2-diketone, 1-(4-hydroxy-3-methoxyphenyl)-1,2-propanedione (VIII), are obtained both when the bromo derivative (II) is refluxed with 5% aqueous potassium acetate and when 1-acetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (I)[3] is refluxed with an aqueous suspension of barium carbonate. In both cases the principal product of hydrolysis is 2-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone (IX).

It has been shown previously[4] that a considerable amount of diketone, 1-(3,4-dimethoxyphenyl)-1,2-propanedione is obtained by the action of 5% aqueous potassium acetate on 3-chloro-1-(3,4-dimethoxyphenyl)-2-propanone, in addition to the main product, 1-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone, the latter being formed as the result of an allyl shift similar to that found more recently[6] with 3-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone.

These results, Chart I, considered in conjunction with those of the present research, Chart II, would seem to provide definite proof of the following interrelated mechanisms and in turn supply



further substantial confirmation of the views of Hibbert that spruce native lignin is derived from building-units of the β-oxyconiferyl alcohol (β,γ-dioxyisoeugenol) type.

Experimental

The synthesis of 1-bromo-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (II) was accomplished by a preliminary acetylation of the phenolic hydroxyl in 1-(4-hydroxy-3-methoxyphenyl)-2-propanone[7] and subsequent bromination in the presence of a trace of benzoyl peroxide.[8] The procedure for isolation of the free hydroxy hydrolysis products, 1-(4-hydroxy-3-methoxyphenyl)-1,2-propanedione (VIII) and 1-(4-hydroxy-3-methoxyphenyl)-2-propanone (X) was similar to that employed for the components of the bisulfite soluble fraction from the ethanolysis of wood.[7]

Synthesis of 1-(4-Acetoxy-3-methoxyphenyl)-2-propanone.—1-(4-Hydroxy-3-methoxyphenyl)-2-propanone[7] (20 g.) was dissolved in aqueous sodium hydroxide (65 cc. of 10% solution) and the solution cooled by the addition of cracked ice. Acetic anhydride (15 cc.) was added rapidly and the mixture shaken for five to ten minutes, sufficient ice being present to maintain the temperature at 0–10°. The heavy oil was separated and the aqueous layer extracted thoroughly with ether. The ether extracts were combined with the oil and the entire solution back-extracted once with dilute sodium hydroxide (1% solution), the ethereal solution washed with water and dried over sodium sulfate. Removal of solvent and vacuum distillation of the crude product at 150–160° (bath temperature) (0.075 mm.) yielded an almost colorless oil which crystallized rapidly; yield, 22.0 g. (98%). This distilled product was sufficiently pure for the succeeding step in the synthesis. When recrystallized from dilute ethanol it melted at 47–48°. *Anal.* Calcd. for $C_{12}H_{14}O_4$: C, 64.8; H, 6.30; OCH_3, 14.0. Found: C, 64.5; H, 6.35; OCH_3, 13.9. The semicarbazone, recrystallized from dilute ethanol, melted at 168–169°. *Anal.* Calcd.: OCH_3, 11.1. Found: OCH_3, 11.1.

Synthesis of 1-Bromo-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (II).—To a solution of 1-(4-acetoxy-3-methoxyphenyl)-2-propanone (15 g.) and benzoyl peroxide (0.15 g.) in anhydrous chloroform (100 cc.) contained in a three-necked flask, fitted with a dropping funnel, a thermometer and a stirrer was added a solution of bromine (12.5 g.) in chloroform (50 cc.) over a period of one hour. During the addition the solution was stirred vigorously and the temperature kept below 10° by means of an ice-bath. At the conclusion of the addition the stirring was continued for an additional one and one-half hours at room temperature. The solution was washed twice with water, once with 1% sodium bicarbonate and, finally, twice again with water. Remaining traces of water were removed by passage through a dry filter paper and the solution evaporated almost to dryness at room temperature under reduced pressure (15 mm.). Addition of ether to the residue precipitated a crude yellowish product which was filtered on a sintered glass funnel and washed with ether until most of the color had been removed. The crude product, only slightly soluble in ether, was dissolved in a large volume of the pure dry solvent, boiled with charcoal, filtered and the solution concentrated to a volume of 50 cc. On cooling, the almost pure compound (12.5 g.), m. p. 98–99°, separated out. From the mother liquors and washings an additional amount (2.5 g.), m. p. 98–99°, was obtained; total yield, 15.0 g. (73%). On recrystallization, alternately from ether and ether–petroleum ether

(5) Kohler, *Am. Chem. J.*, **41**, 417 (1908).
(6) Fisher, Kulka and Hibbert, THIS JOURNAL, **66**, 598 (1944).
(7) Kulka and Hibbert, *ibid.*, **65**, 1180 (1943).
(8) Kharasch, White and Mayo, *J. Org. Chem.*, **3**, 33 (1938).

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CHART I[4,6]

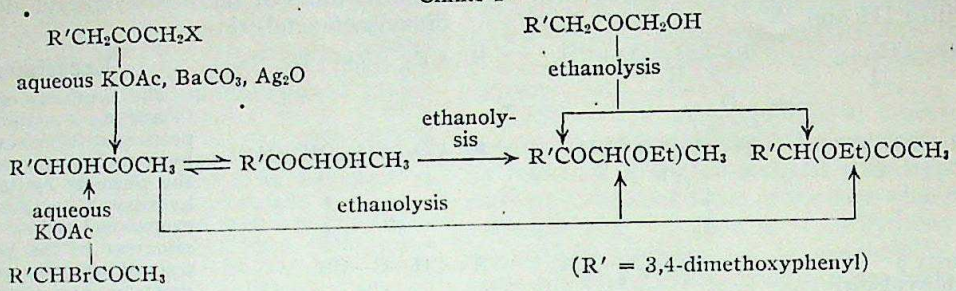
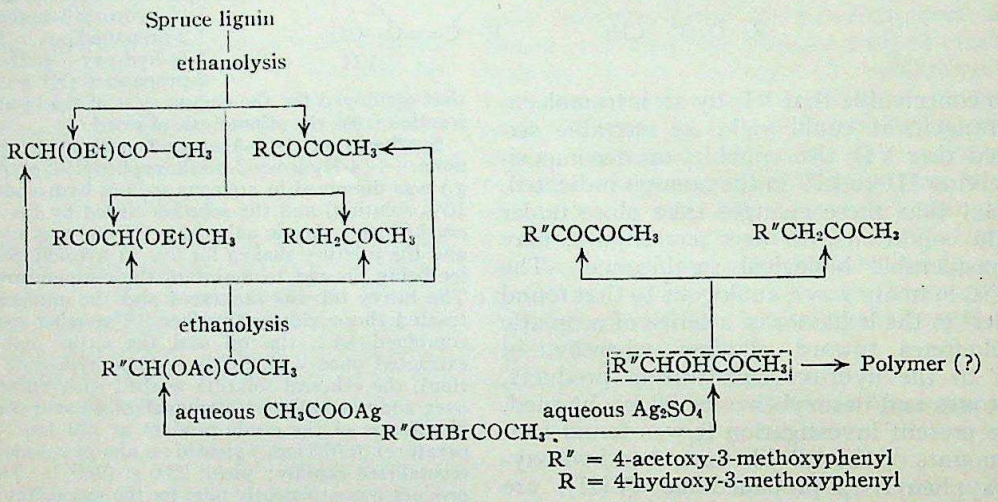


CHART II



(b. p. 30–50°) the melting point was raised to 100–101°. *Anal.* Calcd.: OCH_3, 10.3; Br, 26.5. Found: OCH_3, 10.2; Br, 26.5. The semicarbazone, recrystallized from dilute methanol, melted at 180–181°. *Anal.* Calcd.: OCH_3, 8.65. Found: OCH_3, 8.5.

Action of Aqueous Silver Sulfate on 1-Bromo-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (II).—1-Bromo-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (3.5 g.) was dissolved in a mixture of dioxane (100 cc.) and water (50 cc.). Freshly precipitated silver sulfate (3.0 g.) and barium carbonate (3.0 g.) were added and the mixture stirred at room temperature in an atmosphere of nitrogen for five days. The insoluble salts were filtered off and the filtrate concentrated at room temperature (using a carbon dioxide bubbler under reduced pressure) to a volume of 25 cc. This solution was extracted thoroughly with chloroform, and the extract dried over sodium sulfate, filtered and the solvent removed under reduced pressure leaving a crude yellowish-orange oil (3.0 g.) which could not be crystallized. Vacuum distillation of this product at 150–180° (bath temperature) (0.10 mm.) yielded a mobile orange-colored distillate (A), 1.5 g. (60%) and a non-distillable residue (B), 0.90 g. (35%). The low methoxyl value of the distillate (A), 13.2%, as compared with that of 15.8% for IX and 17.2% for X indicated that the phenolic acetate group was still intact. The highly colored residue (B) was dissolved in chloroform (5 cc.) and poured in a fine stream into petroleum ether (b. p. 30–50°) (100 cc.), the dark-colored precipitated tar separated by decantation and dried *in vacuo* leaving a brittle resinous material (0.75 g.), probably a condensation polymer of the intermediate 1-hydroxy derivative.

(a) **Isolation of 1-(4-Hydroxy-3-methoxyphenyl)-1,2-propanedione (VIII) from (A).**—The oil (A) (1.5 g.), nickel chloride (15 cc. of 5% solution), hydroxylamine sulfate (1.0 g.) and sodium acetate (8 g.) were dissolved in water (400 cc.) and the nickel glyoxime salt (C) isolated and hydrolyzed as described previously[9]; yield of nickel salt (C), 0.82 g., equivalent to 0.66 g. diketone present in (A) (44%).

Distillation of the crude diketone obtained from the hydrolysis of the nickel glyoxime salt (C) yielded a yellow distillate which solidified rapidly on standing. Recrystallized once from dilute ethanol the product melted at 69–70° and gave no depression in melting point when mixed with an authentic sample of 1-(4-hydroxy-3-methoxyphenyl)-1,2-propanedione (VIII).

(b) **Isolation of 1-(4-Hydroxy-3-methoxyphenyl)-2-propanone (X) from (A).**—The aqueous solution remaining after separation of the nickel glyoxime salt (C) was concentrated to about 250 cc. and extracted continuously with benzene for thirty-six hours. The benzene extract was dried and the solvent removed under reduced pressure, leaving the crude oxime of the desoxybenzoin. After removal of the last traces of solvent this crystallized partially as a yellow solid, yield 0.63 g. Distillation of the crude product remaining after hydrolysis of the oxime yielded a mobile yellow oil analyzing correctly for 1-(4-hydroxy-3-methoxyphenyl)-2-propanone (X); yield, 0.33 g., equivalent to 0.40 g. (27%) of 1-(4-acetoxy-3-methoxyphenyl)-2-propanone (IV) in the oil (A). *Anal.* Calcd.: OCH_3, 17.2. Found: OCH_3, 17.1. The semicarbazone of this distilled product, after one recrystallization from ethanol, melted at 157–158° and showed no depression when mixed with the pure semicarbazone of (X). *Anal.* Calcd.: OCH_3, 13.1. Found: OCH_3, 13.1.

Hydrolysis of 1-Acetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (I) with Barium Carbonate.—1-Acetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone[3] (I) (1.0 g.) was refluxed in an atmosphere of nitrogen for ten hours with a suspension of barium carbonate (2.0 g.) in distilled water (50 cc.). The mixture was cooled, the excess barium carbonate removed and the orange-colored filtrate extracted thoroughly with chloroform. Removal of solvent and vacuum distillation of the residue at 150–180° (bath temperature) (0.075 mm.) gave a clear yellow oil which solidified on standing; yield, 0.50 g. (74%). The

(9) Kulka, Hawkins and Hibbert, THIS JOURNAL, 69, 2671 (1947).

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crude product was washed with small portions of an ether–petroleum ether (b. p. 30–50°) mixture (1:1) until almost colorless. The product (0.28 g.) then melted at 101–102°, this value being raised, following one recrystallization from benzene, to 108–109° and gave no depression in melting point when mixed with a pure sample of 2-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone (IX). The ether–petroleum ether washings were evaporated and the presence of the diketone in the residual yellow oil shown by precipitation of its nickel glyoxime salt; yield of the latter, 0.075 g., equivalent to 0.058 g. diketone (VIII). No attempt was made to isolate the desoxybenzoin from the reaction mixture.

Acknowledgment.—The authors wish to thank the National Research Council of Canada for the award of a Studentship and the Canadian Pulp and Paper Association for financial aid to one of them (L. M.).

Summary

1. The synthesis of 1-bromo-1-(4-acetoxy-3-methoxyphenyl)-2-propanone has been carried out.

2. Aqueous silver sulfate reacts with this product at room temperature (*that is, under approximate biological conditions*) to give a mixture containing 1-(4-acetoxy-3-methoxyphenyl)-1,2-propanedione and 1-(4-acetoxy-3-methoxyphenyl)-2-propanone in a combined yield of 60% based on the starting material. The amounts of these two components present in the mixture were 44 and 27%, respectively, equivalent to 24 and 16% based on the starting material. A possible mechanism for their formation is suggested.

3. Hydrolysis of 1-acetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone with aqueous barium carbonate yielded 2-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-1-propanone as the main product together with small quantities of 1-(4-hydroxy-3-methoxyphenyl)-1,2-propanedione.

4. The formation of these two products (the 1,2-diketone and desoxybenzoin), as indicated, supplies additional evidence in support of Hibbert's β-oxyconiferyl alcohol theory of spruce native lignin structure.

MONTREAL, QUEBEC, CANADA

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[CONTRIBUTION FROM THE DIVISION OF INDUSTRIAL AND CELLULOSE CHEMISTRY, MCGILL UNIVERSITY]

Studies on Lignin and Related Compounds. LXXXII. Synthesis and Properties of 1,3-Diacetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone and 1-Acetoxy-3-chloro-1-(4-acetoxy-3-methoxyphenyl)-2-propanone and their Relation to Lignin Structure[1]

BY J. A. F. GARDNER[2] AND HAROLD HIBBERT

In the two preceding communications[3,4] experimental evidence was presented showing the remarkable ease of formation of 1-(4-hydroxy-3-methoxyphenyl)-1,2-propanedione (I) from 1-hydroxy-1-(4-hydroxy-3-methoxyphenyl)-2-propanone (II) under very mild conditions. The latter product (as its phenolic methyl ether) is, in turn, readily formed[5] under the influence of mild reagents from 3-hydroxy-1-(3,4-dimethoxyphenyl)-2-propanone (III) (the keto form of methylated β-oxyconiferyl alcohol) through an allylic shift. The presence of the diketone (I) in the ethanolysis mixture from spruce wood is thus satisfactorily accounted for by Hibbert's theory of lignin structure[5,6,7] which assumes the presence, in the spruce native lignin complex, of a building unit of the β-oxyconiferyl alcohol (β-γ-dioxyisoeugenol) type.

Consideration of this new type of allyl transformation, involving a *mono*-hydroxylated allyl alcohol indicated the possibility of a similar type of reaction occurring with the analogous *dihydroxy* derivative, R—C(OH)=C(OH)—CH_2OH (IV) (R = 4-hydroxy-3-methoxyphenyl) since in this case the final product should also be the above diketone (I).

$$RC(OH)=C(OH)-CH_2OH \rightleftharpoons \underset{IV}{}$$

$$R-C(OH)_2-C(OH)=CH_2 \longrightarrow R-COCOCH_3 + H_2O \quad (I)$$

The product IV is the ene-diol intermediate of a dismutation system

$$R-COCHOHCH_2OH \rightleftharpoons (V)$$

$$R-C(OH)=C(OH)-CH_2OH \rightleftharpoons (IV)$$

$$R-CHOHCOCH_2OH \quad (VI)$$

and, by analogy, either V or VI (or their halides) might be expected to undergo an allyl shift in the presence of suitable mild chemical reagents.

Formation of a diketone has been observed by Bradley and Eaton[8] in the case of 1-acetoxy-1-phenyl-3-chloro-2-propanone, mild hydrolysis of the latter yielding 1-phenyl-1,2-propanedione. These authors made no comment concerning the mechanism of its formation. Based on the above

(1) Extract from thesis work of J. A. F. Gardner to be presented to the Graduate Faculty of McGill University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Holder of a National Research Council of Canada Studentship for the Session 1942–1943.

(3) Mitchell and Hibbert, THIS JOURNAL, 66, 602 (1944).

(4) Mitchell, Evans and Hibbert, *ibid.*, 66, 604 (1944).

(5) Eastham, Fisher, Kulka and Hibbert, *ibid.*, 66, 26 (1944).

(6) Hibbert, *Paper Trade J.*, 113, No. 4, 35 (1941).

(7) Hibbert, *Ann. Rev. Biochem.*, 11, 183 (1942).

(8) Bradley and Eaton, *J. Chem. Soc.*, 1913 (1937).

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theory, however, it could have been formed as the result of an allyl shift similar to that postulated above

$$R'\text{—CHOAcCOCH}_2\text{Cl} \longrightarrow R'\text{—CHOHCOCH}_2\text{OH} \rightleftharpoons$$
$$R'\text{—C(OH)=C(OH)—CH}_2\text{OH} \rightleftharpoons$$
$$R'\text{—C(OH)}_2\text{—C(OH)=CH}_2 \longrightarrow R'\text{—COCOCH}_3 + H_2O$$
(R′ = phenyl)

In view of the experimental difficulties attendant upon the synthesis of V, the preparation of the triacetate of VI, 1,3-diacetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (VII), and of the corresponding chloride, 1-acetoxy-3-chloro-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (VIII) was carried out by the following series of reactions

$$R\text{—CHO} \xrightarrow[\text{IX}]{\text{NaHSO}_3,\ \text{KCN}} R\text{—CHOHCN} \xrightarrow[\text{X}]{\text{HCl, EtOH}}$$

$$R\text{—CHOH—C}\begin{matrix}\text{NHHCl}\\ \text{OC}_2\text{H}_5\end{matrix} \xrightarrow[\text{XI}]{H_2O}$$

$$R\text{—CHOHCOOC}_2\text{H}_5 \xrightarrow[\text{XII}]{\text{NaOH(2\%)}} R\text{—CHOHCOOH} \xrightarrow[\text{XIII}]{Ac_2O}$$

$$R''\text{—CHOAcCOOH} \xrightarrow[\text{XIV}]{\text{SOCl}_2,\ C_6H_6}$$

$$R''\text{—CHOAcCOCl} \xrightarrow[\text{XV}]{CH_2N_2} R''\text{—CHOAcCOCHN}_2 \xrightarrow[\text{XVI}]{\text{HCl}}$$

$$R''\text{—CHOAcCOCH}_2\text{Cl} \quad \text{VIII}$$

$$R''\text{—CHOAcCOCH}_2\text{OAc} \quad \text{VII}$$

(R = 4-hydroxy-3-methoxyphenyl
R″ = 4-acetoxy-3-methoxyphenyl)

The substituted mandelic ester (XII) has been prepared previously from vanillin through the cyanohydrin (X) and imino ether hydrochloride (XI) in 16% yield by Schwartz and McCarthy.[9] By utilizing the method of Hahn, Stiehl and Schulz,[10] for preparation of the cyanohydrin and carrying out the reactions at lower temperatures the yield was increased to 24%.

The 4-hydroxy-3-methoxymandelic acid (XIII), which readily resinified on heating or on exposure to air, was acetylated to prevent reaction of thionyl chloride with the phenolic and secondary hydroxyls. The resulting diacetate, 4-acetoxy-3-methoxy-acetylmandelic acid (XII), crystallized readily from aqueous solution as a monohydrate, readily dehydrated at room temperature *in vacuo*. Considerable difficulty was experienced in obtaining a good yield of the acid chloride (XV) but this was accomplished by using a solution of thionyl chloride in benzene and employing a much shorter period of reflux than in the case of mandelic acid.[11]

While the diazoketone (XVI) did not react with *cold* glacial acetic, at *reflux* temperature it yielded the desired triacetate (VII).

(9) Schwartz and McCarthy, *Can. J. Research*, **19B**, 150 (1941).
(10) Hahn, Stiehl and Schulz, *Ber.*, **72B**, 1296 (1939).
(11) Thayer, "Organic Syntheses," **4**, 1 (1925).

As anticipated, this triacetate, on ethanolysis, gave the 1,2-diketone (I) together with an amorphous resinous product, in yields of 8 and 66%, respectively. No work has been carried out on the nature of this resin. Hydrolysis of VII with dilute sulfuric acid (2%) gave a 9% yield of I. A much larger amount (75%) of the diketone was obtained on mild hydrolysis of the monochlor derivative (VIII) with acidified sodium acetate solution, little or no resinification taking place.

The 1,2-diketone (I) was determined by precipitation as the nickel glyoxime salt and identified by hydrolysis of this and preparation of the quinoxaline and semicarbazone[12,13] of the hydrolyzed product.

The formation of 1-(4-hydroxy-3-methoxyphenyl)-1,2-propanedione (I), from the intermediary dihydroxy ketone (VI), raises the question as to whether the latter product (VI) or its dismutation isomer (V), might not also be present, *to a limited extent*, as one of the building-stones of the spruce native lignin complex. If the dismutation reactions shown in the chart are capable of taking place under the conditions of spruce wood ethanolysis, then either V or VI could serve as the source of origin of a portion of the 1,2-diketone (I) but neither could account for the presence in the ethanolysis mixture of the remaining ethanolysis products, R—CH(OC$_2$H$_5$)—CO—CH$_3$, R—CO—CH(OC$_2$H$_5$)—CH$_3$ and R—CH$_2$—CO—CH$_3$ (R = 4-hydroxy-3-methoxyphenyl). It is significant, however, that spruce ethanolysis products contain only *small amounts* (3–5%) of monomolecular units and very large amounts of amorphous ethanol lignins. Conceivably VI could be synthesized in the plant by condensation of guaiacol with hydroxypyruvic aldehyde. No *direct* experimental evidence, however, regarding its presence in spruce native lignin has been obtained, as yet.

Experimental

Synthesis of 1-Acetoxy-3-chloro-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (VIII)

Preparation of Ethyl 4-Hydroxy-3-methoxymandelate (XII).—An ethereal solution (200 cc.) of vanillin cyanohydrin, prepared from vanillin (50 g.) by the method of Hahn, Stiehl and Schulz,[10] was dried for twelve hours at −10° over sodium sulfate and drierite and then filtered. Absolute ethanol (20 cc.) was added and dry hydrogen chloride (10 g.) bubbled in at −10°. After forty-eight hours at this temperature the crude imino ether hydrochloride was hydrolyzed by the procedure of Schwartz and McCarthy.[9] The crude ester (21 g.) on distillation (140–160° (0.4 mm.)) gave a light yellow oil (17.8 g.) which crystallized to a white solid; m. p. 75–77°; yield, 24%. One recrystallization from benzene–petroleum ether (b. p. 30–50°) gave colorless crystals, m. p. 77°. *Anal.* Calcd. for C$_{11}$H$_{14}$O$_5$: OR, 27.4. Found: OR, 27.3.

4-Hydroxy-3-methoxymandelic Acid (XIII).—The ester (XII) (17 g.) was refluxed one hour with sodium hydroxide (600 cc., 2%) under a nitrogen atmosphere, the mixture then extracted with benzene (2 × 50 cc.), acidified with hydrochloric acid, saturated with sodium chloride and continuously extracted with ether. Drying of the ethereal extract

(12) Kulka, Hawkins and Hibbert, THIS JOURNAL, **63**, 2371 (1941).
(13) Brickman, Hawkins and Hibbert, *ibid.*, **62**, 2149 (1940).

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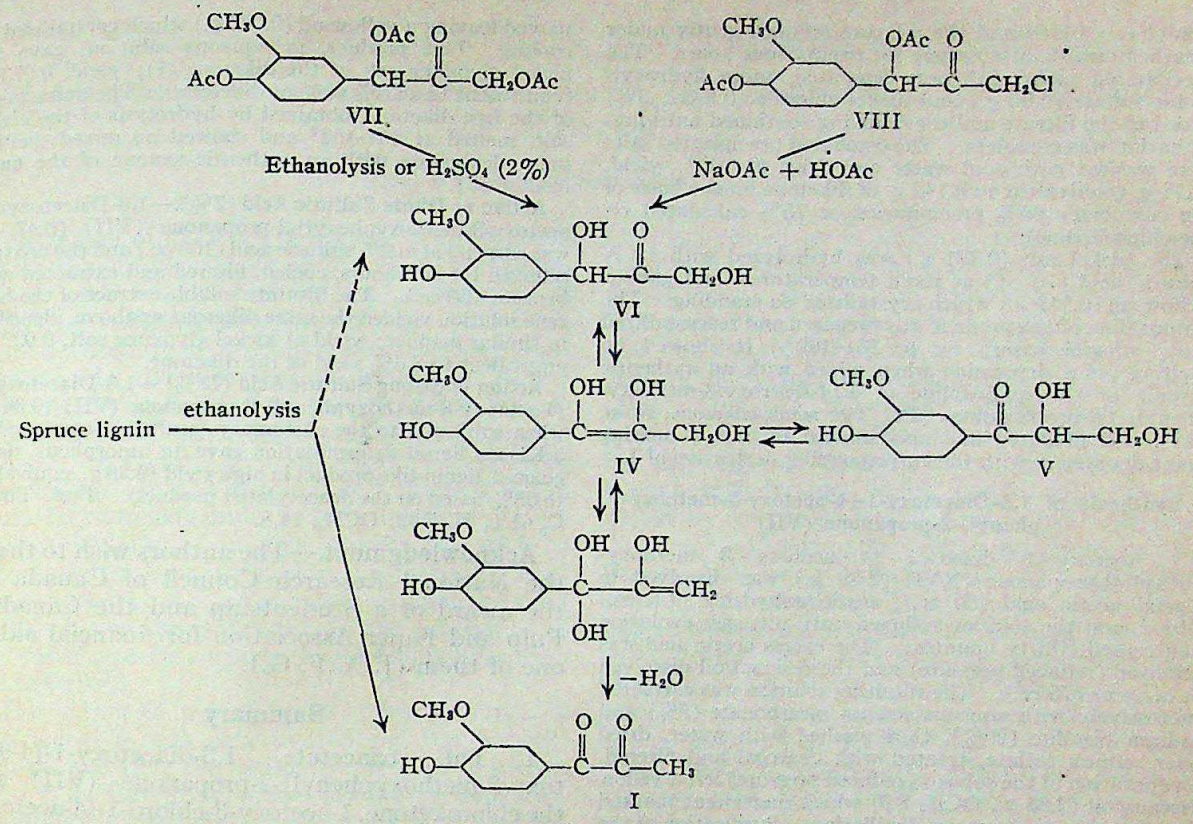

over sodium sulfate and removal of the solvent left a light yellow oil (15.2 g.) which crystallized after washing with a small quantity of benzene. Recrystallization from an acetone–petroleum ether (b. p. 30–50°) mixture gave colorless crystals; m. p. 129–131°; yield, 12.2 g. (80%). Repeated recrystallization from ether–benzene raised the melting point to 133°. The product was very soluble in water and acetone, moderately soluble in ether, and almost insoluble in benzene. *Anal.* Calcd. for $C_9H_{10}O_5$: C, 54.5; H, 5.05; OCH_3, 15.6. Found: C, 54.7; H, 5.15; OCH_3, 15.4.

4-Acetoxy-3-methoxyacetylmandelic Acid (XIV).—Pure 4-hydroxy-3-methoxymandelic acid (XIII) (m. p. 133°) (3.6 g.) was dissolved in a mixture of pyridine (27 cc.) and acetic anhydride (22 cc.), refluxed for twenty-five minutes, and the excess pyridine and acetic anhydride removed under reduced pressure. The residual oil was dissolved in hot water, and the solution decolorized with charcoal and filtered. Crystals of the monohydrate (m. p. 112–113°) separated on cooling. On addition of 6 *N* hydrochloric acid (3 cc.) a further quantity was obtained. The combined products were dehydrated by standing for forty-eight hours in a vacuum desiccator; m. p. 142°; yield, 4.15 g. (81%). Recrystallization from benzene did not raise the melting point. *Anal.* Calcd. for $C_{13}H_{14}O_7 \cdot H_2O$: H_2O, 6.0. Found: H_2O, 5.9. Calcd. for $C_{13}H_{14}O_7$: C, 55.3; H, 5.0; OCH_3, 11.0; neut. equiv., 282. Found: C, 55.5; H, 4.9; OCH_3, 10.9; neut. equiv., 281.

4-Acetoxy-3-methoxy-acetylmandelyl Chloride (XV).—The above diacetate (XIV, 0.8 g.) was dissolved in a mixture of anhydrous benzene (8 cc.) and carefully purified thionyl chloride (3.2 cc.) and then refluxed one and three-quarters hours. The excess thionyl chloride was distilled off (reduced pressure) and the last traces removed by successive addition and distillation (reduced pressure) of two portions (5 cc.) of anhydrous benzene. The residual light yellow oil solidified completely on cooling and was recrystallized from an anhydrous benzene–petroleum ether (b. p. 30–50°) mixture; m. p. 71–72°; yield, 0.804 g. (94%). On repeated recrystallization from petroleum ether (b. p. 30–50°) the m. p. was raised to 72°. *Anal.* Calcd. for $C_{13}H_{13}O_6Cl$: OCH_3, 10.3; Cl, 11.8. Found: OCH_3, 10.2; Cl, 11.8.

1-Acetoxy-3-diazo-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (XVI).—Crude acid chloride (XV) prepared from the acid (XIV) (1.07 g.), was dissolved in benzene (5 cc.) and poured in a fine stream into a well-stirred dry ethereal solution of diazomethane (from 4 g. of nitrosomethylurea) cooled previously to 0° and the mixture allowed to stand at this temperature for twelve hours. The ether solution was decanted from the first crop of crystals, filtered, and evaporated in a stream of dry air. Scratching caused the light yellow residual oil to crystallize. The two crops of crystals were washed with cold ether and combined; yield, 0.96 g. (88%). Recrystallization from benzene gave light yellow crystals, m. p. 129–130°. *Anal.* Calcd. for $C_{14}H_{14}O_6N_2$: C, 55.0; H, 4.61; OCH_3, 10.10. Found: C, 55.2; H, 4.58; OCH_3, 10.05.

1-Acetoxy-3-chloro-1-(4-acetoxy-3-methoxyphenyl)-2-propanone.—The diazoketone (XVI) (0.38 g.), dissolved in anhydrous benzene (10 cc.), was treated with anhydrous ethereal hydrogen chloride (1.6 cc., 0.89 *N*) and the mixture allowed to stand at 0° for three hours. It was washed with 1% sodium bicarbonate solution, then with water, dried over sodium sulfate and the solvent removed. Colorless crystals, m. p. 109–110°; yield, 0.316 g. (81%). Recrystallization from ether or ether–benzene raised the melting point to 110–111°. *Anal.* Calcd. for $C_{14}H_{15}O_6Cl$: C, 53.4; H, 4.81; OCH_3, 9.85; Cl, 11.3. Found: C, 53.09; H, 4.94; OCH_3, 9.80; Cl, 11.2.

Hydrolysis of 1-Acetoxy-3-chloro-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (VIII) and Isolation of the Diketone (I)

Action of Acidified Sodium Acetate Solution.—The above chloro derivative (VIII) (0.31 g.) was suspended in an aqueous solution of sodium acetate (0.4 g. in 50 cc.) and acetic acid (0.5 cc.) and the mixture refluxed for six hours under an atmosphere of carbon dioxide. The deep yellow colored solution was filtered, sodium acetate (0.4 g.), hydroxylamine sulfate (0.2 g.) and 5% nickel chloride solu-

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tion (1 cc.) added and the mixture refluxed gently under a carbon dioxide atmosphere for twenty-four hours. The precipitated nickel salt was separated, more hydroxylamine sulfate (0.05 g.) and nickel chloride (0.5 cc., 5%) added to the filtrate and the refluxing continued until precipitation was complete. The combined precipitated salts were washed with cold water and dried at 100°; yield, 0.171 g. (equivalent to 0.142 g. of diketone on the basis of the customary 90% precipitation or 75% calculated on the chloroketone).

The nickel salt (0.171 g.) was hydrolyzed with 12 *N* sulfuric acid (70 cc.) at room temperature[12] and gave a yellow oil (0.119 g.) which crystallized on standing. The quinoxaline of the product was prepared and recrystallized from ethanol–water; m. p. 161–162°. It showed no melting point depression when mixed with an authentic sample of the quinoxaline of 1-(4-hydroxy-3-methoxyphenyl)-1,2-propanedione (I). The semicarbazone, m. p. 213°, was prepared and also showed no mixed melting point depression with the corresponding derivative of I.

Synthesis of 1,3-Diacetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (VII)

1 - Acetoxy - 3 - diazo - 1 - (4 - acetoxy - 3 - methoxyphenyl)-2-propanone (XVI) (2.89 g.) was dissolved in glacial acetic acid (60 cc.), acetic anhydride (1.5 cc.) added, and the solution refluxed until nitrogen evolution had ceased (thirty minutes). The excess acetic acid was removed (reduced pressure) and the residual oil dissolved in benzene (75 cc.). The resulting solution was extracted successively with aqueous sodium bicarbonate (5%) and sodium bisulfite (20%), then washed with water, dried over sodium sulfate, treated with charcoal and filtered. Evaporation of the solvent (reduced pressure) left a yellow viscous oil (2.85 g., OCH_3 8.9) which underwent marked decomposition on vacuum distillation. Purification of the product was achieved by solution in acetone (95 cc.) and addition of this in a fine stream to vigorously-stirred petroleum ether (b. p. 30–50°, 950 cc.). The solvent was removed (the last traces under reduced pressure, two hours at 65–70° (0.025 mm.)), leaving a homogeneous light yellow oil ($n^{50}D$ 1.5028); yield, 2.46 g. (77%). *Anal.* Calcd. for $C_{16}H_{18}O_8$: C, 56.8; H, 5.34; OCH_3, 9.17. Found: C, 56.9; H, 5.48; OCH_3, 9.13.

Hydrolysis of 1,3-Diacetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (VII)

Action of Ethanolic Hydrogen Chloride.—1,3-Diacetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (VII) (1.35 g.) was refluxed with 2% ethanolic hydrogen chloride (130 cc.) for thirty-six hours in an atmosphere of carbon dioxide. The reaction mixture was neutralized with freshly precipitated calcium carbonate, filtered, and evaporated to dryness (reduced pressure) in a stream of carbon dioxide. The residual reddish-brown tar was extracted thoroughly with hot benzene (50 cc.) and then washed with hot water (to remove calcium acetate), leaving an amorphous black powder (0.56 g., 66%). The benzene solution was extracted with sodium bisulfite solution (20%, 50 cc.), the extract acidified with sulfuric acid and sulfur dioxide removed in a stream of carbon dioxide (reduced pressure). The acid solution was extracted with benzene (30 cc.), the benzene extract dried, and the solvent removed leaving a yellow oil (0.086 g.) which crystallized on cooling. This product, in aqueous solution, gave the nickel glyoxime salt of the diketone (I); yield, 0.073 g. (equivalent to an 8% yield of diketone). The quinoxaline of the free diketone, obtained by hydrolysis of the nickel salt, melted at 161–162° and showed no mixed melting point depression with an authentic sample of the quinoxaline of I.

Action of Dilute Sulfuric Acid (2%).—1,3-Diacetoxy-(4-acetoxy-3-methoxyphenyl)-2-propanone (VII) (0.47 g.) was suspended in 2% sulfuric acid (100 cc.) and the mixture refluxed for two hours, cooled, filtered and extracted with benzene (50 cc.). The bisulfite soluble extract of the benzene solution yielded the same diketone as above, identified in similar manner; yield of nickel glyoxime salt, 0.027 g., equivalent to 8.6% yield of the diketone.

Action of Strong Sulfuric Acid (72%).—1,3-Diacetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (VII) (0.66 g.) when subjected to the customary treatment employed in a Klason lignin determination gave an amorphous, dark-colored, lignin-like product in high yield (0.28 g., equivalent to 68% based on the deacetylated product). *Anal.* Found C, 61.1; H, 5.32; OCH_3, 14.8.

Acknowledgment.—The authors wish to thank the National Research Council of Canada for the award of a Studentship and the Canadian Pulp and Paper Association for financial aid to one of them (J. A. F. G.).

Summary

1. The triacetate, 1,3-diacetoxy-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (VII) and the chloroketone, 1-acetoxy-3-chloro-1-(4-acetoxy-3-methoxyphenyl)-2-propanone (VIII) have been synthesized.

2. Under the influence of mild hydrolytic agents, both the triacetate and chloro derivative are converted into 1-(4-hydroxy-3-methoxyphenyl)-1,2-propanedione (I) (found in the ethanolysis products of spruce wood) in yields of 8 and 75%, respectively.

3. It is concluded that the 1,2-diketone is formed as the result of an allyl shift in a dismutation ene-diol product arising from the hydrolysis intermediate, 1,3-dihydroxy-1-(4-hydroxy-3-methoxyphenyl)-2-propanone. The allyl shift is thus indicated as taking place with a dihydroxy substituted allyl alcohol.

4. Attention is drawn to the possibility that a dihydroxy ketone of the type R—CO—CHOH—CH_2OH or R—CHOH—CO—CH_2OH (R = 4-hydroxy-3-methoxyphenyl) may function to a limited extent as a lignin progenitor.

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4-Hydroxylaminobenzenesulfonamide, its Acetyl Derivatives and Diazotization Reaction

BY HUGO BAUER AND SANFORD M. ROSENTHAL

As a result of the work of Mayer,[1] who proposed that products formed by oxidation of the amino group were responsible for the mechanism of action of sulfanilamide, considerable study has been devoted to 4-hydroxylaminobenzenesulfonamide.[2] An attempt was made[2a] to develop a colorimetric method for the detection of 4-hydroxylaminobenzenesulfonamide based upon its unusual behavior to diazotization following acetylation. It was found that a diazo reaction could be obtained under certain conditions even after acetylation. In this respect it could be differentiated from sulfanilamide, although later work showed that this procedure was not specific.[3] In this paper the isolation and the properties of the substance responsible for the diazo reaction are described.

The action of nitrite upon hydroxylamines in acid solution was investigated by Bamberger,[4] who showed that the action of one mole of nitrite upon phenylhydroxylamine produces N-nitrosophenylhydroxylamine. This compound decomposes easily either in dry state or in solution with formation of various products, one of them being diazobenzene nitrate. The diazo compound was formed more readily by action of sodium nitrite upon nitrosophenylhydroxylamine in glacial acetic acid solution[4b]

$$C_6H_5NHOH + HNO_2 \longrightarrow C_6H_5N(NO)OH + H_2O \quad (1)$$

$$C_6H_5N(NO)OH + HNO_2 \longrightarrow C_6H_5{-}N_2{-}NO_3 + H_2O \quad (2)$$

The N-nitroso derivative of 2-hydroxylaminobenzoic acid which was obtained only in solution,[5] gave the diazo reaction with an excess of nitrite.

Our study of the 4-hydroxylaminobenzenesulfonamide and of the 4-hydroxylaminobenzoic acid confirms and supplements the observations of Bamberger.

By action of nitrous acid on 4-hydroxylaminobenzenesulfonamide, the N-nitroso-4-hydroxylaminobenzenesulfonamide, $H_2NSO_2C_6H_4N(NO)$-OH, is formed as a white crystalline, sparingly soluble precipitate, while diazotization occurs to a small extent only. The nitrosohydroxylaminobenzenesulfonamide is fairly stable in dry state and can be recrystallized by dissolving in ethyl acetate with subsequent addition of petroleum ether. However, it behaves differently in glacial acetic acid solution. This solution, without showing any sign of decomposition, contains diazobenzenesulfonamide which can readily be detected by coupling with N-(1-naphthyl)-ethylenediamine.[6] Colorimetric determinations of the purple dye, using sulfanilamide as a standard, showed that about 34% of the nitrosohydroxylamine was changed to the diazo compound.

For comparison, 4-hydroxylaminobenzoic acid,[7] which has not hitherto been isolated, and its N-nitroso derivative were prepared. The latter, when dissolved in glacial acetic acid and compared with an equivalent solution of 4-aminobenzoic acid, formed about 15% of diazo compound.

N-Nitrosophenylhydroxylamine behaved in the same way. About 18% of diazo compound was found, using aniline for comparison.

With all three nitrosohydroxylamines, the amount of diazo compound spontaneously formed in glacial acetic acid solution was only slightly changed by addition of nitrite or acetic anhydride (see below).

The spontaneous formation of a diazo compound from a nitrosohydroxylaminobenzene derivative requires the simultaneous formation of oxidation products. If we assume that a nitrosobenzene derivative is the main oxidation product, the following equation shows that three moles of nitrosohydroxylamine form two moles of diazo compound

$$3R{-}N\begin{matrix}NO\\OH\end{matrix} \longrightarrow 2R{-}N{=}N{-}OH + RNO + HNO_3 \quad (3)$$

The amount of diazo compound actually found was less than required by this equation.

To a small extent, formation of a diazo compound occurs also, as previously mentioned, with the preparation of the nitrosohydroxylaminobenzene sulfonamide. A larger amount of the diazo compound is formed by treating hydroxylaminobenzenesulfonamide in dilute acid solution with an excess of nitrite. The yield of diazo compound was considerably increased by treating the hydroxylaminobenzenesulfonamide with acetic an-

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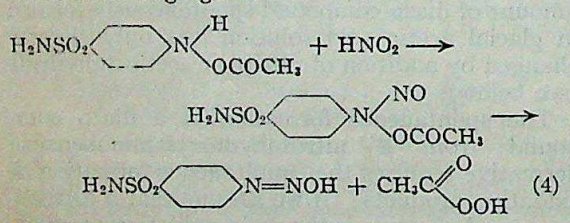
hydride before adding sodium nitrite. The amount of diazo compound formed was increased from 23 to 48% with 4-hydroxylaminobenzenesulfonamide, from 45 to 63% with 4-hydroxylaminobenzoic acid, from a trace to 10% with phenylhydroxylamine.

It was found that acetylation of 4-hydroxylaminobenzenesulfonamide in dilute aqueous solution yields two derivatives, one of which can be diazotized, the other cannot. As already pointed out by Bamberger,[8] for the 2-hydroxylaminobenzoic acid, the non-diazotizable product contains the acetyl group linked to the nitrogen. If acetylation is carried out in very dilute aqueous solution, little of the N-acetyl derivative is formed. The mother liquor contains the diazotizable product which can be extracted with ether or ethyl acetate. This isomer, which was not obtained in a pure state, apparently contains the acetyl group linked to the oxygen of the hydroxylamino group. Upon diazotization, about 65% was converted to the diazo compound; not more than 66.7% could be expected, according to equation 3.

The presence of the oxygen-bound acetyl group facilitates the formation of the diazo compound. It may be assumed that, in the first stage of reaction, an acetylated nitrosohydroxylamine is formed which is easily hydrolyzed in dilute aqueous solution with formation of peracetic acid (see equation 4). The latter could not be detected inasmuch as it is consumed immediately as an oxidizing agent.



(4)

As mentioned above, the diazotization reaction of the acetylated 4-hydroxylaminobenzenesulfonamide can be applied to the detection of this compound in body fluids in presence of sulfanilamide,[2a] although positive results must be confirmed by other methods because of the lack of specificity of this reaction. Other conjugation products of sulfanilamide which give a diazo reaction similar to 4-hydroxylaminobenzenesulfonamide may possibly be formed in the body. While acetylsulfanilamide cannot be diazotized, those conjugation products which are split by nitrous acid with formation of the diazo compound cannot be differentiated from the hydroxylamine. For example, a glucoside of sulfanilamide, tested with the acetylation–diazotization reaction, gave a positive result.[3]

Experimental

4-Hydroxylaminobenzenesulfonamide, $H_2NSO_2C_6H_4NHOH$.—The procedure for the preparation of 4-hydroxylaminobenzenesulfonamide differs in details from the method used by Bratton, White and Marshall,[2b] and in the present work the mother liquor was employed for the preparation of nitrosobenzenesulfonamide.

To a warm solution of 6 g. of 4-nitrobenzenesulfonamide[9] in 200 cc. of alcohol a solution of 10 g. of ammonium chloride in 100 cc. of water was added. With vigorous stirring, 8 g. of zinc dust was added gradually while the temperature was kept between 45 and 52°. After fifteen minutes stirring, the reaction mixture was kept in ice, for ninety minutes. The zinc sludge was filtered by suction and washed with alcohol. The yellow filtrate was concentrated under diminished pressure at 35°, while passing through a stream of nitrogen. When crystals separated, the distillation flask was cooled in an ice–salt mixture for two hours. The yellowish crystals of the hydroxylamine which separated, were filtered and washed twice with ice water. The yield varied between 3.5 (63% of the calcd.) and 4.95 g. (88.5% of the calcd.), the melting point of the crude product varied between 135 and 140°.

For further purification, the substance was dissolved in ethyl acetate, and petroleum ether was added. The colorless crystals thus obtained melted at 143–144° to a liquid which, on further heating, became yellow and decomposed between 148–158° to an orange solid.

Anal. Calcd. for $C_6H_8O_3N_2S$: C, 38.27; H, 4.29; S, 17.04. Found: C, 38.56; H, 4.40; S, 17.20.

Bratton, *et al.*,[2b] give the m. p. 139.5–140.5°. Formation of a substance of m. p. 163–164°, as obtained by Burton,[2g] consisting of a complex of two molecules of the hydroxylamine and one molecule of sulfanilamide, according to Sevag,[2i] was not observed when using the method described above.

4-Hydroxylaminobenzenesulfonamide is soluble in water, alcohol, ether, ethyl acetate, sparingly soluble in benzene, insoluble in petroleum ether. A water solution, saturated at 22.5°, contained 2.7 g. in 100 cc. Fehling solution and silver nitrate solution are immediately reduced at room temperature.

When titrated with 0.1 *N* sodium nitrite in dilute acetic acid solution, one mole of nitrite was used for one mole of 4-hydroxylaminobenzenesulfonamide, forming the nitroso derivative. The assay varied between 98 and 102%.

Reduction of the hydroxylamine with stannous chloride, following the procedure of Limpricht,[10] gave an assay of 94%.

N-Nitroso-4-hydroxylaminobenzenesulfonamide, $H_2NSO_2C_6H_4N(NO)OH$.—To an ice-cold solution of 1.2 g. of 4-hydroxylaminobenzenesulfonamide in 60 cc. of water and 7 cc. of 2 *N* hydrochloric acid, 6 cc. of *N* sodium nitrite solution were added at once. The colorless needles of the nitroso derivative which separated immediately, were filtered after half an hour standing and washed with ice water; 1.04 g. of the nitroso compound (75% of the calcd. amount) was obtained which melted with violent decomposition at 117°. It is soluble in alcohol or ethyl acetate, slightly soluble in water, not soluble in ether, benzene and petroleum ether. When recrystallized by dissolving in cold ethyl acetate and adding petroleum ether, the substance melted at 120°. It gives a beautiful Liebermann nitroso reaction; an intense blue color is formed with diphenylamine sulfuric acid reagent, a red color with ferric chloride. When dissolved in glacial acetic acid, the nitroso compound immediately forms diazobenzenesulfonamide; about 34% were found by coupling with N-(naphthyl)-ethylenediamine[6] (Table II).

Analysis. For nitrogen determination, the Kjeldahl method was modified in the following way: about 120 to 150 mg. of substance was dissolved in 10 cc. of water with addition of 3 drops of 10 *N* sodium hydroxide. 1 g. of sodium dithionite was added and the mixture was gently heated for one-half hour. After addition of 10 cc. of 2 *N* sulfuric acid the heating was continued for one more hour. Then 10 cc. of concentrated sulfuric acid was added, the water was evaporated and the digestion finished in the

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TABLE I

FORMATION OF DIAZO COMPOUND FROM HYDROXYLAMINES

	Compared with diazotized	Diazotized found, %	Treated with acetic anhydride and diazotized found, %
4-Hydroxylaminobenzenesulfonamide	Sulfanilamide	23	48
4-Hydroxylaminobenzoic acid	4-Aminobenzoic acid	45	63
Phenylhydroxylamine	Aniline	Trace	10
O-Acetylhydroxylaminobenzenesulfonamide	Sulfanilamide	63–67	..

TABLE II

SPONTANEOUS FORMATION OF DIAZO COMPOUND FROM N-NITROSOHYDROXYLAMINES IN GLACIAL ACETIC ACID SOLUTION

	Dissolved in glacial acetic acid, found, %	Dissolved in glacial acetic acid with addition of acetic anhydride, found, %	Dissolved in glacial acetic acid with addition of sodium nitrite, found, %
N-Nitroso-4-hydroxylaminobenzenesulfonamide	34	33	35–36
N-Nitroso-4-hydroxylaminobenzoic acid	15	15–16	22
N-Nitrosophenylhydroxylamine	17–18	23–24	18

usual manner. The results obtained were about one per cent. low.

Anal. Calcd. for $C_6H_7O_4N_3S$: N, 19.35; S, 14.76. Found: N, 18.46; S, 15.04.

N-Acetyl-4-hydroxylaminobenzenesulfonamide.—To 1 g. of 4-hydroxylaminobenzenesulfonamide 10 cc. of acetic anhydride was added. The substance changed its appearance but did not dissolve, while the mixture became warm. After standing for several hours, the mixture was diluted with ethyl acetate. The crystalline substance was filtered and washed with ethyl acetate. It melted at 228°, showed no diazo reaction, and gave a red color with ferric chloride.[8] No diacetyl derivative was formed, as is the case with phenylhydroxylamine.[8]

Anal. Calcd. for $C_8H_{10}N_2O_4S$: S, 13.93. Found: S, 14.21.

O-Acetyl-4-hydroxylaminobenzenesulfonamide, $H_2N\text{-}SO_2C_6H_4NH(OCOCH_3)$.—A 1% aqueous solution of the hydroxylamine was shaken with acetic anhydride and repeatedly extracted with ethyl acetate. The combined extracts were concentrated under diminished pressure and petroleum ether was added. The precipitate thus formed was washed with alcohol and further purified by dissolving in a little methyl alcohol and mixing with petroleum ether. The latter was separated from the alcoholic layer and yielded yellowish crystals of m. p. 138°.

Anal. Calcd. for $C_8H_{10}O_4N_2S$: S, 13.93. Found: S, 13.40.

A solution in aqueous acetic acid is readily diazotized by addition of sodium nitrite; 63–67% was converted to the diazo compound. The calculated value according to equation 3 is 66.7%.

4-Nitrosobenzenesulfonamide.—After separation of the 4-hydroxylaminobenzenesulfonamide a considerable amount of this compound remained in the mother liquor. It was oxidized by addition of an excess of 10% ferric chloride solution. The white precipitate of the nitroso compound thus produced was filtered and crystallized from alcohol; the alcoholic solution was green. The compound did not show a melting point; decomposition started at 155° and was complete at 268°. With diphenylamine–sulfuric acid reagent a vivid red color was formed.

Anal. Calcd. for $C_6H_6O_3N_2S$: S, 17.23. Found: S, 17.45.

4-Hydroxylaminobenzoic Acid.—Seventeen grams of 4-nitrobenzoic acid was dissolved in 350 cc. of water and 10 cc. of 10 *N* sodium hydroxide. After addition of 20 g. of ammonium chloride, the mixture was cooled to 15°, and 15 g. of zinc dust was added gradually with stirring. The temperature rose to 20°. After one-half hour stirring, the zinc sludge was filtered off. To the filtrate hydrochloric acid (sp. gr. 1.12) was added slowly. Amorphous flakes, which separated while the reaction was still neutral, were removed by filtration. Upon addition of more hydrochloric acid to the filtrate, white needles separated; yield 4.8 g. (31% of the calculated amount). The substance did not melt up to 300°, became dark at about 240°; sparingly soluble in cold water; readily in hot water; soluble in alcohol, ether, and ethyl acetate; not soluble in petroleum ether. Fehling solution is reduced immediately at room temperature.

Anal. Calcd. for $C_7H_7NO_3$: N, 9.15. Found: N, 9.15.

N-Acetyl-4-hydroxylaminobenzoic Acid.—To a solution of 1 g. of 4-hydroxylaminobenzoic acid in ether, acetic anhydride was added: colorless crystals separated, 0.6 g.: melted at 210° with darkening and decomposition; gave an intense red color with ferric chloride.

Anal. Calcd. for $C_9H_9O_4N$: N, 7.18. Found: N, 7.11.

N-Nitroso-4-hydroxylaminobenzoic Acid.—To an ice-cold solution of 1.5 g. of 4-hydroxylaminobenzoic acid in 400 cc. of water, 10.5 cc. of 2 *N* hydrochloric acid and 9 cc. of *N* sodium nitrite solution were added. A white, amorphous precipitate separated, 1.3 g. It did not melt up to 270°, but decomposed gradually with blackening. With ferric chloride solution a red color was produced. When dissolved in glacial acetic acid and coupled with Marshall's reagent,[6] about 15% of diazo compound was formed (Table II).

Coupling of Hydroxylamines.—For colorimetric determination of diazo compound formed by diazotization of hydroxylamines, the procedure of Bratton and Marshall[6] was used with slight modifications. Treatment of hydroxylamines with acetic anhydride before diazotizing increases the amount of diazo compound formed (Table I). N-Nitrosohydroxylamines, when dissolved in glacial acetic acid, spontaneously form diazo compounds (Table II).

Summary

Nitrous acid acts upon 4-hydroxylaminobenzenesulfonamide with formation of N-nitroso-4-hydroxylaminobenzenesulfonamide. The latter, when dissolved in glacial acetic acid, is partly transformed to diazobenzenesulfonamide. 4-Hydroxylaminobenzoic acid and phenylhydroxylamine behave the same way. To some degree, dilute solutions of hydroxylamines form the corresponding diazo derivative with nitrous acid. By treating dilute solutions of hydroxylamines with acetic anhydride before diazotization, an increase of diazo compound was obtained. It was found that acetylation yields two derivatives. The

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derivative which gives the diazo reaction was isolated. It contains the acetyl group presumably linked to the oxygen of the hydroxylamino group. The other derivative is acetylated on the nitrogen and cannot be diazotized. The application of this reaction to the detection of hydroxylaminobenzenesulfonamide in body fluids is discussed. The preparation of 4-nitrosobenzenesulfonamide is described.

BETHESDA, MD. RECEIVED JANUARY 6, 1944

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Gliotoxin, the Antibiotic Principle of *Gliocladium fimbriatum*. II. General Chemical Behavior and Crystalline Derivatives[1]

BY WILLIAM F. BRUCE, JAMES D. DUTCHER,[2] JOHN R. JOHNSON AND LEON L. MILLER[3]

In a preliminary examination of the chemical behavior of gliotoxin, Weindling[4] has observed that in spite of its nitrogen content, gliotoxin has no basic properties. By prolonged heating with acid, it was slowly converted to a gum from which none of the original material could be recovered. In a partition between ether and 1% potassium hydroxide, practically none of the gliotoxin was dissolved in the alkaline layer. This showed the non-acidic nature of the material. It was, however, rapidly altered by treatment with alkali. Boiling with 5% potassium hydroxide rapidly eliminated sulfur and, even in the ether partition, a large proportion of the material was altered. Gliotoxin was found strongly reducing toward permanganate.

To extend these observations, a quantitative study of the effect of alkali on gliotoxin seemed desirable. By connecting a trap containing 0.1 *N* hydrochloric acid with a refluxing alkaline suspension of gliotoxin, evolution of a volatile base was readily demonstrated. On evaporation of the acid solution, a hydrochloride and from it a chloroplatinate were prepared which showed that the volatile base was methylamine, and in an amount which accounted for about half the nitrogen in the sample. The amount of sulfur liberated as sulfide by the action of alkali was then determined by acidification and steam distillation of the solution which remained. From 40–60% of the total sulfur was liberated as hydrogen sulfide, and some as elementary sulfur. In the non-volatile portion, a red amorphous solid remained, insoluble in acid, but soluble in alkali, containing nitrogen and sulfur. By using barium hydroxide in place of sodium hydroxide, the same volatile products were observed, but the residue was not as highly colored. On purification by sublimation *in vacuo*, it yielded a small amount of crystalline solid. This solid, slightly soluble in water, dissolved readily in sodium bicarbonate solution, and formed a silver salt, methyl and ethyl esters through which it was identified as indole-2-carboxylic acid.

Gliotoxin proved inert toward phenyl isocyanate, either when refluxed in benzene solution or on long standing at ordinary temperature: the original material was recovered unchanged. With diazomethane, methyl iodide and dimethyl sulfate, some reaction may have occurred since none of the original material was recovered; only gums and sirups were obtained.

A Zeisel determination showed the absence of methoxyl or ethoxyl groups. The N-methyl determination[5] was positive in agreement with the isolation of methylamine. No reaction occurred with the carbonyl reagents hydroxylamine, semicarbazide or 2,4-dinitrophenylhydrazine. The Ehrlich reaction, pine splint test, Keller's indole reaction and the ninhydrin reaction were all negative. Clowes' test for $CH_2\begin{matrix}O\\O\end{matrix}$ or $CH_2\begin{matrix}S\\S\end{matrix}$, using phloroglucinol and 50% sulfuric acid,[6] was also negative. Ammoniacal silver nitrate (Tollens reagent) and phosphotungstic acid (Folin reagent) in the presence of sulfite were reduced. These reactions and a positive nitroprusside reaction could be attributed to the products, particularly sulfide, formed as a result of the lability of gliotoxin in alkaline media.

Oxidizing agents such as permanganate, bromine water and sodium hypochlorite rapidly converted the sulfur of gliotoxin to sulfate. Reducing agents, including sodium sulfite, stannous chloride, hydriodic acid, aluminum amalgam, zinc or tin and acid, reduced the sulfur in gliotoxin to hydrogen sulfide. Certain of these procedures will be considered in detail in later papers. By treatment of gliotoxin with mercuric acetate or silver nitrate, *one* sulfur atom was removed. Cupric sulfate, lead acetate, and barium chloride gave no reaction.

A Zerewitinoff determination of active hydrogen in gliotoxin dissolved in pyridine gave somewhat uncertain results, for a rather large blank from the pyridine was observed, and while the blank was constant under given conditions, it was variable with time. It was necessary to use pyridine because gliotoxin is insoluble in the isoamyl ether

(1) First paper, THIS JOURNAL, 65, 2005 (1943).

(2) Du Pont post-doctorate fellow; present address, Squibb Institute for Medical Research, New Brunswick, N. J.

(3) Present address, 134 Westview Terrace, Rochester, N. Y.

(4) Weindling, *Phytopathology*, 26, 1068 (1936).

(5) Herzig and Meyer, *Monatsh.*, 18, 379 (1897).

(6) Clowes, *Z. physiol. Chem.*, 38, 260 (1903).

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used for preparing the Grignard reagent. Our conclusion from this determination is that gliotoxin has two, or perhaps three, active hydrogens.

In attempts to replace these active hydrogens by acyl groups, a solution of gliotoxin in pyridine was boiled with acetic anhydride and with benzoyl chloride, but only gums resulted. By conducting the reaction at room temperature, however, and adding water cautiously, a crystalline dibenzoate was secured. A di-*p*-bromobenzoate and a di-*p*-nitrobenzoate were similarly prepared in crystalline form. No crystalline acetyl derivative was obtained; but by a quantitative acetylation following the method of Shriner,[7] the introduction of one acetyl radical into gliotoxin was established. No reaction with *p*-toluenesulfonyl chloride could be discovered; neither did phthalic anhydride in pyridine or on fusion react with gliotoxin.

From this examination of the chemistry of gliotoxin, the presence of an indole structure appears probable in the original substance, although the yield of indole derivative was low. The ultraviolet absorption spectrum[1] supports this conception, and the consistent isolation of indole-2-carboxylic acid under different conditions of reaction makes it difficult to believe that this product is the result of a secondary reaction. A further study of the alkaline hydrolysis to determine whether the yield of indole derivative can be improved is desirable in order to help remove any doubt on this point. It is worth noting that the benzene ring in the indole nucleus is unsubstituted. This greatly reduces the number of possible locations of the other atoms in gliotoxin. Of the thirteen carbon atoms in the gliotoxin molecule, the indole-2-carboxylic acid fragment accounts for nine. One more is known to be present as a methyl radical attached to nitrogen. The disposition of the remaining three carbons, of two, possibly three, active hydrogens is still unknown; and the relation of the one other nitrogen and of the two sulfur atoms to the portion of the molecule thus far outlined also remains to be elucidated. In the following paper of this series, the position of these three carbon atoms is elucidated by means of a study of the reduction of gliotoxin by hydriodic acid. The arrangement of the functional groups and the nature of the sulfur atoms in gliotoxin will be the subject of subsequent papers.

We wish to thank the Cornell Research Foundation and E. I. du Pont de Nemours and Co. for generous support of this work.

Experimental Part

Alkaline Degradation of Gliotoxin.—To a 10% solution of sodium hydroxide in a Kjeldahl distillation apparatus equipped with a separatory funnel and spray trap was added a weighed sample of gliotoxin. The solution was boiled for an hour and the volatile base collected in standard 0.1 *N* hydrochloric acid. The unused acid was determined by standard 0.1 *N* sodium hydroxide using methyl red as indicator. A receiver containing ammoniacal zinc sulfate was then substituted for that containing the standard acid. After addition of excess 15% sulfuric acid through the funnel, the liberated hydrogen sulfide was distilled into the zinc sulfate solution, the precipitated sulfide was treated with hydrochloric acid and determined iodometrically. The results are presented in Table I.

TABLE I

ALKALINE HYDROLYSIS OF GLIOTOXIN

Sample, mg.	% N volatile with base	% N by analysis[1]	% S volatile with acid	% S by analysis[1]
236.9	3.02	8.27	9.0	19.38
236.1	3.31	8.27	7.7	19.38
146.5	..	8.27	11.6	19.38
210.3	3.25[a]	8.27	..	19.38

[a] Hydrolysis by barium hydroxide.

A small amount of free sulfur steam distilled during the distillation of hydrogen sulfide and was identified by mixed melting point, 118°, with an authentic sample. From 450 mg. of gliotoxin, 130 mg. of a brick red residue insoluble in water or mineral acid remained. It was soluble in sodium hydroxide, contained nitrogen and sulfur, and did not melt, but merely charred gradually.

Concentration of a solution of the volatile base in dilute hydrochloric acid gave a white deliquescent solid melting at 222–225°. This was compared with an authentic sample of methylamine hydrochloride melting at 223–227°; no depression was observed on determination of the mixed melting point. Conversion to the chloroplatinate gave a yellow solid which was analyzed.

Anal. Calcd. for $C_2H_{12}Cl_6N_2Pt$: C, 6.4; H, 3.2; Pt, 41.3. Found: C, 6.12, 6.67; H, 2.96, 3.11; Pt, 41.2, 41.3.

By boiling 500 mg. of gliotoxin with 70 ml. of a 15% solution of barium hydroxide for one and one-half hours, followed by removal of the barium as sulfate, a clear yellow faintly acid solution was obtained. On evaporation to dryness, this yielded 80 mg. of a red-brown but crystalline residue. By subliming this material at 110–120° at 1 mm., 25 mg. of a white crystalline sublimate was secured. This substance melted at 201–202°, reacted with potassium permanganate and bromine water and contained nitrogen but not sulfur.

Anal. Calcd. for $C_9H_7NO_2$: C, 66.1; H, 4.35, N, 8.70. Found: C, 66.5; H, 4.26; N, 8.6.

By adding 5% silver nitrate to a solution of 5 mg. of the substance in water, a flocculent precipitate was obtained.

Anal. Calcd. for $C_9H_6AgNO_2$: Ag, 41.1. Found: Ag, 40.6.

These data give $C_9H_7NO_2$ as the best molecular formula.

The methyl and ethyl esters, each made from 5 mg. of sublimate by the action of the alcohol saturated with hydrogen chloride, melted at 149.5–151.5° and 121–123°, respectively. These data agree with those reported for indole-2-carboxylic acid and its esters,[8] and each of the three substances melted without depression on admixture with the corresponding authentic samples.

Oxidation by Bromine Water.—Into a 1% solution of gliotoxin in acetic acid bromine vapor was aspirated until a definite yellow orange color persisted. After two hours, a slight excess of barium chloride solution was added and the precipitate was digested at 50°, filtered, washed, ignited and weighed. The data are given in Table II.

Reaction of Gliotoxin with Mercuric Acetate and with Silver Nitrate.—To a solution of 50 mg. of gliotoxin in 25 ml. of absolute alcohol was added a solution of 200 mg. of

(7) Shriner, "Quantitative Analysis of Organic Compounds," Edwards Brothers, Inc., Ann Arbor, Michigan, 1935.

(8) Reissert, *Ber.*, **30**, 1045 (1897); Ciamician and Zatti, *ibid.*, **21**, 1931 (1888); Grānacher, Mahal and Gerō, *Helv. Chim. Acta*, **7**, 579 (1924). The ethyl ester reported by Oddo and Sessa, *Gazz. chim. ital.*, **41**, 247 (1911), melting at 107° is not in agreement with an authentic sample prepared from indole-2-carboxylic acid synthesized by the method of Reissert. Our authentic ethyl ester melts at 121–122° and the methyl ester at 150–151°. These values agree with those reported by Grānacher.

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TABLE II

OXIDATION BY GLIOTOXIN BY BROMINE WATER

Sample, mg.	$BaSO_4$, mg.	% S	% S (Carius)
97.8	138.5	19.46	19.37
133.7	190.9	19.60	19.37

mercuric acetate in 10 ml. of alcohol to which 10 drops of acetic acid was added to decrease hydrolysis. After standing in the dark for twenty-four hours, the amorphous, slowly-deposited white complex containing mercuric acetate and mercuric sulfide, when filtered, washed and dried, weighed 90 mg. corresponding to 5.22 mg. of sulfur or 53% of the total sulfur. The filtrate was treated with hydrogen sulfide to remove excess mercury, filtered and evaporated. A resinous sulfur-containing solid remained.

A solution of 100 mg. of gliotoxin in 25 ml. of absolute alcohol was treated with a solution of 350 mg. of silver nitrate in 25 ml. of 95% alcohol. A black precipitate of silver sulfide soon settled out, and a slight silver mirror formed. After an hour, the precipitate was collected on a filter. It weighed 80 mg., corresponding to 10.3 mg. of sulfur, or 53% of the total sulfur in the sample.

Determination of Active Hydrogen.—The sample, dissolved in 10 ml. of anhydrous pyridine, after standing an hour to ensure complete solution and temperature equilibrium, was treated with ethylmagnesium bromide in an apparatus similar to that of Soltys.[9] Gas was at once evolved. After fifteen to twenty minutes the gas evolution subsided and the reaction vessel was warmed at 50° with shaking for five minutes. After the original temperature was established, the volume increase was determined. The data in Table III show that the pyridine gave a high blank. The pyridine was dried over solid potassium hydroxide, kept over barium oxide for a week, and redistilled.[10] The constancy of the blank, determined on the same sample, permitted a reasonably satisfactory estimation of active hydrogen.

TABLE III

DETERMINATION OF ACTIVE HYDROGEN IN GLIOTOXIN BY REACTION WITH ETHYLMAGNESIUM BROMIDE

Sample, mg.	Volume increase, ml.	Active hydrogens
86.6	30.2 (28°, 733 mm. cor.)	2.2
109.7	38.0 (29°, 730 mm. cor.)	3.2
105.5	32.7 (29°, 730 mm. cor.)	2.2
0	15.4 (31°, 730 mm. cor.)	Blank
0	15.3 (29°, 730 mm. cor.)	Blank

The quantitative acetylation method of Shriner[7] was used to determine how many acetyl groups can be introduced into gliotoxin. Two samples of 100 mg. each were dissolved in 1.0 ml. of dry pyridine and 5 ml. of the acetyl chloride–toluene reagent was added. After twelve hours at room temperature water was added and the mixture titrated with 0.1 *N* sodium hydroxide. The two samples showed acetylation equivalent to 3.3 and 3.1 ml. of 0.1 *N* sodium hydroxide, respectively. The average equivalent weight from these data is 312. If the molecular weight is taken to be 326,[1] this represents 1.05 acetyl groups introduced per molecule. No crystalline acetate could be secured from these reactions.

A sample of 55 mg. of gliotoxin was treated with 2.0 ml. of 20% acetic anhydride in pyridine. Water was added after half an hour and the residual acetic acid determined by titration. The combined acetic acid, obtained by difference, was equivalent to 1.5 ml. of 0.1 *N* sodium hydroxide. The equivalent weight per acetyl group is then 366, representing 0.9 acetyl groups on the basis of a molecular weight of 326.

Crystalline Acylation Products of Gliotoxin.—A solution of 1 g. (3.07 millimoles) of gliotoxin in 10 ml. of dry pyridine was cooled in an ice-bath. During an hour 1.4 g. (10 millimoles) of benzoyl chloride was added with stirring. After standing for twelve hours at room temperature, the solution was red-brown and contained a deposit of pyridine hydrochloride. After cooling in an ice-bath, water was added dropwise with stirring. Crystallization was initiated by scratching. After one volume of water was added, the precipitate which formed was allowed to stand for an hour, filtered, washed with alcohol and dried to give 1.5 g. of product. Digestion with hot alcohol removed a yellow impurity. The product was recrystallized from hot chloroform by the addition of methanol, yielding nearly colorless glistening plates melting at 192–193° with decomposition; $[\alpha]^{22}D$ −20° (1% in $CHCl_3$).

Anal. Calcd. for $C_{27}H_{22}N_2O_6S_2$ (dibenzoate): C, 60.70; H, 4.12; N, 12.00; S, 5.25. Found: C, 60.02; H, 3.95; N, 12.26; S, 5.22.

The substance is sparingly soluble in acetone and alcohol, but soluble in pyridine and dioxane. In the latter solvent it appeared to undergo alteration since the specific rotation varied. Recrystallization from acetic acid also caused alteration since the melting point was lowered to 186–188°. The dibenzoate gave no reaction with acetyl chloride in pyridine.

The di-*p*-bromobenzoate of gliotoxin was prepared by a similar procedure from 1 g. of gliotoxin in pyridine and 1.5 g. of *p*-bromobenzoyl chloride. The product crystallized from dioxane solution on addition of water to give 1.8 g. of colorless needles melting at 193° with decomposition; $[\alpha]D$ +20° (1% in $CHCl_3$).[11]

Anal. Calcd. for $C_{27}H_{20}Br_2N_2O_6S_2$ (di-*p*-brombenzoate): C, 46.80; H, 2.90; Br, 23.10. Found: C, 46.50; H, 2.72; Br, 24.17.

The di-*p*-nitrobenzoate was prepared from 326 mg. (1 millimole) of gliotoxin dissolved in pyridine and 930 mg. (5 millimoles) of *p*-nitrobenzoyl chloride in the manner previously described. The product was insoluble in alcohol, ether, or acetone. It crystallized from chloroform, on addition of methanol, in pale yellow prismatic rods which melted with decomposition at 189°; $[\alpha]^{22}D$ +13° (1% in $CHCl_3$).

Anal. Calcd. for $C_{27}H_{20}N_4O_{10}S_2$ (di-*p*-nitrobenzoate): N, 9.0; S, 10.25. Found: N, 9.2; S, 9.84. Calcd. for $C_{34}H_{23}N_5O_{13}S_2$ (tri-*p*-nitrobenzoate): N, 9.05; S, 8.28.

Summary

An investigation of the chemical behavior of gliotoxin has shown that a part of the carbon skeleton probably includes that of indole-2-carboxylic acid. The presence of an N-methyl grouping has been demonstrated. The lability of the sulfur atoms in gliotoxin makes it difficult to secure crystalline reaction products. A number of reactions by which sulfur can be removed have been discovered, including oxidation by bromine water, reaction with mercuric acetate and silver nitrate, and reduction by various acidic and neutral reducing agents. Three crystalline derivatives of gliotoxin have been prepared: the dibenzoate, the di-*p*-bromobenzoate and the di-*p*-nitrobenzoate. In each case the formulation of the product agrees with the formulation of gliotoxin previously proposed.

ITHACA, NEW YORK RECEIVED JANUARY 17, 1944

(9) Soltys, *Mikrochemie*, **20**, 107 (1936).

(10) MacArdle, "Solvents in Organic Chemistry," D. Van Nostrand Co., New York, N. Y., 1925, p. 108.

(11) In a preliminary experiment, a smaller sample of a product was obtained for which the melting point, 189–191°, and specific rotation, $[\alpha]D$ +20° (1% in dioxane), agree with those given above. The analytical values, however, indicated that the substance was a tri-*p*-bromobenzoate. *Anal.* Calcd. for $C_{34}H_{23}Br_3N_5O_{13}S_2$ (tri-*p*-bromobenzoate): C, 46.60; H, 2.63; Br, 27.40; N, 3.20; S, 7.32. Found: C, 46.00; H, 2.62; Br, 27.17; N, 3.07, 3.65; S, 7.91. All subsequent preparations, regardless of the amount of *p*-bromobenzoyl chloride employed, afforded the di-*p*-bromobenzoate.

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[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Gliotoxin, The Antibiotic Principle of *Gliocladium fimbriatum*. III. The Structure of Gliotoxin: Degradation by Hydriodic Acid[1]

BY JAMES D. DUTCHER,[2] JOHN R. JOHNSON AND WILLIAM F. BRUCE

The isolation and general physical properties of gliotoxin, as well as a preliminary study of the nature of the functional groups have been previously described.[1,3] In an effort to elucidate the chemical structure of gliotoxin, it was early observed that the sulfur atoms possess marked lability; this lability made the degradation of gliotoxin to a discrete product very difficult. A reaction was therefore sought which would eliminate the sulfur atoms and leave a more tractable compound with which to work. The reactions which were known to remove sulfur were accordingly examined more closely in order to determine the nature of the organic residue. While the majority of these procedures gave organic products which could not be crystallized, they gave some indication of the nature of the combination of sulfur in gliotoxin and will therefore be described in a later paper. By reduction with hydriodic acid and red phosphorus in glacial acetic acid, a crystalline, neutral, optically inactive organic product (I) was secured. By analysis its empirical formula was found to be $C_{13}H_{12}N_2O_2$. This substance was therefore derived from gliotoxin simply by the apparent loss of two molecules of water and two of hydrogen sulfide, as equation 1 shows

(1) $C_{13}H_{14}N_2O_4S_2 + 6H\ (HI \text{ and } P) \longrightarrow C_{13}H_{12}N_2O_2 + 2H_2S + 2H_2O$

It may be seen from this formulation that both of the sulfur atoms and two of the four oxygen atoms in gliotoxin were eliminated without the loss of any carbon or nitrogen.

The determination of the chemical nature of this reduction product was achieved in the following manner: Treatment with 0.5 *N methanolic* potassium hydroxide at room temperature resulted in reaction with one mole of alkali to yield the salt of a 13-carbon acid of formula $C_{13}H_{14}N_2O_3$, which was characterized by the preparation of the ethyl ester. The equation for this hydrolysis may be written

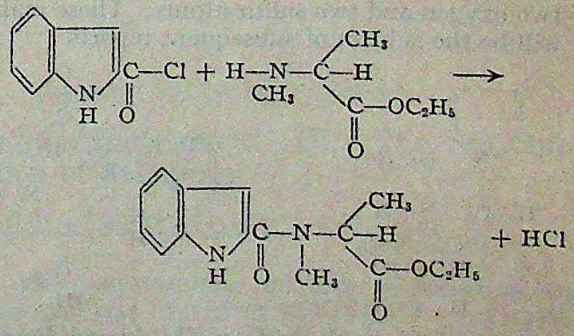
(2) $C_{13}H_{12}N_2O_2 + H_2O \xrightarrow[KOH]{0.5\ N \text{ methanolic}} C_{12}H_{13}N_2OCO_2H$

The formation from the original neutral product of an acid with the same number of carbon atoms is indicative of the presence of a lactam or lactone linkage. Further cleavage of this acid was accomplished by refluxing with 20% *aqueous* potassium hydroxide solution. One mole of alkali was consumed beyond that required for neutralization and from this hydrolysis mixture was isolated in good yield an acid of the composition $C_9H_7NO_2$. The equation for this hydrolysis may be written

(3) $C_{13}H_{14}N_2O_3 + H_2O \xrightarrow[KOH]{20\%\ \text{aqueous}} C_8H_6NCO_2H + C_4H_9NO_2$

This acid was identified as indole-2-carboxylic acid by comparison with an authentic specimen of the free acid. The methyl and ethyl esters of indole-2-carboxylic acid also proved identical with the corresponding derivatives of the hydrolysis product. The isolation of this acid confirmed the presence in gliotoxin of an indole nucleus substituted in the 2-(or α) position.[1]

An examination of the equation 3 shows that a 4-carbon fragment and a nitrogen atom were split off. It was known that one of the nitrogen atoms of gliotoxin bore a methyl group[1] (Herzig–Meyer determination of N-methyl groups) and since indole-2-carboxylic acid which was isolated has an unsubstituted nitrogen atom it could be assumed as a working hypothesis that the four carbon fragment represented an α- or β-methyl-aminopropionic acid residue. Because of the small amount of material available it was not possible to isolate this product from the hydrolysis mixture but verification of the hypothesis was obtained by the synthesis of the ethyl ester of the 13-carbon acid previously mentioned (equation 2) from indole-2-carboxylic acid chloride and *dl*-α-N-methylalanine ethyl ester.

(4) 

Furthermore, it was observed that under suitable conditions this ester of the 13-carbon acid could be cyclized by the elimination of a mole of ethyl alcohol to yield a product identical with I, the neutral product obtained by the hydriodic acid reduction of gliotoxin. In view of both the ready hydrolysis and ease of cyclization of this product there seems little doubt that this cyclization takes place through the imide hydrogen of the indole nitrogen atom.

(1) Second paper, THIS JOURNAL, 66, 614 (1944).

(2) Du Pont post-doctorate fellow; present address, Squibb Institute for Medical Research, New Brunswick, N. J.

(3) Johnson, Bruce and Dutcher, THIS JOURNAL, 65, 2005 (1943).

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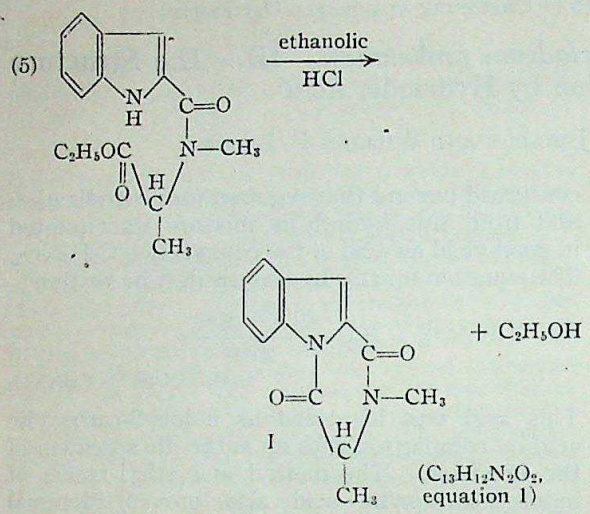
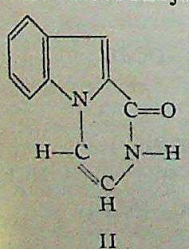


A compound with a similar ring system has been prepared by Kermack, Perkin and Robinson,[4] who found that indole-2-carboxyacetalyl amide cyclized readily to give a compound of formula II.

According to the Ring Index such a system is called pyrazino-[1.2-a]-indole (No. 1630). Employing the preferred numbering of the Ring Index, the compound obtained from gliotoxin is named 2,3-dimethyl-1,4-diketotetrahydropyrazino-[1.2-a]-indole (equation 5). In a later report dealing with the synthesis of various homologs of this neutral degradation product it will be shown more conclusively that the alternative formulation involving cyclization through the 3-(or β)-carbon atom of the indole nucleus to form a carboline derivative corresponding to formula III does not represent the structure of the product (I) derived from gliotoxin.

The elucidation by this means of the complete carbon and nitrogen skeleton of gliotoxin leaves undetermined only the position and function of two oxygen and two sulfur atoms. These matters will be the subject of subsequent reports.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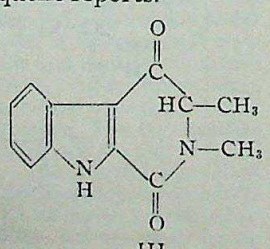
III

We wish to thank the Cornell Research Foundation and E. I. du Pont de Nemours and Co. for generous support of this work.

Experimental

Hydriodic Acid Reduction of Gliotoxin.—One gram of gliotoxin was refluxed in 25 ml. of glacial acetic acid with 1.0 g. of red phosphorus and 1.0 ml. of hydriodic acid, sp. gr. 1.7, until no more hydrogen sulfide was evolved. This required approximately four hours. The hydrogen sulfide which was formed was trapped in alkaline plumbite solution. An amount of lead sulfide equivalent to 96% of the sulfur in the gliotoxin was obtained. The warm acetic acid solution was filtered from excess phosphorus and the filtrate and washings poured into 200 ml. of cold water containing 2.0 g. of sodium bisulfite. The solution was thoroughly extracted with ether and the ether washed free of acetic acid with dilute sodium carbonate solution. After drying over anhydrous sodium sulfate the ether solution was evaporated in vacuum and yielded a pale yellow sirup which weighed 380 mg. After addition of a few drops of ethanol and storage in the ice-chest for several days the sirup crystallized. The crystalline material was washed free of pigmented mother liquor and then recrystallized from ethanol. It was obtained as large, dense, rhombic crystals which melted at 122°.[5] It was optically inactive. This compound was slightly soluble in hot water but insoluble in cold water or dilute acid or alkali solution. It was moderately soluble in most organic solvents. It was readily oxidized by potassium permanganate solution, gave a negative Ehrlich reaction (an alcoholic solution treated with *p*-dimethylaminobenzaldehyde and concentrated hydrochloric acid) and coupled immediately in 1% sodium carbonate solution with diazotized sulfanilic acid to yield a deep orange-red solution.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.40; H, 5.26; N, 12.30. Found: C, 68.25; H, 5.24; N, 12.69.

Hydrolysis of Hydriodic Acid Reduction Product.—A methanol solution of 480 mg. of the compound m. p. 122° was treated with 5.0 ml. of 0.5 *N* methanolic potassium hydroxide at room temperature for four hours. Titration with standard acid showed the consumption of 4.2 ml. of the 0.5 *N* alkali, corresponding to a saponification equivalent of 228. With the assumption that one mole of alkali per mole of compound was consumed, the formula of the substance was $C_{13}H_{12}N_2O_2$, molecular weight 228. The methanolic solution was strongly acidified and concentrated in vacuu to a small volume from which a crystalline precipitate separated. This precipitate, which weighed 320 mg., was recrystallized from acetic acid and was obtained as rosets of colorless needles, m. p. 187°. This compound was shown to be an acid by titration with standard alkali using phenolphthalein as indicator. Neutral equivalents of 247, 250 and 245 were obtained. The formula $C_{12}H_{13}N_2O\cdot CO_2H$ requires a molecular weight of 246.

Anal. Calcd. for $C_{13}H_{14}N_2O_3$: C, 63.40; H, 5.70; N, 11.40. Found: C, 63.23; H, 5.98; N, 11.32, 11.63.

The *ethyl ester* was prepared by refluxing the acid in absolute alcohol with a trace of sulfuric acid. Addition of water to the hot solution caused the precipitation, on cooling, of long shining needles. The ester was recrystallized from aqueous alcohol and from benzene–petroleum ether mixture. It melted at 127°.

Anal. Calcd. for $C_{15}H_{18}N_2O_3$: C, 65.70; H, 6.57; N, 10.22. Found: C, 66.10; H, 6.85; N, 10.51.

The yield of ester was good and there was no evidence of any cyclization under these conditions to yield the neutral product $C_{13}H_{12}O_2N_2$, m. p. 122°. This product was obtained from the same ester, as shown below, under other reaction conditions.

Further Hydrolysis of the Acid $C_{13}H_{14}N_2O_3$.—Two hundred and thirty-three mg. of this acid was dissolved in 5.0 ml. of 20% aqueous potassium hydroxide and refluxed for four hours. A stream of nitrogen was passed through the flask during refluxing and then passed into standard acid solution. It was found that *no* volatile amine was produced during hydrolysis. The cooled solution was made up to 50 ml. in a volumetric flask and 5.0-ml. aliquots titrated. A blank on the alkali was run in the same manner. By subtracting one equivalent of alkali for the neutralization of the original carboxyl group, a saponification equivalent of 233 was obtained, in good agreement with the molecular weight of the acid, 246. After acidification of the entire solution, the material was concentrated in

(4) Kermack, Perkin and Robinson, *J. Chem. Soc.*, **119**, 1602 (1921).

(5) All m. p.'s are uncorrected.

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vacuum. At a small volume a colorless product crystallized out. This product was filtered off, washed with water and recrystallized from acetic acid. The melting point was 204° with sublimation and decomposition; 150 mg. was obtained.

Anal. Calcd. for $C_9H_7NO_2$: N, 8.70; neut. equiv., 161. Found: N, 8.67; neut. equiv., 160, 165.

The **methyl ester** was prepared by refluxing for one hour with methanol and a trace of sulfuric acid. It crystallized from aqueous acetone as platelets; m. p. 151°.

Anal. Calcd. for $C_{10}H_9NO_2$: N, 8.00. Found: N, 8.02.

The **ethyl ester** was prepared in a similar way with ethanol and sulfuric acid. Needles were obtained on recrystallization from aqueous ethanol or benzene–petroleum ether; m. p. 121°.

Anal. Calcd. for $C_{11}H_{11}NO_2$: N, 7.40. Found: N, 7.36.

These compounds were proved to be identical with indole-2-carboxylic acid, m. p. 204°, indole-2-carboxylic acid methyl ester, m. p. 151°, and indole-2-carboxylic acid ethyl ester, m. p. 122°, by mixed melting point determinations with synthetic samples.

Synthesis of the Hydriodic Acid Reduction Product of Gliotoxin.—After the isolation of indole-2-carboxylic acid from the strong aqueous alkaline hydrolysis of the 13-carbon acid it was found impossible to obtain any further crystalline material. In view of the possibility that the remainder of the molecule might be either α- or β-N-methylalanine the following synthesis was carried out. Indole-2-carboxylic acid was synthesized by the method of Reissert[6] and converted to the acid chloride by the action of thionyl chloride. To 25 ml. of dry ether containing 1.0 g. of thionyl chloride, 175 mg. of finely powdered indole-2-carboxylic acid was slowly added. Solution occurred readily and after all the acid had been added the mixture was allowed to stand at room temperature for forty minutes before the ether and excess thionyl chloride were removed in vacuum. The slightly pigmented semi-crystalline residue was redissolved in dry ether and used without further purification since it decomposed readily. Since the 13-carbon acid obtained from gliotoxin possessed no optical activity, inactive α-N-methyl alanine ethyl ester, prepared by the method of Zelinsky, *et al.*,[7] was used. An ethereal solution of 175 mg. of this ester was added to the solution of indole-2-carboxylic acid chloride. The mixture warmed slightly and became cloudy. It was allowed to stand at room temperature for one hour after which the ether and excess amino acid ester were removed in vacuum. The crystalline residue was taken up in absolute alcohol and recrystallized by the addition of water to the warm solution. Colorless needles melting at 126° were obtained. The yield was 148 mg. and represented 55% of the theoretical yield on the basis of the indole-2-carboxylic acid used.

This synthetic ester agreed exactly in all properties with the ester of the 13-carbon acid and showed no depression in a mixed melting point determination. On saponification it yielded the identical 13-carbon acid; m. p. 187°.

It was observed in a second preparation of this ester that if the alcoholic solution of the initial condensation product of the indole-2-carboxylic acid chloride and *dl*-α-N-methyl alanine ester was allowed to stand for thirty-five hours, instead of obtaining the open chain ester of the 13-carbon acid, a product melting at 122° and identical with the hydriodic acid reduction product of gliotoxin was obtained. The presence of a small amount of hydrochloric acid was apparently responsible for this cyclization since the addition of solid sodium carbonate to the ethereal solution, after condensation, to remove all traces of hydrochloric acid prevented the cyclization. The neutral, cyclized product was then obtained from the ester by allowing an alcoholic solution containing 1% hydrochloric acid to stand for forty-eight hours. From 750 mg. of indole-2-carboxylic acid, 525 mg. of the cyclized product was obtained; this represents 50% of the theoretical yield.

(6) A. Reissert, *Ber.*, **30**, 1036 (1897).

(7) Zelinsky, Annenkoff and Kulikoff, *Z. physiol. Chem.*, **73**, 468 (1911).

Summary

Treatment of gliotoxin with phosphorus and hydriodic acid in acetic acid gave a crystalline product in which analysis showed that no sulfur and two less oxygen atoms were present; but the same number of carbons as in gliotoxin were found. This product was degraded stepwise to N-(indole-2-carboxoyl)-N-methyl-α-alanine and to indole-2-carboxylic acid. The crystalline reduction product, 2,3-dimethyl-1,4-diketotetrahydropyrazino-[1,2-a]-indole (I) and the several degradation products have been identified by synthesis.

ITHACA, N. Y. RECEIVED JANUARY 20, 1944

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Gliotoxin, the Antibiotic Principle of *Gliocladium fimbriatum*. IV. The Structure of Gliotoxin: The Action of Selenium

BY JAMES D. DUTCHER,[1] JOHN R. JOHNSON AND WILLIAM F. BRUCE

In seeking to establish the structure of gliotoxin, the antibiotic substance produced by the fungus *Gliocladium fimbriatum*,[2] a distillation with selenium was carried out. A curious but informative reaction occurred which yielded a product that shed considerable light upon the structure of the gliotoxin molecule and served to verify the observations previously reported for the hydriodic acid reduction of gliotoxin.[3]

When an intimate mixture of selenium and gliotoxin was heated at 230 to 250° a crystalline sublimate was obtained which analysis showed to have the formula $C_{12}H_8N_2O_3$. Sulfur, hydrogen sulfide and water were the only other products of the reaction which were observed, but under the conditions of the reaction carbon dioxide formaldehyde or methane might have been overlooked. Expressed in the form of an equation the reaction was

$$C_{13}H_{14}N_2O_4S_2 \xrightarrow[250°]{Se} C_{12}H_8N_2O_3\ (II) + 2H_2S + [C] + H_2O$$

(1) Du Pont post-doctorate fellow; present address, Squibb Institute for Medical Research, New Brunswick, N. J.

(2) Johnson, Bruce and Dutcher, THIS JOURNAL, **65**, 2005 (1943).

(3) Dutcher, Johnson and Bruce, *ibid.*, **66**, 617 (1944).

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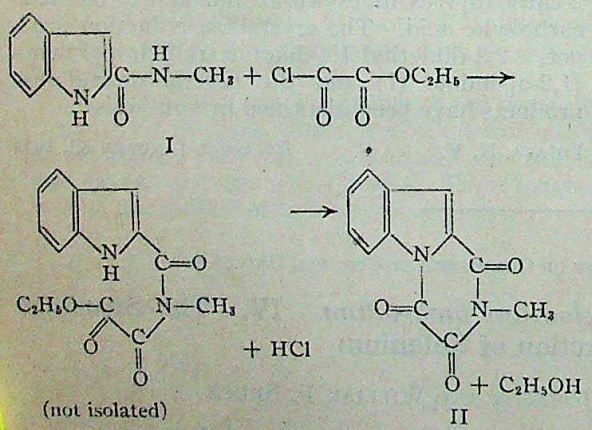
The structure of this product, II, was determined by means of alkaline hydrolysis. It was found to be split rapidly by methanolic potassium hydroxide at room temperature; approximately two moles of alkali were consumed. The product isolated from this hydrolysis was a neutral compound (I) possessing the formula $C_{10}H_{10}N_2O$. The equation for this reaction is

$$C_{12}H_8N_2O_3 + 2H_2O \xrightarrow[\text{methanol}]{KOH} C_{10}H_{10}N_2O(I) + H_2C_2O_4$$

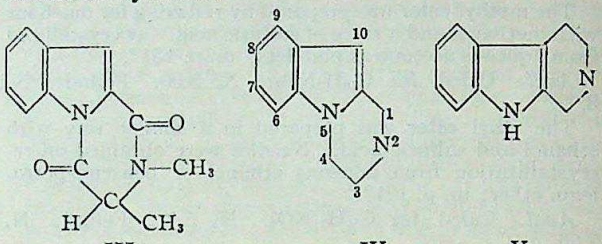
The neutral 10-carbon compound yielded indole-2-carboxylic acid and methylamine on vigorous hydrolysis with 25% aqueous potassium hydroxide. That I was the methyl amide of indole-2-carboxylic acid was shown by comparison with a synthetic sample. The other product of the original hydrolysis appeared from the equation to be oxalic acid although it was not isolated.

The structure assigned to the selenium degradation product is shown in formula II. This structure was proved by the synthesis of II from the methyl amide of indole-2-carboxylic acid and ethyl oxalochloride. When these two compounds were condensed in the presence of pyridine the product which was obtained was identical in all respects with the material obtained from gliotoxin by distillation with selenium. This synthesis is similar to that by which the hydriodic acid reduction product of gliotoxin, 2,3-dimethyl-1,4-diketotetrahydropyrazino[1,2-a]-indole (III), was prepared[3] and the reaction may be represented as follows



It has thus been possible to obtain by two different procedures degradation products of gliotoxin whose structures have been proved by synthesis. Both of these products contain the same tricyclic nucleus, IV, which according to the Ring Index No. 1630 is called pyrazino-[1.2-a]-indole. The selenium degradation product is therefore named 2-methyl-1,3,4-triketotetrahydropyrazino-[1.2-a]-indole. As in the synthesis of III,[3] the readiness with which the ring is opened and closed makes improbable the alternative mode of cyclization (V).

The action of selenium in splitting off a carbon atom from C_3 is difficult to explain in this particular case although it is well known that methyl groups are split off by this reagent in the dehydrogenation of sterols and polyterpenes to yield aromatic systems.[4]



We wish to thank the Cornell Research Foundation and E. I. du Pont de Nemours and Co. for generous support of this work.

Experimental

Selenium Distillation of Gliotoxin.—One gram of powdered gliotoxin was intimately ground with 5.0 g. of powdered black selenium. The gray mixture was placed in the bottom of a 50-ml. Erlenmeyer flask equipped with a short air condenser and heated in a metal bath. At approximately 200° water vapor and a yellow sublimate, apparently sulfur, began to come off. The mix was held at this temperature until all the water was off. The temperature was then allowed to rise gradually; at 230° a yellow, crystalline sublimate began to appear on the walls of the flask just above the surface of the melt. This product was collected over a period of one hour. When no more formed the temperature was raised to 250° but without further yield of product. About 50 mg. of crude sublimate was obtained. An additional 50 mg. of this compound was obtained by pulverizing the cooled melt in an iron mortar, extracting the powder in a Soxhlet with benzene and resubliming the benzene residue. Recrystallization of the combined sublimate from acetic acid gave rhombic plates with a pale yellow color, m. p. 253–255° with sublimation.[5]

Anal. Calcd. for $C_{12}H_8N_2O_3$: C, 63.20; H, 3.51; N, 12.30. Found: C, 63.40; H, 3.57; N, 12.38.

This product (II) was insoluble in water or dilute aqueous acid or alkali. It was insoluble in cold ethanol, methanol or ether and only slightly soluble in a large volume of hot ethanol. It was somewhat more soluble in acetone, benzene and chloroform, and dissolved readily in pyridine or dioxane. It was insoluble in concentrated hydrochloric acid but dissolved unchanged in concentrated sulfuric acid from which it was precipitated by the addition of water.

Alkaline Hydrolysis of the Selenium Sublimate.—A suspension of 75 mg. of the yellow crystals in 2.0 ml. of methanol was treated with 5.0 ml. of 1 *N* methanolic potassium hydroxide. The crystalline material dissolved on gentle warming. After standing for half an hour at room temperature the excess alkali was back-titrated with standard acid; 0.65 ml. of 1 *N* alkali had been consumed. Saponification equivalent found, 115; since the molecular weight for $C_{12}H_8N_2O_3$ is 228, two moles of alkali per mole of sublimate were used. The neutral solution was then concentrated in vacuum until all of the methanol had been removed. The colorless, crystalline precipitate (I) which had separated from the aqueous solution was filtered off, dried and recrystallized from benzene. Long, glistening

(4) L. Ruzicka and Thomann, *Helv. Chim. Acta*, **16**, 216 (1933); L. Ruzicka, Goldberg and Thomann, *ibid.*, **16**, 812 (1933); *ibid.*, **17**, 200 (1934); Harper, Kon and F. C. J. Ruzicka, *J. Chem. Soc.*, 124 (1934).

(5) All melting points are uncorrected.

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needles were obtained which melted at 220° with sublimation. The yield was 55 mg. corresponding to 96% of the theoretical.

Anal. Calcd. for $C_{10}H_{10}N_2O$: C, 69.00; H, 5.75; N, 16.10. Found: C, 69.19; H, 5.89; N, 16.40.

Picrate.—The picrate of this neutral hydrolysis product was obtained by adding a solution of picric acid in benzene to a hot benzene solution of the compound. The picrate separated on cooling as long, deep red needles which melted at 168–170° with decomposition.

Anal. Calcd. for $C_{16}H_{13}N_5O_7$: N, 17.35. Found: N, 17.36.

Iodo Derivative.—The iodo derivative was easily prepared by adding a solution of iodine in potassium iodide to a dilute solution of the compound in 5% aqueous sodium hydroxide. It crystallized in clusters of long colorless needles, m. p. 186°. It was soluble in alcohol and acetone, insoluble in water, and quite stable under ordinary conditions.

Anal. Calcd. for $C_{10}H_9IN_2O$: I, 42.30. Found: I, 42.31.

Hydrolysis of Compound $C_{10}H_{10}N_2O$.—Forty mg. of the product of methanolic alkaline hydrolysis, $C_{10}H_{10}N_2O$ (I), was refluxed for two hours with a 25% aqueous solution of potassium hydroxide. Nitrogen was passed through the solution during the hydrolysis and the volatile base trapped in hydrochloric acid. This base was identified as monomethylamine by preparation of the hydrochloride and the chloroplatinate. From the alkaline solution indole-2-carboxylic acid was isolated in good yield. It melted at 204° and did not depress the melting point of an authentic sample.

Synthesis of Indole-2-carboxylic Acid Methyl Amide (I).—To confirm the identity of the neutral $C_{10}H_{10}N_2O$ product with indole-2-carboxylic acid N-methyl amide this compound was synthesized by the following two methods. 1. Indole-2-carboxylic acid chloride was prepared in the manner previously described[3] and was condensed in benzene solution with methylamine. Long, lustrous needles were obtained on recrystallization from benzene and melted at 219° with sublimation. No depression was observed in a mixed m. p. determination with the neutral product derived from gliotoxin. 2. The methyl amide was also obtained in good yield when indole-2-carboxylic acid ethyl ester reacted with a concentrated alcoholic solution of methylamine. The monomethyl amide of indole-2-carboxylic acid was readily soluble in ethanol, methanol and acetone; less soluble in cold benzene but soluble in hot benzene; it dissolved in hot water and crystallized out on cooling as lustrous, hexagonal platelets. It absorbed bromine in acetic acid solution to yield a crystalline bromo derivative, m. p. 185°. The iodo derivative was described above. The methyl amide coupled in alkaline solution with diazotized sulfanilic acid to form a deep orange-red solution; it gave a positive Ehrlich reaction (*p*-dimethylaminobenzaldehyde and concentrated hydrochloric acid).

Synthesis of the Selenium Degradation Product, $C_{12}H_8N_2O_2$ (II).—Although oxalic acid was not isolated from the hydrolysis products of the selenium sublimate, in view of the structure established for the remainder of the molecule, there was little doubt but that this dicarboxylic acid represented the missing fragment. This assumption was fully justified by the synthesis of the selenium degradation product (II) in the following manner.

Six hundred mg. of indole-2-carboxylic acid methyl amide (I) was dissolved in 10 ml. of dry pyridine and 25 ml. of dry ether added; to this solution was added slowly and with cooling a solution of 600 mg. of ethyl oxalochloride in 25 ml. of anhydrous ether. As the two solutions were mixed, a crystalline precipitate was formed which consisted partially of unchanged amide and partially of pyridine hydrochloride. The mixture was allowed to stand at room temperature for fifteen hours. The crystalline material was removed by filtration and the filtrate evaporated in vacuum. The sirupy residue crystallized upon the addition of ethanol; 115 mg. of pale yellow rhombs was obtained, m. p. 255°. The mother liquors contained some unchanged amide which was recovered and some non-crystalline oil, which probably represented uncyclized condensation products. The synthetic compound was identical in every respect with that isolated from gliotoxin. A mixed m. p. determination showed no depression.

Summary

The degradation of gliotoxin by selenium has been shown to yield 2-methyl-1,3,4-triketotetrahydropyrazino-[1.2-a]-indole. The structure of this substance has been determined by degradation and by synthesis. This formulation is in agreement with the structure of the product of the hydriodic acid reduction of gliotoxin previously published.

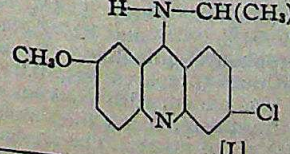
ITHACA, N. Y. RECEIVED JANUARY 20, 1944

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

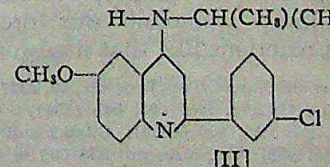
Some Quinolines Patterned as "Open Models" of Atabrine

BY HENRY GILMAN AND SYDNEY M. SPATZ[1]

It seemed of interest to prepare some so-called open models of atabrine [I] in connection with studies on attempted correlations of constitution with antimalarial action. One of these models is 6-methoxy-2-(3′-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-quinoline [II]. This compound has a chlorophenyl group in place of the fused chlorobenzo group in atabrine.



[I]



[II]

Compound [II] was synthesized by the sequence of reactions shown beyond.

The over-all yield is quite satisfactory. *m*-Chlorophenyllithium was prepared in 70% yield

(1) Present address: National Aniline Division, Allied Chemical and Dye Corporation, Buffalo, New York.

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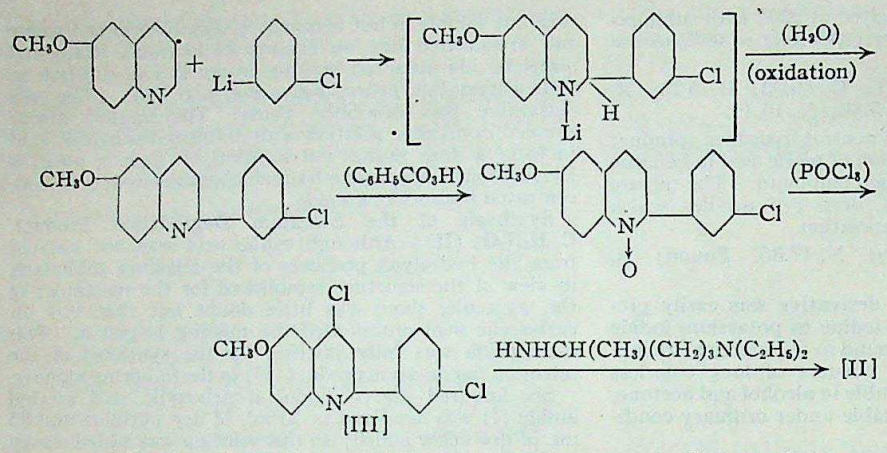


by the following halogen-metal interconversion reaction, which recent[2] related studies show to be of broad applicability for the preparation of a wide variety of substituted aryllithium compounds.

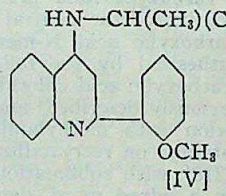
$$m\text{-ClC}_6\text{H}_4\text{Br} + n\text{-C}_4\text{H}_9\text{Li} \longrightarrow m\text{-ClC}_6\text{H}_4\text{Li} + n\text{-C}_4\text{H}_9\text{Br}$$

4 - Chloro - 6 - methoxy - 2 - (3′ - chlorophenyl)-quinoline [III] was also prepared from 4-chloro-6-methoxyquinoline and *m*-chlorophenyllithium, thereby establishing the position of N-oxide halogenation. It is interesting to note in connection with this reaction that the γ-quinolyl chlorine which is sufficiently reactive to undergo condensation with 1-diethylamino-4-aminopentane, but relatively unreactive toward the RLi compound, does not show any deactivating effect on the anil linkage.[3] The use of substituted RLi compounds provides, in general, a better approach than other more involved procedures hitherto used for the preparation of variously substituted aryl-quinolines.

Although a shift of the chlorine from the 6-position to the 7-position in atabrine extinguishes the antimalarial action,[4a] there was no basis for predicting the effect of a compound in which the *m*-chlorophenyl group of [II] was replaced by a *p*-chlorophenyl group. It is known that 6-chloro-8-dialkylaminoalkylaminoquinolines are weakly active in avian malaria, but a shift of the chlorine atom to the 7-position confers increased activity upon the molecule. Accordingly, 6-methoxy-2-(4′-chlorophenyl) - 4 - [(α - methyl - δ - diethylaminobutyl) - amino] - quinoline was prepared by a sequence of reactions like that used for [II], *p*-chlorophenyllithium being used in place of *m*-chlorophenyllithium. This compound, as well as [II], showed *antimalarial* activity.

This suggested an examination of a chlorine-free type, because some quinoline antimalarials are known to retain their biologic effect without the presence of a chlorine. 6 - Methoxy - 2 - phenyl - 4 - [(α - methyl - δ - diethylaminobutyl) - amino]-quinoline was synthesized, and found to be active in experimental malaria.

Although the positions of the chlorine in the new compounds previously mentioned are without appreciable effect, the position of the methoxy group is important. A chlorine-free compound having the methoxy group in the phenyl and not in the quinolyl nucleus was prepared. This 2-(2′ - methoxyphenyl) - 4 - [(α - methyl - δ - diethylaminobutyl) - amino] - quinoline [IV] was found to be inactive.



Experimental

***m*-Chlorophenyllithium.**—To a vigorously stirred, clear filtered solution of 0.2 mole of *n*-butyllithium in 250 cc. of ether, cooled to −35°, was added 38.3 g. (0.2 mole) of *m*-chlorobromobenzene in 50 cc. of ether. Fifty-cc. aliquots were withdrawn at three-minute intervals and carbonated with finely powdered dry-ice. The yields of *m*-chlorobenzoic acid were: 50.3% (3 min.); 66% (6 min.); 69.7% (9 min.); 67.7% (12 min.); and 48.4% (16 min.). Therefore, the optimal yield of this RLi compound at −35° is obtained over a range of six to twelve minutes. From a related experiment at room temperature and for a twelve minute period, the yield of crude *m*-chlorobenzoic acid was 29.4%. Mr. Wright Langham obtained 50% of crude acid (m. p. 145–149°) or 42% of purer acid (m. p. 149–151°) by the rapid addition at room temperature of 0.03 mole of *n*-butyllithium to 0.02 mole of *m*-chlorobromobenzene, with carbonation being carried out at the end of two minutes.

Temperature Effect on Addition of *m*-Chlorophenyllithium to 6-Methoxyquinoline.—These addition reactions were carried out as an index to the more favorable temperature of addition of the RLi compound to some of the quinolines. The yields of anil addition product (2-*m*-chlorophenyl-6-methoxyquinoline) were: 11.1% (−35°); 29.6% (−7 to −5°); 49–54% (0°); and 16.7% (36°).

6-Methoxy-2-(3′-chlorophenyl)-quinoline.—To a solution of *m*-chlorophenyllithium (prepared from 0.2 mole of *m*-chlorobromobenzene) was added, with vigorous stirring and in a dry nitrogen atmosphere, 15.9 g. (0.1 mole) of 6-methoxyquinoline in 100 cc. of ether. The ice-bath was removed, and stirring was continued for ten minutes. After hydrolyzing by pouring the entire reaction mixture into ice water, the ether layer was separated, concentrated

(2) Gilman, Langham and Moore, THIS JOURNAL, **62**, 2327 (1940); Langham, Brewster and Gilman, *ibid.*, **63**, 545 (1941); Gilman, Langham and Jacoby, *ibid.*, **61**, 106 (1939); Gilman and Jacoby, *J. Org. Chem.*, **3**, 108 (1938); see, also, pp. 538–539 in Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y. (1943) for some newer illustrations.

(3) Gilman and Spatz, THIS JOURNAL, **62**, 446 (1940), and *ibid.*, **63**,1553 (1941).

(4) (a) Krichevskii, Shternberg and Halperin, *J. Microbiol. Epidemiol., Immuniol.*, (U. S. S. R.), **14**, 642 (1935) [*C. A.*, **30**, 4218 (1936)]; Magidson and Grigorovskii, *Ber.*, **69B**, 396 (1936); Feldman and Kopeliovich, *Org. Chem. Ind.*, (U. S. S. R.), **1**, 31 (1936) [*C. A.*, **30**, 3821 (1936)]; (b) Magidson and Bobyshev, *J. Gen. Chem.* (U. S. S. R.), **8**, 899 (1938) [*C. A.*, **33**, 3217 (1939)].

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to about one-half the volume, and to this solution was added a hot alcoholic solution of 27 g. of picric acid. The picrate was filtered off (after chilling the solution in an ice box overnight), dried, and decomposed by boiling with dilute alkali. The crude red-brown product was dissolved in hot benzene–petroleum ether (b. p. 60–70°) mixture and separated from an insoluble dark-colored gum by filtration. On cooling, there was obtained 11.9 g. of almost colorless crystals of 6-methoxy-2-(3′-chlorophenyl)-quinoline melting at 110–111°. An additional 1.4 g. from the filtrate gave a total yield of 49.3%. From a duplicate experiment, the yield was 53%. When the synthesis was carried out at −35°, the yield was only 11.1%; and a preparation at room temperature gave 16.7%.

Anal. Calcd. for $C_{16}H_{12}ONCl$: N, 5.20. Found: N, 5.28.

The **picrate,** prepared in a customary manner, as glistening yellow crystals, melted at 196–197°.

Anal. Calcd. for $C_{22}H_{15}O_8N_4Cl$: N, 11.24. Found: N, 11.35.

6-Methoxy-2-(3′-chlorophenyl)-quinoline-N-oxide.—A 700 cc. chloroform solution of 32.5 g. (0.12 mole) of 6-methoxy-2-(3′-chlorophenyl)-quinoline and 32 g. (0.23 mole) of perbenzoic acid was kept in an ice box for three days. The ruby red solution was concentrated to a volume of about 250 cc., diluted with 100 cc. of ethanol, brought to a boil and then added with stirring to a hot concentrated alcoholic solution of 32 g. of hydrated picric acid. On cooling, the yellow crystalline picrate (m. p. 155–158°) precipitated. The unrecrystallized picrate was dried and then decomposed by dilute alkali to yield 25 g. (73%) of the crude N-oxide (m. p. 147–149°). Recrystallization from a 1:1 alcohol–benzene mixture gave 23 g. (67%) of N-oxide melting at 153–154°.

Anal. Calcd. for $C_{16}H_{12}O_2NCl$: N, 4.91. Found: N, 4.99.

The **picrate,** prepared in hot alcohol solution from the N-oxide, separated on cooling as pale yellow rosets melting at 158.5–159°.

Anal. Calcd. for $C_{22}H_{15}O_9N_4Cl$: N, 10.89. Found: N, 10.96.

4-Chloro-6-methoxy-2-(3′-chlorophenyl)-quinoline.—Ten grams (0.035 mole) of 6-methoxy-2-(3′-chlorophenyl)-quinoline-N-oxide was treated with 43 g. (0.28 mole) of phosphorus oxychloride. Reaction was instantaneous, and the mixture was heated, first on a water-bath for ten minutes, and then gently over asbestos for twenty minutes. The mixture was then poured upon 300 g. of chopped ice, and the crude chlorination product filtered off. An additional quantity was obtained by making the filtrate alkaline. Crystallization from a 3:1 ethanol–pyridine mixture gave a product melting at 153–154°. The yield was 6.7 g. (63.2%). A mixed m. p. with the parent N-oxide (which melts at the same temperature) was 129–133°. From a second preparation, the yield was 63.8%.

Anal. Calcd. for $C_{16}H_{11}ONCl_2$: N, 4.61. Found: N, 4.77.

The same compound (mixed m. p.) was obtained by interaction of 1.1 g. (0.0057 mole) of 4-chloro-6-methoxyquinoline and *m*-chlorophenyllithium in ether in a yield of 34.7%.

6-Methoxy-2-(3′-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-quinoline.—Four grams of 4-chloro-6-methoxy-2-(3′-chlorophenyl)-quinoline and 5.0 g. (2.4 equivalents) of 1-diethylamino-4-aminopentane were heated at 200–205° for 100 hours. The melt was worked up in the manner described later for the preparation of the 4′-chlorophenyl isomer. The 6-methoxy-2-(3′-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-quinoline was obtained as a yellow, amorphous powder in a yield of 3.4 g. (60.7%).

Anal. Calcd. for $C_{26}H_{32}ON_3Cl$: N, 9.87. Found: N, 9.63.

The compound is soluble in cold ethanol, forming a brown solution with a marked greenish fluorescence. It is also soluble in cold acetone and in cold benzene with red-blue fluorescence, but difficultly soluble in ether.

6-Methoxy-2-(4′-chlorophenyl)-quinoline.—To an ether solution of *p*-chlorophenyllithium (prepared from 0.2 mole of *p*-chlorobromobenzene) was added a solution of 27 g. (0.18 mole) of 6-methoxyquinoline in 30 cc. of ether. The addition was over a two-minute period, and stirring was continued for an additional five minutes. The orange colored, crystalline intermediate N-lithium compound settled out immediately. After hydrolysis, the ether layer was dried; and removal of the ether left an oily residue which crystallized on cooling to long needles melting at 194–195°. Recrystallization from an ethanol–pyridine mixture did not raise the melting point. The yield was 23 g. (50.2%).

Anal. Calcd. for $C_{16}H_{12}ONCl$: N, 5.20; Cl, 13.15. Found: N, 5.35; Cl, 12.99.

The **picrate,** prepared from a hot glacial acetic acid solution of the quinoline compound and a hot ethanolic solution of picric acid, formed yellow glistening crystals which melted at 205°.

Anal. Calcd. for $C_{22}H_{15}O_8N_4Cl$: N, 11.24. Found: N, 11.30.

6-Methoxy-2-(4′-chlorophenyl)-quinoline-N-oxide.—A tetrachloroethane solution of 19 g. (0.07 mole) of 6-methoxy-2-(4′-chlorophenyl)-quinoline was added slowly with shaking to an ice-cold solution of 18.4 g. (0.13 mole) of perbenzoic acid in 500 cc. of chloroform. Oxidation proceeded slowly as indicated by the gradual conversion of the difficultly soluble parent compound to the more soluble N-oxide. At the end of one week, the red solution was concentrated to a volume of about 400 cc.; and extracted with dilute alkali. After drying and further concentration, the oil was dissolved in ethanol and treated with a slight excess of picric acid in hot alcohol to give 27 g. (73%) of the picrate (m. p. 171–172°). From the picrate and alkali was obtained the N-oxide which after crystallization from ethanol softened at 164° and melted at 166–168°. The yield of pure N-oxide was 11 g. (55%).

Anal. Calcd. for $C_{16}H_{12}O_2NCl$: N, 4.91; Cl, 12.42. Found: N, 4.74; Cl, 12.22.

4-Chloro-6-methoxy-2-(4′-chlorophenyl)-quinoline.—Seven grams (0.025 mole) of 6-methoxy-2-(4′-chlorophenyl)-quinoline-N-oxide was treated with 40 g. (0.26 mole) of phosphorus oxychloride in the manner described for the other chlorination. After hydrolysis, the gummy material solidified to an amorphous body, which after crystallization from hot methanol melted at 163.5–164°. The yield was 5.7 g. (76.5%).

Anal. Calcd. for $C_{16}H_{11}ONCl_2$: N, 4.61; Cl, 23.33. Found: N, 4.72; Cl, 23.06.

A mixed m. p. with a specimen prepared from 6-methoxy-4-chloroquinoline and *p*-chlorophenyllithium in 48% yield showed no depression. A mixed m. p. with the parent N-oxide was 138–145°.

6-Methoxy-2-(4′-chlorophenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-quinoline.—Two and one-half grams of 4-chloro-6-methoxy-2-(4′-chlorophenyl)-quinoline and 2.85 g. (2.2 mole equivalents) of 1-diethylamino-4-aminopentane were heated at 200° for 72 hours. The melt was dissolved in warm ethanol, and added to a slight excess of dilute alkali. The gummy product was dissolved in warm ethanol and precipitated as a yellow amorphous product by the slow addition of water. The yield of dry powdery product was 2.4 g. (69%). The compound is soluble in cold ethanol, forming a brown solution which has a blue-green fluorescence.

Anal. Calcd. for $C_{26}H_{32}ON_3Cl$: N, 9.87. Found: N, 9.72.

2-(2′-Methoxyphenyl)-quinoline.—To an ether solution of *o*-methoxyphenyllithium (prepared by a halogen-metal interconversion starting with 0.26 mole of *o*-bromoanisole, in a three-minute reaction with *n*-butyllithium) was added 28.5 g. (0.22 mole) of freshly distilled quinoline in 30 cc. of ether. The reaction was carried out at −14° over a period

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of about twelve minutes, and hydrolysis was effected by ice water. The picrate, formed from the hydrolyzate, was decomposed by boiling with 5% sodium hydroxide. After distilling off the benzene used to extract the oil, the largest fraction was a heavy yellow oil distilling at 201–204° (2 mm.) (chiefly at 203.5°). The yield was 24 g. (41.2%).

Anal. Calcd. for $C_{16}H_{13}ON$: N, 5.96. Found: N, 6.11.

In two subsequent preparations, approximately the same yields were obtained, an 18% recovery of quinoline was effected, and no *n*-butylquinoline was isolated. Accordingly, it appears that an improved yield might be had by a longer period of reaction of the RLi compound and quinoline at the temperature used.

2-(2′-Methoxyphenyl)-quinoline hydrochloride was prepared in quantitative yield by treating a dry ether solution of the quinoline compound with hydrogen chloride. The hydrochloride is precipitated from an ethanolic solution by dry ether, as cream colored, fine crystals which melt at 184.5–185° with decomposition. The salt is easily hydrolyzed to the free base.

Anal. Calcd. for $C_{16}H_{14}ONCl$: N, 5.16; Cl, 13.06. Found: N, 5.17; Cl, 12.74.

2-(2′-Methoxyphenyl)-quinoline picrate, prepared from either the free base or the hydrochloride, melts at 177–178°.

Anal. Calcd. for $C_{22}H_{16}O_8N_4$: N, 12.07. Found: N, 12.01.

2-(2′-Methoxyphenyl)-quinoline-N-oxide.—A one-liter chloroform solution of 46.4 g. (0.2 mole) of 2-(2′-methoxyphenyl)-quinoline and two equivalents of perbenzoic acid were kept in a refrigerator for two days. The solution was concentrated to a volume of about 300 cc., and to it was added a hot solution of 52 g. of picric acid in 300 cc. of ethanol. The crude picrate, decomposed by dilute alkali, gave a dark tan product. Crystallization from ethanol–water gave 34 g. (68.6%) of large, glassy, tan-colored crystals melting at 178–178.5°.

An alternate procedure for isolating the N-oxide is to concentrate the chloroform solution to one-third its volume; extract with dilute alkali to remove the benzoic acid; dry the chloroform solution over sodium sulfate, and then recrystallize the 16.2 g. of crude residue (after removing the chloroform) from ethanol. The yield was 11.7 g. (64%) of product melting at 178–178.5°.

Anal. Calcd. for $C_{16}H_{13}O_2N$: N, 5.58. Found: N, 5.76.

The **picrate** of 2-(2′-methoxyphenyl)-quinoline-N-oxide melts at 133.5–134°.

Anal. Calcd. for $C_{22}H_{16}O_9N_4$: N, 11.67. Found: N, 11.66.

4-Chloro-2-(2′-methoxyphenyl)-quinoline.—From a reaction between 5.8 g. (0.023 mole) of 2-(2′-methoxyphenyl)-quinoline-N-oxide and 21.5 g. (0.14 mole) of phosphorus oxychloride was obtained 3.5 g. (56.5%) of the 4-chloro compound as pale yellow needles melting at 96–98° after crystallization from petroleum ether (b. p. 60–68°). The compound is very soluble in ethyl ether, hot methanol, and hot ethanol. A mixed m. p. determination with a specimen prepared from *o*-methoxyphenyllithium and 4-chloroquinoline showed no depression.

Anal. Calcd. for $C_{16}H_{12}ONCl$: N, 5.20; Cl, 13.15. Found: N, 5.37; Cl, 12.91.

The **picrate** of 4-chloro-2-(2′-methoxyphenyl)-quinoline melts at 200–201°.

Anal. Calcd. for $C_{22}H_{15}O_8N_4Cl$: N, 11.24. Found: N, 11.19.

Quinoline-N-oxide hydrochloride was prepared with some modifications of the procedure of Meisenheimer.[5] The yield, in the following typical experiment, was practically quantitative. A 600-cc. chloroform solution of 25.2 g. (0.2 mole) of quinoline and 32.2 g. (0.23 mole) of perbenzoic acid was kept in an ice box for thirty-six hours. After concentrating to a volume of about 400 cc., the solution was extracted with 10% hydrochloric acid, and the extract washed with chloroform. The extract was evaporated to dryness under reduced pressure, and the residue was crystallized by dissolving in hot absolute ethanol followed by the addition of anhydrous ether. The product was filtered, after cooling, and dried ***in vacuo*** over calcium chloride. The hydrochloride melted at 130–132°, and the picrate at 142–143°. The 4-chloroquinoline was prepared from the N-oxide by Meisenheimer's[6] procedure, with the yield and m. p. reported by him.

2-(2′-Methoxyphenyl)-4-[(α-methyl-δ-diethylaminobutyl)-amino]-quinoline.—Four grams of 4-chloro-2-(2′-methoxyphenyl)-quinoline and 5.15 g. (2.2 mole equivalents) of 1-diethylamino-4-aminopentane were heated at 190–200° for seventy-five hours. The product was purified by distillation (b. p. 248–255° (0.025 mm.)). The yellow oil cooled at room temperature to a glass-like, transparent substance, and the yield was 4 g. (69%).

Anal. Calcd. for $C_{25}H_{33}ON_3$: N, 10.74. Found: N, 10.56.

6-Methoxy-2-phenylquinoline.—From 12.7 g. (0.08 mole) of 6-methoxyquinoline and 0.1 mole of phenyllithium was obtained 12.4 g. (66%) of pure product, melting at 132–133°. (The m. p. of the picrate was 205°.) These constants agree with those reported by Döbner,[6] who prepared 6-methoxy-2-phenylquinoline by decarboxylation of α-phenylquininic acid; the latter was prepared in an 18% yield from *p*-anisidine, pyruvic acid and benzaldehyde.

6-Methoxy-2-phenylquinoline-N-oxide.—From a reaction between 22.9 g. (0.17 mole) of perbenzoic acid in 400 cc. of chloroform and 26.5 g. (0.11 mole) of 6-methoxy-2-phenylquinoline was obtained, through the picrate, 6-methoxy-2-phenylquinoline-N-oxide as thick, lustrous crystals melting at 170–171° after crystallization from ethanol. The yields were in the range of 55–65%.

Anal. Calcd. for $C_{16}H_{13}O_2N$: N, 5.58. Found: N, 5.66.

4-Chloro-6-methoxy-2-phenylquinoline.—From 15.7 g. (0.063 mole) of 6-methoxy-2-phenylquinoline-N-oxide and 76.5 g. (0.5 mole) of phosphorus oxychloride was obtained 13.7 g. (81%) of 4-chloro-6-methoxy-2-phenylquinoline as long needles melting at 110–111° after crystallization from ethanol. In smaller-sized preparations using 1–5 g. of the N-oxide, the yields were in the range of 88–91%. Incidentally, the over-all yield by our three-stage procedure starting with 6-methoxyquinoline is larger than that obtained by the longer method of John and Lukas.[7]

The same compound (mixed m. p.) was obtained (in 61.5% yield) by the reaction of 4-chloro-6-methoxyquinoline with phenyllithium. The 4-chloro-6-methoxyquinoline, together, coincidentally, with 2-chloro-6-methoxyquinoline, was prepared by the method of Magidson and Rubtsov.[8] The yield of the 4-chloro isomer was 35.5%, and that of the 2-chloro isomer was 58.4%. The necessary precursor, 6-methoxyquinoline-N-oxide hydrochloride, was obtained in 87.5% yield; m. p., 192–194°, and the m. p. of the picrate was 173–174°.[8]

6-Methoxy-2-phenyl-4-[(α-methyl-δ-diethylaminobutyl)-amino]-quinoline.—Four grams of 4-chloro-6-methoxy-2-phenylquinoline and 5.15 g. (2.2 mole equivalents) of 1-diethylamino-4-aminopentane were heated at 135° for twenty-four hours, at 175–180° for twenty-four hours and then at 210° for twenty-four hours. From the glassy melt was obtained (after solution in ethanol and treatment with 2% sodium hydroxide) 4 g. (69%) of a pale tan, amorphous powder, insoluble in water, and soluble in ethanol acetone and benzene. In the latter two solvents the compound exhibits a weak bluish fluorescence.

Anal. Calcd. for $C_{25}H_{33}ON_3$: N, 10.74. Found: N, 10.60.

(5) Meisenheimer, *Ber.*, **59**, 1848 (1926); Meisenheimer and Stotz, *ibid.*, **58**, 2335 (1925).

(6) Döbner, *Ann.*, **249**, 106 (1888).

(7) John and Lukas, *J. prakt. Chem.*, [2] **130**, 328 (1931).

(8) Magidson and Rubtsov, *J. Gen. Chem.* (U. S. S. R.), **7**, 1896 (1937); *C. A.*, **32**, 564 (1938).

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Acknowledgments.—The authors are grateful to Parke Davis and Company for arranging for the biological tests, the results of which will be reported in detail elsewhere. In addition to the general results mentioned previously, the following data include some of the intermediates examined for antimalarial activity in avian infections: 4-chloro-6-methoxy-2-phenylquinoline, 2-(2′-methoxyphenyl)-quinoline hydrochloride, 6-methoxy-2-(4′-chlorophenyl)-quinoline, 6-methoxy-2-(4′-chlorophenyl)-quinoline-N-oxide, 4-chloro-6-methoxy-2-(4′-chlorophenyl)-quinoline, 6-methoxy-2-(3′-chlorophenyl)-quinoline, 6-methoxy-2-(3′-chlorophenyl)-quinoline-N-oxide, and 4-chloro-6-methoxy-2-(3′-chlorophenyl)-quinoline were inactive; and 4-chloro-2-(2′-methoxyphenyl)-quinoline was of doubtful activity.

Summary

Four α-aryl-γ-chloroquinolines have been conveniently prepared through a three-step sequence of reactions involving: (1) RLi addition to the anil linkage; (2) N-oxide formation of the anil addition product; and (3) halogenation of the latter with phosphorus oxychloride. Condensation of these variously substituted γ-chloroquinolines with 1-diethylamino-4-aminopentane resulted in a series of compounds having essentially the functional groups of the more highly fused atabrine.

Antimalarial activity in avian malaria was shown by 6-methoxy-2-(3′-chlorophenyl)-4-[(α-methyl - δ - diethylaminobutyl) - amino] - quinoline, and by the isomeric (4′-chlorophenyl) compound. The presence of chlorine is not a necessary condition for activity, for 6-methoxy-2-(phenyl) - 4 - [(α - methyl - δ - diethylaminobutyl) - amine]-quinoline is also active. However, the position of the methoxy group (in the chlorine-free type) is important, because 2-(2′-methoxyphenyl) - 4 - [(α - methyl - δ - diethylaminobutyl)-amino-quinoline, unlike the 6-methoxy isomer, is inactive.

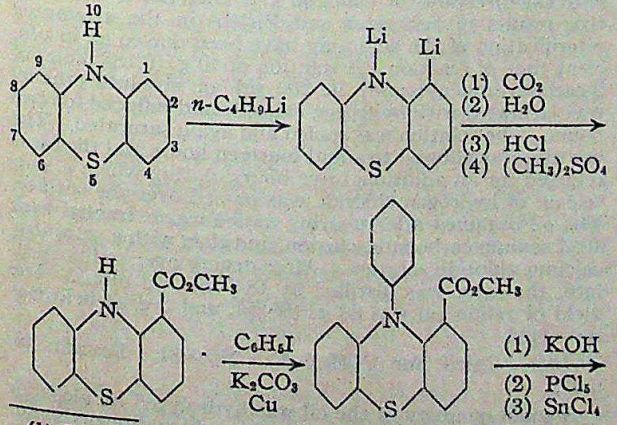
AMES, IOWA RECEIVED JANUARY 3, 1944

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Metalation of Phenothiazine[1]

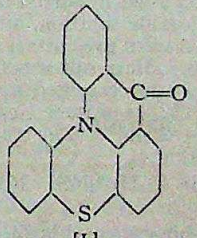
BY HENRY GILMAN, DAVID A. SHIRLEY AND PAUL R. VAN ESS

Phenothiazine is mono-metalated by *n*-butyllithium to give an RLi compound which, subsequent to carbonation, yields a mono-carboxylic acid. On the basis of earlier studies on metalations,[2] it appeared probable that metalation occurred in the 1- or the 4-position. After some unsuccessful attempts to prepare 1-carboxyphenothiazine by ring closure reactions, the acid obtained by metalation was shown to have the carboxyl group in the 1-position by the following indirect proof.



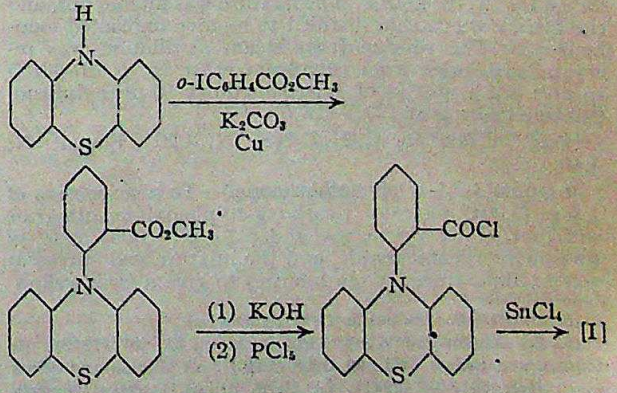
(1) Paper LIV in the series: "The Relative Reactivities of Organometallic Compounds"; the preceding paper is in THIS JOURNAL, 65, 1729 (1943).

(2) See p. 536 of Gilman, "Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943.



[I]

The identity of 9-quino(3,2,1-kl)phenothiazinone [I] prepared by the above sequence of reactions was established by comparison with the product obtained by the following transformations



The metalation of phenothiazine by *n*-butyllithium in the 1-position is of interest for two reasons. First, all previously described nuclear

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substitution reactions of phenothiazine take place in the 3-position, or para to the nitrogen. This is an additional[2] illustration of the applicability of metalation in making available positions otherwise inaccessible by the more common nuclear substitution reactions. Second, in view of a subsequent observation, one might have expected metalation to be ortho to sulfur rather than ortho to nitrogen. In a reaction[3] in which molar equivalents of N-ethylcarbazole and dibenzothiophene were allowed to compete for one molar equivalent of *n*-butyllithium, the dibenzothiophene was metalated exclusively.

It should be mentioned that exceptions to the rule of metalation by *n*-butyllithium of an ortho-position to a hetero element are methyl phenyl sulfide,[4a] triphenylamine,[4b] and the closely related triphenylarsine[4c] and triphenylphosphine.[4d]

Experimental

Metalation of Phenothiazine.—To 800 ml. of an ethereal solution of *n*-butyllithium, prepared from 104 g. (0.76 mole) of *n*-butyl bromide and 20 g. (2.9 g. atoms) of lithium was added slowly with stirring 40 g. (0.20 mole) of phenothiazine.[5] The mixture was stirred at room temperature under an atmosphere of dry nitrogen for twenty hours, and then allowed to stand an additional fifteen hours before pouring jetwise on a slurry of ether and excess crushed solid carbon dioxide. The mixture was allowed to stand until all solid carbon dioxide had disappeared, and was then hydrolyzed by the addition of excess water. The aqueous layer was separated, and the aqueous extracts were acidified with hydrochloric acid to precipitate 32 g. of crude acid. This solid was dissolved in a minimal amount of 10% sodium hydroxide solution, and then 40% sodium hydroxide was added until precipitation of the sodium salt was complete. This sodium salt was filtered off, dissolved in water, and the solution acidified with hydrochloric acid to precipitate 25 g. (52%) of pure 1-carboxyphenothiazine which melted at 264–264.5°. The compound can be crystallized from 70% ethanol.

Anal. Calcd. for $C_{13}H_9O_2NS$: N, 5.76. Found: N, 6.01.

The 1-carbomethoxyphenothiazine, melting at 113–113.5°, was obtained in a 32% yield by the action of dimethyl sulfate on an alkaline solution of the acid.

1-Carbomethoxy-10-phenylphenothiazine.—Four grams (0.016 mole) of 1-carbomethoxyphenothiazine, 100 g. of iodobenzene, 20 g. of finely ground anhydrous potassium carbonate, and 2.5 g. of copper bronze were stirred and refluxed for twelve hours. The mixture was filtered hot, and the filtrate was steam distilled to remove unreacted iodobenzene. The residue from steam distillation was recrystallized twice from petroleum ether (b. p. 80–110°) to give 3.2 g. (60%) of 1-carbomethoxy-10-phenylphenothiazine melting at 123.5–124.5°.

Anal. Calcd. for $C_{20}H_{15}O_2NS$: N, 4.20. Found: N, 4.40.

9-Quino(3,2,1-*kl*)phenothiazinone.[6]—To a suspension of 1.5 g. (0.0047 mole) of 1-carboxy-10-phenylphenothiazine in 60 ml. of dry xylene was added 1.4 g. (0.0067 mole) of phosphorus pentachloride, and the mixture was stirred at room temperature for ten minutes to give a clear yellow-brown solution. The solution was cooled in an ice-bath, and a solution of 6.25 g. (0.024 mole) of anhydrous stannic chloride in 20 ml. of xylene was added dropwise to the stirred solution over a period of ten minutes. The stirring was continued for forty-five minutes after the addition had been completed. The dark red mixture was hydrolyzed by the dropwise addition of 25 ml. of cold concentrated hydrochloric acid followed by 30 ml. of water. The yellow xylene layer was separated, washed with dilute sodium carbonate solution to remove acid, and evaporated to dryness to yield a yellow solid. This solid was recrystallized from a mixture of benzene–petroleum ether (b. p. 80–110°) to give 1.2 g. (85%) of bright yellow-green minute crystals. The ketone melted at 218–219°.

Anal. Calcd. for $C_{19}H_{11}ONS$: N, 4.64; mol. wt., 301. Found: N, 4.55; mol. wt. (benzene, cryoscopic), 300.

10-(2′-Carbomethoxy)-phenylphenothiazine.—A mixture of 13.2 g. (0.05 mole) of methyl *o*-iodobenzoate, 10 g. (0.05 mole) of phenothiazine, 6 ml. of nitrobenzene, 7.5 g. of potassium carbonate, 85 ml. of xylene, and 0.2 g. of copper bronze was stirred and refluxed for fourteen hours. The mixture was filtered hot and washed with boiling xylene. Upon cooling, green crystals were precipitated from the xylene solution. Recrystallization from xylene gave 7.0 g. (42%) of light green prisms melting at 143–144°.

Anal. Calcd. for $C_{20}H_{15}O_2NS$: N, 4.20. Found: N, 4.32.

10-(2′-Carboxy)-phenylphenothiazine.—A suspension of 6.5 g. (0.020 mole) of 10-(2′-carbomethoxy)-phenylphenothiazine in 125 ml. of 15% aqueous potassium hydroxide was refluxed for five hours. The resulting solution was diluted with water and acidified with hydrochloric acid to give a quantitative yield of acidic product melting at 209–210°. One recrystallization from glacial acetic acid gave red-yellow plates melting at 214–215°.

Anal. Calcd. for $C_{19}H_{13}O_2NS$: N, 4.38; neut. equiv., 319. Found: N, 4.60; neut. equiv., 320 and 313.

Ring Closure of 10-(2′-Carboxy)-phenylphenothiazine to 9-Quino(3,2,1-*kl*)phenothiazinone.—One and five-tenths grams (0.0047 mole) of 10-(2′-carboxy)-phenylphenothiazine was treated with phosphorus pentachloride and anhydrous stannic chloride in xylene by the procedure described previously. The product weighed 0.85 g. (60%) and melted at 219°. A mixed m. p. with the compound obtained from the metalation-acid showed no depression.

Attempted Ring Closures. [A] 2-Carboethoxydiphenylamine.—This reaction involved heating 2-carboethoxydiphenylamine with sulfur as a means of preparing 1-carboethoxyphenothiazine. First, 2-carboxydiphenylamine was prepared in 86% yield in essential accordance with the directions of Ullmann and Dieterle.[7] The negative results of Schroeter and Eisleb[8] in the attempted esterification of the acid may have been due to an insufficient time of reaction. A solution of 40 g. (0.188 mole) of 2-carboxydiphenylamine in 200 ml. of absolute ethanol was saturated with hydrogen chloride and refluxed for two hours. The solution was cooled and again saturated. The mixture was allowed to stand fourteen hours and then was refluxed for an additional five hours, during which a slow stream of hydrogen chloride was passed over the surface. The oil obtained after pouring on ice was extracted with 10% sodium carbonate solution, and then with a saturated calcium chloride solution. After drying over sodium sulfate, the ester was distilled at 184–187° (6 mm.). The yield of yellow oil was 33 g. (80%), and 5 g. of acid was recovered.

Anal. Calcd. for $C_{15}H_{15}O_2N$: N, 5.81. Found: N, 6.07.

A small quantity of the oil was hydrolyzed by alcoholic potassium hydroxide to give 2-carboxydiphenylamine (mixed m. p.).

A solution of 4.26 g. (0.02 mole) of 2-carboxydiphenyl-

(3) Unpublished studies by C. G. Stuckwisch.

(4) (a) Gilman and Webb, THIS JOURNAL, **62**, 987 (1940); (b) Gilman and Brown, *ibid.*, **62**, 3208 (1940); (c) Gilman and Stuckwisch, *ibid.*, **63**, 3532 (1941); (d) G. E. Brown, Doctoral Dissertation, Iowa State College (1941).

(5) Knoevenagel, *J. prakt. Chem.*, **89**, 1 (1913).

(6) This nomenclature was recommended by Drs. E. J. Crane and L. T. Capell.

(7) Ullmann and Dieterle, *Ann.*, **355**, 322 (1907).

(8) Schroeter and Eisleb, *ibid.*, **367**, 144 (1909).

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amine, 1.28 g. (0.04 g. atom) of sulfur, and 0.04 g. of iodine in 20 ml. of *o*-dichlorobenzene was refluxed at 180° for fifteen minutes. The acid is unstable under these conditions for carbon dioxide as well as hydrogen sulfide was evolved. The reaction mixture yielded 2.2 g. of the acid.

In another experiment, 4.82 g. (0.02 mole) of 2-carboethoxydiphenylamine and 1.28 g. of sulfur was heated without solvent in a bath at 285–300°. Hydrogen sulfide was evolved slowly at first, and then the odor of ethyl mercaptan was quite pronounced. Heating was discontinued after two hours, when the evolution of gas had ceased. The products isolated were 1.5 g. of the ester initially used, 0.2 g. of phenothiazine, but no phenothiazine-ester. The phenothiazine is probably formed as a consequence of pyrolysis of the ester, or decarboxylation of the acid (formed by cleavage of the ester) to give diphenylamine which then reacts with sulfur in the usual manner.

[B] Coupling Reactions with 2,2′-Diaminodiphenyl Disulfide.—One of these coupling reactions was patterned after the method used by Kehrmann and Nossenko[9] for the preparation of 1-nitrophenothiazine. A solution of 2,2′-diaminodiphenyl disulfide,[10] 2-bromo-3-nitrobenzoic acid,[11] and of sodium acetate in ethanol was refluxed for twenty-four hours. The diamine and acid were recovered.

A second coupling reaction was a modification of a procedure by Ullmann and Hoz.[12] A mixture of 2,2′-diaminodiphenyl disulfide, potassium *o*-chlorobenzoate, sodium acetate, amyl alcohol, and a trace of copper bronze was refluxed for two hours. The diamine and *o*-chlorobenzoic acid were recovered.

Summary

Phenothiazine is metalated by *n*-butyllithium in the 1-position or ortho to the nitrogen. The structure of the 1-carboxyphenothiazine, obtained by carbonation of the metalation product, was established indirectly by cyclization reactions.

(9) Kehrmann and Nossenko, *Ber.*, **46**, 2809 (1913).

(10) Teppema and Sebrell, THIS JOURNAL, **49**, 1751 (1927).

(11) Culhane, "Organic Syntheses," Coll. Vol. I, 125 (1941).

(12) Ullmann and Hoz, *Ann.*, **355**, 352 (1907).

AMES, IOWA RECEIVED JANUARY 17, 1944

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY No. 296]

A Large-Scale Preparation of D-Altrose. D-Altrose Oxime and its Rate of Mutarotation[1]

BY ROBERT C. HOCKETT AND LEONARD B. CHANDLER[2]

In 1926, Kunz and Hudson,[3] by the action of aluminum chloride on a chloroform solution of octaäcetyl β-lactose, obtained the "acetochloro" derivative of a new disaccharide which they named neolactose, and which was proved to be a D-galactosyl-D-altrose. Richtmyer and Hudson[4] later improved this preparation by using phosphorus pentachloride along with aluminum chloride, isolated crystalline neolactose and a number of its derivatives, and showed how crystalline D-altrose may be obtained from the disaccharide despite the tendency of this hexose to form an anhydride when it is treated with hydrochloric acid.

When a sample of D-altrose was needed in this Laboratory, we undertook to repeat the preparation described by these authors, both on a much increased scale and with the introduction of short-cuts to eliminate a number of manipulations.

The chief modification was as follows: "α-aceto-chloroneolactose" formed from octaäcetyl lactose but not isolated, was subjected directly to hydrolysis by hydrochloric acid in a water–acetone solution under such conditions as to (1) hydrolyze the chlorine, (2) to remove the acetate groups, and (3) to break the disaccharide link all in a single operation yielding a mixture containing hydrochloric acid, acetic acid, glucose, galactose, altrose and altrosan. Hydrochloric acid was removed with lead carbonate followed by silver carbonate, metallic ions by hydrogen sulfide, acetic acid by distillation, and glucose and galactose by yeast fermentation. Finally, altrose and altrosan were recovered as D-altrose dibenzyl mercaptal as described by Richtmyer and Hudson.[4] From this derivative the crystalline sugar was obtained without seed, as described by Richtmyer and Hudson.[4]

The over-all yield from one kilogram of D-lactose monohydrate was 18 g. of crystalline D-altrose or 3.7% of the theoretical. A more efficient method of preparation of this sugar from α-methyl-D-glucoside was subsequently described by Richtmyer and Hudson.[5]

The oxime of D-altrose and measurements of the rate of mutarotation of this derivative in aqueous solution are described for the first time.

We wish to thank Doctors Hudson and Richtmyer, with whom we made arrangements in connection with this work.

Experimental

D-Altrose Oxime.—Two grams (0.0111 mole) of crystalline altrose was treated with 0.0282 mole of hydroxylamine in methanol at room temperature overnight. After a brief warming on the steam-bath, the solution was concentrated to a colorless sirup (diminished pressure) which was dissolved in a minimum volume of dry methanol. Absolute ethanol was added to turbidity and the solution soon deposited 1.7 g. of fine prisms. Recrystallized by dissolving in 10 cc. of water, filtering, concentrating to a sirup and repeating the process described above, the compound was obtained with a maximum melting point of 143–144° and a

(1) This paper is taken from a thesis submitted by Leonard B. Chandler to the Graduate School of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, in October, 1939.

(2) Present address: Nylon Division, E. I. du Pont de Nemours and Company, Wilmington, Delaware.

(3) Kunz and Hudson, THIS JOURNAL, **48**, 1978, 2435 (1926).

(4) Richtmyer and Hudson, *ibid.*, **57**, 1716 (1935).

(5) Richtmyer and Hudson, *ibid.*, **63**, 1729 (1941).

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rotation[6] at equilibrium (103 hr.) of −9.8° (*C*, 2.408; *t*, 24.9°; H_2O). The crystals are easily soluble in water, slightly in methanol, and insoluble in ethanol, ether, acetone and chloroform.

Anal. Calcd. for $C_6H_{13}O_6N$: C, 36.9; H, 6.66; N, 7.17. Found: C, 36.9, 37.1, 36.7; H, 6.15, 6.84, 6.86; N, 6.93, 7.04.

Mutarotation of D-Altrose Oxime.—A sample of 0.2422 g. of twice recrystallized material was dissolved into 10.06 cc. of aqueous solution. Twenty-two measurements of the rotations were made in a 2-dm. tube at 25.0 ± 0.5°. The reaction followed an unimolecular course, the calculated velocity constant ($k_1 + k_2$) being 0.0040 with an average variation of ±0.0001. In making this calculation the value obtained for the rotation at t = 748 min. was taken as the rotation at infinite time rather than that at t = 6540 min. since hydrolysis is appreciable after very long contact with water. The *p*H of the water was 5.8.

By plotting log ($\alpha_t - \alpha_\infty$) against time in minutes, a very nearly straight line was obtained. By extrapolation of this line to zero time, the value of log ($\alpha_0 - \alpha_\infty$) was determined graphically and the initial specific rotation[6] found to be −64.0°.

(6) All rotations referred to in this paper represent specific rotations of the D line of sodium unless specified otherwise. Concentrations are grams of solute in 100.0 cc. of solution.

Summary

A large-scale and abbreviated procedure for the preparation of crystalline D-altrose from D-lactose by the method of Richtmyer and Hudson is described.

The oxime of D-altrose is described and measurements of its rate of mutarotation recorded.

CAMBRIDGE, MASSACHUSETTS
RECEIVED NOVEMBER 1, 1943

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Condensation of Cyclohexene Oxide, 1,2-Dichlorocyclohexane, and 3,4-Dichlorohexane with Anisole[1]

BY CHARLES C. PRICE AND GEORGE P. MUELLER[2]

This investigation was undertaken to explore the possibility of synthesizing vicinal *bis*-(*p*-hydroxyphenyl)-hexanes and cyclohexanes by some modification of the Friedel–Crafts type reaction. Such substances are of particular interest in connection with their ability to simulate the physiological activity of the hormone, estrone.

Kursanoff[3,4] has reported the isolation of a diphenylcyclohexane, m. p. 169–171°, which he believed to be the 1,2-isomer, from the aluminum chloride-catalyzed condensation of 1,2-dichlorocyclohexane with benzene. This material has now been shown to be the 1,4-isomer.[5,6] Nenitzescu and Curcaneanu isolated a greater amount of liquid 1,3-diphenylcyclohexane than the crystalline 1,4-isomer. It is thus obvious that, as so frequently happens with the Friedel–Crafts reaction, rearrangement occurred in the replacement of the chlorine atoms. Other similar rearrangements in vicinal, negatively-substituted halides also have been observed.[7]

It was hoped that, due to the greater reactivity of the aromatic nucleus in anisole or phenol, or by modification of the conditions of the Friedel–Crafts condensation, this tendency toward rearrangement might be modified. This hope was only partially realized. Condensations of anisole with 1,2-dichlorocyclohexane using aluminum chloride as the catalyst or with cyclohexene oxide or 1,2-dihydroxycyclohexane using boron fluoride as the catalyst produced poor yields of mixtures of condensation products from which two diastereoisomeric 1,3-dianisylcyclohexanes (I and II), *m*-dianisylbenzene (III) and anisylcyclohexane (IV) were isolated and identified. The fact that no 1,4-dianisylcyclohexane or *p*-dianisylbenzene was isolated is an indication that the tendency to rearrangement was at least somewhat less with anisole than with benzene.

The terphenyl was assigned the meta-orientation on the basis of the non-identity of the free phenol, its dimethyl ether and diacetate with the corresponding ortho and para isomers[8] and zinc dust distillation to yield a small amount of material with the proper melting point for *m*-terphenyl itself.

The 1,3-dianisylcyclohexane, the free phenol and its diacetate each differs from the known 1,1-isomers.[9]

The production of 1,3-dianisylcyclohexane, as well as *m*-dianisylbenzene and anisylcyclohexane, may be accounted for by the intermediate formation of 3-anisylcyclohexene (V). The anisyl group in the cycloölefin should direct addition of a second molecule of anisole to form 1,3-dianisylcyclohexane.[10] Disproportionation of hydrogen between the 3-anisylcyclohexene (V) and the 1,3-dianisylcyclohexanes would account for the

(1) Presented before the Organic Division at the 104th Meeting of the American Chemical Society, Buffalo, New York, September 7, 1942.

(2) Eli Lilly and Company Fellow, 1941–1943.

(3) Kursanoff, *Ann.*, **318**, 309 (1901).

(4) Bodroux, *Ann. chim.*, [10] **11**, 511 (1929).

(5) Nenitzescu and Curcaneanu, *Ber.*, **70B**, 346 (1937).

(6) Corson and Ipatieff, THIS JOURNAL, **60**, 747 (1938).

(7) Nenitzescu and Gavat, *Ann.*, **519**, 260 (1935); *Ber.*, **70B**, 1883 (1937); Nenitzescu and Przemetzki, *ibid.*, **69B**, 2706 (1936); Nenitzescu and Curcaneanu, *Bull. chim. soc. Romania*, [2] **1**, 125 (1939) (*C. A.*, **37**, 3740 (1943)).

(8) Price and Mueller, THIS JOURNAL, **66**, 632 (1944).

(9) Schmidlin and Lang, *Ber.*, **43**, 2819 (1910); von Braun, *Ann.*, **472**, 55 (1929).

(10) See, *e. g.*, Price and Karabinos, THIS JOURNAL, **62**, 1159 (1940).

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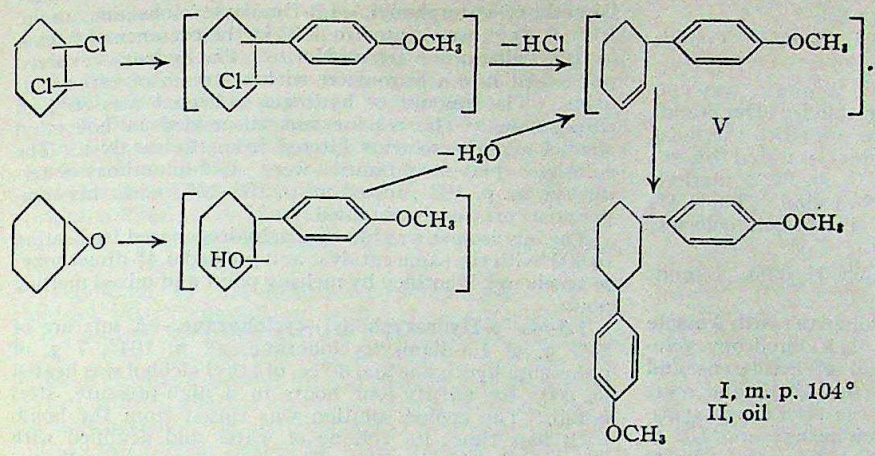
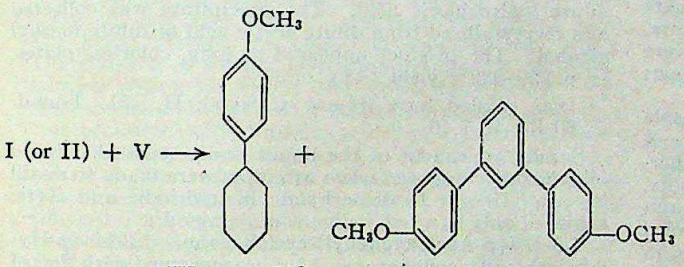
anisylcyclohexane (IV) and *m*-dianisylbenzene (III) actually isolated.



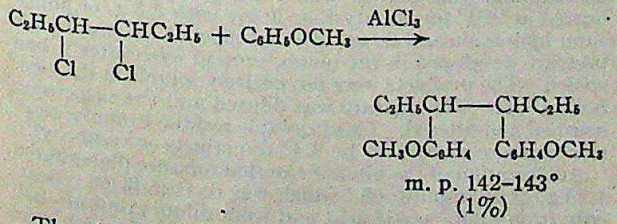
I, m. p. 104°
II, oil



IV, m. p. 58° III. m. p. 198°

For the case of the cyclohexene oxide, opening of the oxide ring has been shown in general to involve an inversion of configuration[11] and would thus produce the *trans*-alcohol as indicated. Dehydration of the corresponding alcohol without the methoxyl group has already been shown to produce 3-phenylcyclohexene.[10]

The open-chain analog of 1,2-dichlorocyclohexane, 3,4-dichlorohexane, was also condensed with anisole. This halide was extremely unreactive in the presence of aluminum chloride but it was possible to obtain a 14% yield of condensation product from which a 1% yield of hexestrol dimethyl ether was crystallized. In view of the work of Nenitzescu,[7,12] it seems likely that the remainder of the condensation product consisted of isomers of hexestrol.



m. p. 142–143°
(1%)

The dihalide used was obtained by ethylation of acetylene with ethyl bromide[13] (20% yield), hydrogenation to *cis*-3-hexene[14] (95% yield) and chlorination[15] (84% yield).

The crystalline and oily isomers of 1,3-*bis*-(*p*-hydroxyphenyl) - cyclohexane and 4,4″-dihydroxy-*m*-terphenyl were found to possess no estrogenic activity when administered to spayed mice in doses up to 0.4 mg. per mouse. 1,3-*bis*-(*p*-Hydroxyphenyl)-cyclohexane showed no androgenic activity at a maximum total dose of 18 mg. per animal in castrated rats.[16]

Experimental[17]

Condensation of Cyclohexene Oxide with Phenol in the Presence of Boron Fluoride.—Boron fluoride was passed through a stirred mixture consisting of 28.8 g. (0.306 mole) of phenol and 5.0 g. (0.051 mole) of cyclohexene oxide at 40–70°. After six hours the purple complex was decomposed in water, extracted with 75 cc. of benzene and the benzene solution washed thoroughly with water and dried. The benzene and excess phenol were removed by distillation, the latter at 16 mm. pressure, and 7.5 g. of a dark oil remained as residue.

A portion of this was dissolved in aqueous sodium hydroxide; in a few minutes a crystalline sodium salt had separated from the solution. All qualitative tests for phenolic compounds failed as did attempts to crystallize the free phenol, its benzoate, 3,5-dinitrobenzoate, *p*-toluenesulfonate, picrate or aryloxyacetic acid derivatives.

A second reaction was carried out using five times the above quantities of reactants by passing boron fluoride through the mixture for ten hours. Fractional distillation of the crude oil yielded 8.9 g. of an oil, b. p. 135–175° (9 mm.). This crystallized upon cooling. It was redistilled and recrystallized, m. p. 103.4°, and proved to be *trans*-1,2-dihydroxycyclohexane. From this fraction a small amount of *p*-cyclohexylphenol was also obtained, m. p. 125–128°.[18] It was identified by conversion to the 3,5-dinitrobenzoate, m. p. 164–166°, and by analysis.

Anal. Calcd. for $C_{12}H_{16}O$: C, 81.76; H, 9.15. Found: C, 81.86; H, 8.71.

Condensation of Cyclohexene Oxide with Anisole in the Presence of Boron Fluoride.—Boron fluoride was bubbled into a mixture of 25 g. (0.255 mole) of cyclohexene oxide and 165 g. (1.53 mole) of anisole at 50° for three hours, with constant stirring. The dark-red complex was decomposed with 400 cc. of water. The organic liquid was extracted with ether, washed thoroughly with water and distilled at reduced pressure from a Claisen flask modified with a Vigreux column.

The first fraction collected was a colorless liquid, b. p. 89–91° (1 mm.). This was redistilled, b. p. 273–276° (740 mm.), and recrystallized several times from dilute ethyl alcohol. The colorless plates, m. p. 56.8–57.5°, were, according to these physical constants,[4] *p*-cyclohexylanisole. It was obtained in 8% yield.

A second fraction, 20 g., was collected, b. p. 95–183°

(11) Kuhn and Ebel, *Ber.*, **58**, 921 (1925); Böeseken, *Rec. trav. chim.*, **47**, 683 (1928); Wilson and Lucas, THIS JOURNAL, **58**, 2396 (1936).

(12) Nenitzescu, Gavat and Corcora, *Ber.*, **73**, 233 (1940).

(13) Bried and Hennion, THIS JOURNAL, **59**, 1310 (1937).

(14) Campbell and Eby, *ibid.*, **63**, 216 (1941).

(15) Spiegler and Tinker, *ibid.*, **61**, 940 (1939).

(16) We are indebted to Eli Lilly and Company for the results of these physiological tests.

(17) The analyses were carried out by Miss Margaret McCarthy, Miss Theta Spoor and Miss Dorothy Schneider.

(18) Schrauth and Görig, *Ber.*, **56**, 1900 (1923); Kursanoff, *Ann.* **318**, 325 (1901).

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(1 mm.). Redistillation gave a colorless oil, b. p. 160–165° (1 mm.); n^{25} 1.5694. This proved to be the liquid isomer of 1,3-dianisylcyclohexane. It contained an impurity which gave the liquid a violet fluorescence.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 81.50; H, 8.39.

The third fraction, b. p. 190–245° (1 mm.), was collected as a brown oil, part of which crystallized after standing for a few days. A little ether was added to the mass and the crystals collected. They were purified by recrystallization from petroleum ether (b. p. 96°), methylcyclohexane, and ethyl, butyl or amyl alcohol. The 4,4″-dimethoxy-*m*-terphenyl crystallized in large, colorless plates, m. p. 197–198° (cor.).

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.67; H, 6.55.

Condensation of 1,2-Dihydroxycyclohexane with Anisole in the Presence of Boron Fluoride.—1,2-Dihydroxycyclohexane was prepared by the method of Senderens and Aboulenc.[19] The equimolecular mixture of *dl* and *meso* forms was used, m. p. 73°.[20] As in the preceding experiment, 27 g. (0.233 mole) of the cyclohexane and 152 g. (1.4 mole) of anisole were stirred at 45° for three hours while boron fluoride was bubbled through the mixture. The same products as in the preceding condensation were isolated with an over-all yield of condensed material about one-fourth as great.

Condensation of 1,2-Dichlorocyclohexane with Anisole in the Presence of Anhydrous Aluminum Chloride.—A 500-cc. flask was equipped with a reflux condenser, thermometer, sealed stirrer and dry-solid addition appendix. 1,2-Dichlorocyclohexane,[21] 41.8 g. (0.273 mole), and anisole, 155 g. (1.43 mole), were placed in the flask and cooled to 5°; 15 g. of anhydrous aluminum chloride was added in small enough portions that the temperature did not rise appreciably. The mixture was stirred for six hours and permitted to stand for sixteen hours in the ice-bath. When worked up, as before, the complex yielded 20 g. of an oil which deposited 2 g. of 4,4″-dimethoxy-*m*-terphenyl upon standing. The crystals were separated and the oil distilled. The lower-boiling fractions yielded 1,2-dichlorocyclohexane and 3 g. of *p*-cyclohexylanisole.

A fraction, 8 g., b. p. 180–220° (3 mm.), was redistilled and a portion, b. p. 191–205° (1 mm.), partially crystallized. The whole was dissolved in a large volume of hot methyl alcohol. A small amount of the terphenyl crystallized and was separated from the solution. Upon standing overnight the solution deposited more crystals, 2 g. of long, white needles. These were recrystallized three times from methyl alcohol and once from ethyl alcohol, m. p. 102.8–104.0°. This proved to be the solid isomer of 1,3-dianisylcyclohexane.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16; mol. wt., 296.39. Found: C, 80.93; H, 7.81; mol. wt., 280 (Rast).

The oil remaining from evaporation of the recrystallization liquors was combined with the corresponding fraction from another run, and from 10 g. of oil 4 g. was collected, b. p. 207–210° (1 mm.); n^{25} 1.5769. This oil was the liquid form of 1,3-dianisylcyclohexane, isolated before from cyclohexene oxide and anisole. Its structure and relationship to the solid isomer above was shown by catalytic dehydrogenation to 4,4″-dimethoxy-*m*-terphenyl.

A similar reaction using 76.5 g. (0.5 mole) of the cyclohexane, 324 g. (3.0 mole) of anisole and 50 g. (0.37 mole) of aluminum chloride at 0° for fifty hours gave 16 g. of crude condensation products which were separated into 2 g. of *p*-cyclohexylanisole, 3.5 g. of the crystalline cyclohexane, 9 g. of the oily isomer and 0.5 g. of the terphenyl. The same reaction at 15° for sixty-five hours produced 30 g. of condensation products.

The course of the reaction did not appear to differ materially if carried out at 150–160° for two hours. An attempt to use carbon disulfide as a solvent resulted in a vigorous reaction which produced only ill-smelling, sulfur-containing oils and much tar.

Dehydrogenation of 1,3-Dianisylcyclohexane: 4,4″-Dimethoxy-*m*-terphenyl.—1,3-Dianisylcyclohexane, m. p. 104°, 0.10 g., was heated to 300° in the presence of 0.05 g. of 10% palladium black on Norite. The hydrogen evolved was swept into a nitrometer with a stream of carbon dioxide. The amount of hydrogen collected was 86% of three moles. The residue was suspended in hot ethyl alcohol and the solution filtered from the catalyst. The colorless plates obtained were 4,4″-dimethoxy-*m*-terphenyl, m. p. 193°, mixed m. p. 196–197° with this compound as previously obtained.

The oily isomer was likewise dehydrogenated by heating to 300° with the same catalyst and yielded 4,4″-dimethoxy-*m*-terphenyl, identified by melting point and mixed melting point.

1,3-*bis*-(*p*-Hydroxyphenyl)-cyclohexane.—A mixture of 2.47 g. of 1,3-dianisylcyclohexane, m. p. 104°, 7 g. of potassium hydroxide and 40 cc. of ethyl alcohol was heated at 200° for twenty-four hours in a high-pressure, steel bomb. The cooled solution was rinsed from the bomb with four times its volume of water and acidified with dilute hydrochloric acid. The precipitate was collected and recrystallized from dilute acetic acid or dilute methyl alcohol. The product appeared as long, colorless plates, m. p. 229–232°; yield 2.18 g. or 97%.

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.40; H, 7.76.

Similar treatment of the liquid isomer yielded only an oil which decomposed when attempts were made to distill it. An attempt to demethylate in hydriodic and acetic acids led only to a red, iodine-containing oil.

1,3-*bis*-(*p*-Acetoxyphenyl)-cyclohexane.—1,3-*bis*-(*p*-Hydroxyphenyl)-cyclohexane, 0.5 g. was warmed with 2 g. of freshly-fused sodium acetate and 10 cc. of acetic anhydride on a steam-bath for three hours. The mixture was hydrolyzed in water, yielding the theoretical amount of product. This was recrystallized four times from methyl alcohol, m. p. 74.5–75.5°.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 74.98; H, 6.86. Found: C, 74.87; H, 7.05.

4,4′′-Dihydroxy-*m*-terphenyl.—The dimethoxy compound, 0.35 g., was heated with 1.0 g. of potassium hydroxide and 20 cc. of ethyl alcohol at 200° for twenty-four hours. The solution was treated as before and 0.29 g. (93%) of the diphenol was obtained. The product crystallized from dilute acetic acid or dilute methyl alcohol as fine plates having a slight lavender tint, m. p. 182–183°.

Anal. Calcd. for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.41; H, 5.51.

Demethylation was also accomplished in 94% yield by refluxing 0.85 g. of the ether with 3 cc. of hydriodic acid (d. 1.7) and 6 cc. of glacial acetic acid for three hours. Dilution and cooling precipitated the product.

The potassium hydroxide cleavage could not be successfully repeated on occasions. An experiment that behaved anomalously was one in which 2.5 g. of the ether was heated at 200° for twenty-four hours with 7.5 g. of potassium hydroxide and 20 cc. of ethyl alcohol. Considerable pressure developed in the bomb, present even after it had cooled. The products were not entirely soluble in the alcoholic alkali. The mixture was diluted and the suspension warmed and filtered. This insoluble residue from the reaction mixture proved to be 4,4″-dimethoxy-*m*-terphenyl.

Acidification of the filtered reaction mixture precipitated 1.25 g. of an impure solid which was recrystallized repeatedly from dilute acetic acid and from dilute ethyl alcohol; white plates, m. p. 66.0–67.5°, were obtained which were insoluble in 10% sodium hydroxide. This was probably 4,4″-dimethoxyperhydro-*m*-terphenyl. The analysis indicated a substance containing about four more hydrogen atoms than 4,4″-dimethoxyperhydroterphenyl.

Anal. Calcd. for $C_{20}H_{36}O_2$: C, 77.86; H, 11.76. Calcd. for $C_{20}H_{36}O_2 \cdot {}^1/_2C_2H_6O$: C, 76.08; H, 11.86. Found: C, 76.73, 76.90; H, 12.59, 12.89.

(19) Senderens and Aboulenc, *Compt. rend.*, **173**, 1365 (1921).

(20) Leroux, *ibid.*, **148**, 931 (1909).

(21) Kharasch and Brown, THIS JOURNAL, **61**, 3432 (1939).

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In agreement with its formulation as the ether, this compound was resistant to the action of sodium dichromate and sulfuric acid in water at the reflux temperature. Demethylation with constant-boiling hydriodic acid in glacial acetic acid yielded a white product crystallizing from the acid mixture. Attempts to recrystallize this only gave gels, even from large amounts of benzene or alcohol. The gel was dried, m. p. 245–295°.

4,4″-Diacetoxy-*m*-terphenyl.—This derivative was obtained by treating the diphenol with fused sodium acetate and acetic anhydride, as described above. The compound was recrystallized from ethyl alcohol and obtained as white needles, m. p. 130.1–131.5°.

Anal. Calcd. for $C_{22}H_{18}O_4$: C, 76.28; H, 5.24. Found: C, 76.39; H, 5.79.

Oxidation of 4,4″-Dihydroxy-*m*-terphenyl.—The diphenol, 0.1 g., was refluxed with 8 cc. of water, 0.1 cc. of 10% sodium hydroxide and 1.0 g. of potassium permanganate. The solution was cooled, acidified and the manganese dioxide dissolved by additions of sodium bisulfite. The resulting solution contained only a slight haze of insoluble material. It was evaporated to dryness and some of the salt residue heated for three minutes at 160° with resorcinol and one drop of concentrated sulfuric acid. The fused mixture was cooled and diluted with water. The addition of sodium hydroxide produced a red-brown solution with a weak, but deep green fluorescence. This fluorescence and color had a very different character than that produced with phthalic acid. It matched perfectly with the colors obtained from iso- and terephthalic acid controls. The red solution obtained with resorcinol and sulfuric acid under the same conditions was of a distinctly different character.

Oxidations with 50% nitric acid yielded a yellow powder containing nitrogen. The crude product melted at 218–225°. This was not identified.

Zinc Dust Treatment.—A 0.05-g. sample of the cyclohexane was heated at 250° for one hour with 10% palladium-on-Norite catalyst. Zinc dust, 0.1 g., was then added to the melt. The heating was continued for two hours at 300°. The mixture was cooled, pulverized and extracted with benzene. When concentrated, decolorized, filtered and concentrated again to 0.3 cc., the benzene solution yielded a minute amount of crystals. The melting point of 85–90° indicated that this material was *m*-terphenyl (m. p. 89°).[22]

Condensation of Anisole with 3,4-Dichlorohexane in the Presence of Anhydrous Aluminum Chloride.—In the apparatus described previously for the Friedel–Crafts reactions were placed 7.75 g. (0.05 mole) of 3,4-dichlorohexane,[13,14,15] 14.4 g. (0.3 mole) of anisole and 50 cc. of petroleum ether (b. p. 95–96°). The reactants were cooled to 2° and 5 g. of anhydrous aluminum chloride was added in small portions to the stirred mixture. The reaction mixture was then heated to 80° for one and one-half hours, but no gas evolution was observed. Another 5-g. portion of catalyst was added, and subsequent heating to 95° brought about hydrogen chloride evolution for one hour. Heating was continued for ten hours.

The mixture was decomposed in water and treated in the usual manner. Distillation yielded 3 cc. of clear liquid, b. p. 90–123° (1 mm.), and 1 cc. of viscous straw-yellow liquid, b. p. 140–190° (1 mm.). The yield of the latter fraction was 7%.

To a mixture of 3.88 g. (0.025 mole) of 3,4-dichlorohexane, 5.4 g. (0.05 mole) of anisole and 25 cc. of petroleum ether was added 6.7 g. (0.05 mole) of anhydrous aluminum chloride during an hour. The reaction was heated on a steam-bath for four hours. The mixture was cooled and treated as before. This time 2.6 g. of liquid, b. p. 95–150° (1 mm.), and 0.9 g. of a viscous straw-colored oil, b. p. 150–190° (1 mm.), were collected. The latter fraction was combined with the similar product above and methylated, using alternately 2 cc. of dimethyl sulfate and 2.5 cc. of 20% sodium hydroxide. The excess dimethyl sulfate was destroyed with ammonia and the product extracted with ether.

Distillation of the dried ethereal extract yielded a cloudy, yellow oil, b. p. 180–190° (1 mm.). This was diluted with an equal volume of petroleum ether (b. p. 38–45°), seeded and placed in the refrigerator. After four days about 0.05 g. of crystals had been deposited. These were purified by recrystallization from methyl alcohol and appeared as needles, m. p. 142–143° (cor.). A mixed melting point with an authentic sample of hexestrol dimethyl ether[23] remained unchanged.

Anal. Calcd. for $C_{20}H_{26}O_2$: C, 80.59; H, 8.74. Found: C, 80.35; H, 8.89.

The yield of the unmethylated oil was about 14% and that of the crystals about 1%, calculations being based on the amount of 3,4-dichlorohexane used in both reactions.

Summary

1,2-Dichlorocyclohexane and cyclohexene oxide react with anisole in the presence of aluminum chloride or boron fluoride to form a solid and a liquid 1,3-dianisylcyclohexane, *p*-cyclohexylanisole and 4,4″-dimethoxyterphenyl.

3,4-Dichlorohexane condenses with anisole to give a small amount of oily products from which a 1% yield of hexestrol dimethyl ether was isolated.

URBANA, ILLINOIS RECEIVED DECEMBER 22, 1943

(22) France, Heilbron and Hey, *J. Chem. Soc.*, 369 (1940).

(23) This sample was furnished through the courtesy of Eli Lilly and Company.

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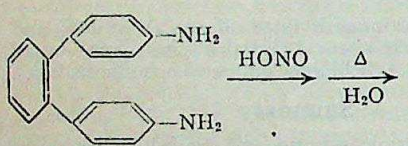
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

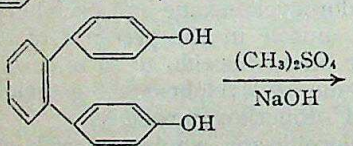
The Synthesis of Two Dihydroxyterphenyls

BY CHARLES C. PRICE AND GEORGE P. MUELLER[1]

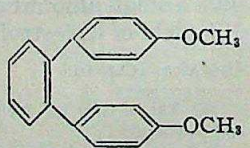
In an attempt to prepare 1,2-di-(*p*-methoxyphenyl)-cyclohexane by the condensation of *p*-methoxyphenylmagnesium bromide with 1,2-dibromocyclohexane, the only products which were isolated in a pure state were 4,4′-dimethoxybiphenyl (I) and a substance (II), m. p. 273–275°, having the proper elementary analysis for a dimethoxyterphenyl.

The possibility that this substance was the dimethoxy-*o*-terphenyl resulting from dehydrogenation of the desired 1,2-di-(4-methoxyphenyl)-cyclohexane was dispelled by synthesis of 4′,4″-dimethoxy-*o*-terphenyl (IV) through tetrazotization of the corresponding diamine, recently described by Allen and Pingert.[2] The hydrolysis with steam proceeded in practically quantitative yield. Methylation of the phenol, however, yielded an isomer of the product (II) from the Grignard condensation.



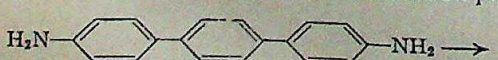


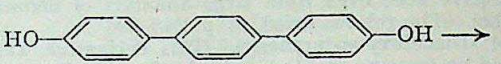
III, m. p. 231°



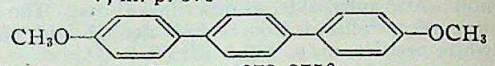
IV, m. p. 106°

Demethylation of the unknown dimethoxyterphenyl (II) followed by permanganate oxidation yielded terephthalic acid, which was identified as the dimethyl ester. The *p*-terphenyl derivative was, therefore, synthesized in the same manner[3–6] as the ortho isomer above and it proved to be identical with the Grignard condensation product.



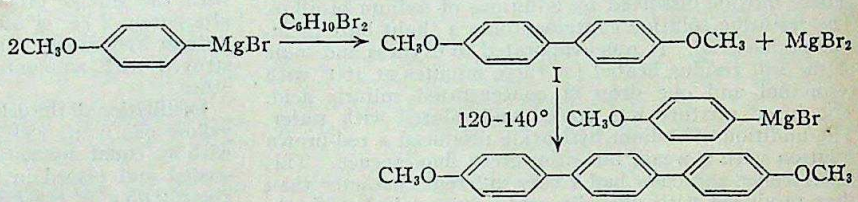


V, m. p. 375°



II, m. p. 273–275°

An experiment demonstrated that this dimethoxy-*p*-terphenyl could arise from a condensation of 4,4′-dimethoxybiphenyl and *p*-methoxyphenylmagnesium bromide.



This reaction recalls the formation of isoamylbenzene as a by-product in the demethylation of anisole with isoamylmagnesium bromide.[7,8] Coupling reactions of Grignard reagents with aryl ethers have also been reported by Fuson and Speck.[9]

Experimental[10]

4′,4″-Dihydroxy-*o*-terphenyl.—The tetrazotization of 4′,4″-diamino-*o*-terphenyl was carried out as prescribed by Allen and Pingert, using 2.6 g. (0.01 mole) of the diamine in 200 cc. of water, 17 cc. of 6 *N* hydrochloric acid solution and 1.38 g. (0.02 mole) of sodium nitrite in water. Apparatus had previously been arranged consisting of a 1-l. three-necked flask fitted with a 30-in. Allihn condenser, and a vertical glass tube measuring 2.5 by 100 cm. Into the top of the latter a 6-mm. glass tube projected 3 cm., and through this was passed steam from boiling, distilled water. Projecting exactly as far into the large tube was the tip of an addition funnel which had been drawn to a capillary at a slight angle so that the solution dripping therefrom would flow down the wall of the column instead of dropping through. This addition funnel was packed in an ice-bath. A little water was placed in the three-necked flask and this was kept boiling while, with the passage of steam down through the tube, the tetrazonium chloride solution was added very slowly. The flask had collected about 850 cc. of water by the time the addition was completed. White needles, sometimes containing an orange impurity, separated from the solution; the yield of the crude material, m. p. 223–228°, was 2.58 g. or 98%. Four recrystallizations from benzene gave colorless plates, m. p. 230.2–231.4° (cor.).

Anal. Calcd. for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.39; H, 5.62.

4′,4″-Diacetoxy-*o*-terphenyl.—By warming 0.5 g. of the diphenol with 2 g. of freshly-fused sodium acetate in 10 cc. of acetic anhydride for two and one-half hours, hydrolyzing the suspension in cold water and collecting the remaining solid, the theoretical quantity, 0.66 g., of crude, dry product was obtained, m. p. 175–183°. After four re-

(1) Eli Lilly and Company Fellow, 1941–1943.
(2) Allen and Pingert, THIS JOURNAL, **64**, 2639 (1942).
(3) Vorländer, *Z. physik. Chem.*, **106**, 449 (1927).
(4) U. S. Patent 1,993,771 (*Chem. Zentr.*, **106**, II, 3996 (1935)).
(5) (a) von Braun, *Ber.*, **60**, 1180 (1927); (b) France, Heilbron and Hey, *J. Chem. Soc.*, 1364 (1938).
(6) Künster and Schnitzler, *Z. physiol. Chem.*, **149**, 150 (1925).
(7) Späth, *Monatsh.*, **35**, 319 (1914).
(8) Lüttringhaus and Sääf, *Z. angew. Chem.*, **51**, 915 (1938).
(9) Fuson and Speck, THIS JOURNAL, **64**, 2446 (1942).
(10) Microanalyses by Miss Theta Spoor and Miss Dorothy Schuckert.

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crystallizations from 50% ethyl alcohol the tiny platelets melted at 186.0–186.4° (cor.).

Anal. Calcd. for $C_{22}H_{14}O_4$: C, 76.28; H, 5.24. Found: C, 76.43; H, 5.41.

4′,4″-Dimethoxy-*o*-terphenyl.—The diphenol, 0.20 g., was shaken at 80° with 2 cc. of dimethyl sulfate for a few minutes, 2 cc. of 20% sodium hydroxide solution was added and shaking was continued for a short time. This procedure was repeated three times and the mixture cooled and treated with an excess of aqueous ammonia. The product was collected and dried. The yield of crude material was 0.22 g., or the theoretical quantity. Five recrystallizations from ethyl alcohol produced long, flat needles, m. p. 104.8–106.4° (cor.).

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.90; H, 6.43.

4,4″-Diamino-*p*-terphenyl.—4,4″-Dinitro-*p*-terphenyl, 3.02 g., was suspended in 100 cc. of benzene and hydrogenated at 2000 lb. per sq. in. and 100° for two hours in the presence of Raney nickel. The white diamine crystallized in the bomb as beautiful leaflets, m. p. 240–244°.[11] The product was separated from the catalyst by diluting the mush to 200 cc. with benzene, filtering and concentrating. The recovery from two crops was 1.45 g. or 59%. The diamine was very slightly soluble in 5% hydrochloric acid solution; its solutions in organic solvents exhibited violet fluorescence.

4,4″-Diamino-*p*-terphenyl dihydrochloride was prepared by suspending some of the powdered diamine in 5% hydrochloric acid solution and heating at 95° for a few minutes. Its identity was confirmed by precipitation of the same product by the passage of hydrogen chloride through the benzene liquors containing the diamine. The white powder was nearly insoluble in water. It darkened at 315°; m. p. 355–370°, with decomposition.

4,4″-Dihydroxy-*p*-terphenyl.—4,4″-Diamino-*p*-terphenyl dihydrochloride, 1.56 g., was suspended in 200 cc. of water containing 10 cc. of concentrated hydrochloric acid solution and the mixture treated at 0° with 0.69 g. of sodium nitrite. After an hour of stirring, the excess nitrous acid was destroyed by the addition of urea and the suspension was filtered through an ice-cold Büchner funnel. The tetrazonium chloride was decomposed with steam as before and the pink micro-plates appearing were collected from the hot water. The yield of crude material was about 0.1 g. This is not surprising in view of the considerable residue remaining after filtration of the tetrazonium chloride solution. Purification was effected by shaking the diphenol with 6 cc. of 10% sodium hydroxide solution and 50 cc. of water, filtering, acidifying and centrifuging. This product was washed three times with water and recrystallized three times from ethyl alcohol. The fine, white plates melted at 375°. With very slow heating they melted below this temperature with decomposition. The diphenol is but slightly soluble in dilute alkali solutions, but these solutions show violet fluorescence.

Anal. Calcd. for $C_{18}H_{14}O_2$: C, 82.42; H, 5.38. Found: C, 82.37; H, 5.45.

4,4″-Diacetoxy-*p*-terphenyl.—4,4″-Dihydroxy-*p*-terphenyl, 0.050 g., was warmed with acetic anhydride and fused sodium acetate in the usual way and the mixture hydrolyzed. The crude, dry product weighed 0.085 g., and, when recrystallized three times from ethyl alcohol, appeared as colorless plates, m. p. 244.3–245.3° (cor.).

Anal. Calcd. for $C_{22}H_{18}O_4$: C, 76.28; H, 5.24. Found: C, 76.30; H, 5.37.

4,4″-Dimethoxy-*p*-terphenyl.—The methylation was carried out as with the ortho isomer. The product was recrystallized three times from benzene. It formed white micro-plates, m. p. 273–275°.

Anal. Calcd. for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25. Found: C, 82.89; H, 6.55.

(11) The sample of dinitroterphenyl used contained other isomeric nitroterphenyls which were not completely removed.

Reaction of *p*-Methoxyphenylmagnesium Bromide with 1,2-Dibromocyclohexane.—*p*-Methoxyphenylmagnesium bromide was prepared from 14.6 g. (0.6 mole) of magnesium turnings, 100 cc. of dry ethyl ether and 112.4 g. (0.6 mole) of *p*-bromoanisole in 100 cc. of dry ether. The conventional Grignard-type apparatus with a 500-cc. addition funnel, a sealed stirrer and a condenser carrying a drying tube at the top, all attached to a 500-cc. three-necked flask, was used. After formation of the Grignard reagent was complete, 48.4 g. (0.2 mole) of 1,2-dibromocyclohexane was added at once, the condenser set downward for distillation and ether removed until the volume of the remaining solution was 200 cc. At this time 200 cc. of dry butyl ether was introduced, and the temperature of the mixture brought gradually to 120° where it was maintained for five and one-half hours with constant stirring. After standing at room temperature overnight the mixture was poured into one-half liter of crushed ice containing 35 cc. of concentrated sulfuric acid. A liter of ethyl ether was added, the water layer separated and extracted twice with ether. During these extractions a gray solid separated at the liquid–liquid interface. This was collected on a Büchner funnel and dried; it weighed 0.65 g. and sublimed at 250–300° (1 mm.) to yield clear, colorless plates which were recrystallized three times from benzene; m. p. 273–275°. This product proved to be 4,4″-dimethoxy-*p*-terphenyl. It did not depress the melting point of an authentic sample of this compound. The ether was heated in a steel bomb at 200° for twenty-four hours with 5 g. of potassium hydroxide and 20 cc. of ethyl alcohol. The product, 0.065 g. of the phenol from 0.10 g. of the ether, was soluble in alkali but insoluble in benzene, acetone and alcohol. It was warmed on a steam-bath in 5% sodium hydroxide while a 2% potassium permanganate solution was added until the green manganate color persisted; about 125 cc. was required. The resulting mixture was cooled, acidified and clarified with sodium bisulfite. The fine, white powder separating was collected on a 4-mm. filter. This was soluble in 5% sodium bicarbonate solution. It sublimed above 300°. The dimethyl ester was prepared,[12] m. p. 140–140.5°. Dimethyl terephthalate melts at 140–141° and a mixture of the two had the same melting point.

The ethereal filtrates from the original Grignard reaction were dried over anhydrous sodium sulfate and concentrated at reduced pressure in a dry air stream. The solid separating was collected, crystallized once from a mixture of benzene and petroleum ether (b. p. 95–96°), from which it separated as a mush. This was dried and sublimed at 150° (0.2 mm.) and recrystallized twice from methylcyclohexane. The compound, 4,4′-dimethoxybiphenyl, separated as plates from this solvent but as needles, m. p. 174.5–175.6°, from methyl alcohol.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59; mol. wt., 214.25. Found: C, 78.24; H, 6.68; mol. wt., 194, 208 (Rast).

Distillation of the ethereal liquors gave several liquid and solid fractions, one of which, 1.12 g., was collected at 135–146° (0.2 mm.) and proved to be more of the biphenyl making the total recovery of this product from the reaction 2.18 g.

Reaction of *p*-Methoxyphenylmagnesium Bromide and 4,4′-Dimethoxybiphenyl.—*p*-Methoxyphenylmagnesium bromide was prepared, as before, from 3.65 g. (0.15 mole) of magnesium turnings under 20 cc. of dry ether and 28.1 g. (0.15 mole) of *p*-bromoanisole in 25 cc. of dry ether. The mixture was stirred and warmed for half an hour after the Grignard formation seemed complete. 4,4′-Dimethoxybiphenyl, 2.0 g., and 50 cc. of dry butyl ether were added at once, the condenser set downward for distillation and the temperature of the stirred mixture raised slowly to 140° where it was maintained for eight hours. The mixture was cooled and held below 15° while 50 cc. of

(12) Huntress and Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 178.

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6 *N* sulfuric acid solution was slowly added. Ethyl ether was added, as before, and the solids separating were collected and dried. Sublimation of the 2.5 g. of crude products so obtained yielded 0.7 g. of 4,4′-dimethoxybiphenyl at a bath temperature up to 150° (0.005 mm.) and 0.1 g. of impure 4,4″-dimethoxyterphenyl up to 280°. The residue was infusible. The terphenyl fraction was recrystallized three times from toluene but still softened at 268° and was not entirely fused at 285° though most melting occurred at 275°. The presence of higher-melting impurities is thus indicated, probably the analogous dimethoxyquaterphenyls or even higher members.

Summary

4′,4″-Dihydroxy-*o*-terphenyl and 4,4″-dihydroxy-*p*-terphenyl, the dimethyl ethers and diacetates have been prepared and characterized.

The reaction between 4,4′-dimethoxybiphenyl and *p*-methoxyphenylmagnesium bromide has been found to form small amounts of 4,4″-dimethoxy-*p*-terphenyl.

URBANA, ILLINOIS RECEIVED DECEMBER 22, 1943

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Pinacols and Pinacolone from *p*-Methoxyacetophenone

BY CHARLES C. PRICE AND GEORGE P. MUELLER[1]

The successful dehydration of the pinacols from acetophenone[2,3] and *p*-hydroxyacetophenone[4] to the corresponding butadiene prompted an attempt to carry out a similar conversion for the two stereoisomeric pinacols from *p*-methoxyacetophenone. In every instance, however, dehydration resulted in rearrangement to the pinacolone.

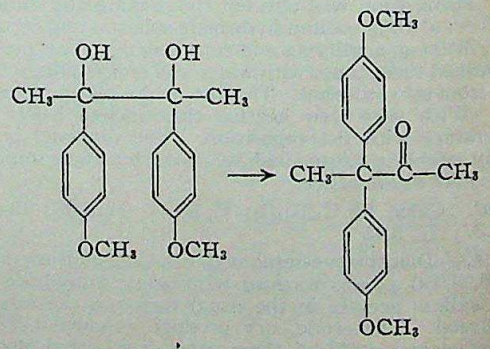
p-Methoxyacetophenone pinacol was prepared in 90% yields by electrolytic reduction of the ketone in potassium acetate, water and alcohol.[5] The crude product, upon repeated recrystallization from methyl alcohol or glacial acetic acid, gave the low- and high-melting isomers, respectively. The low-melting isomer showed some tendency toward solvate formation, the analyses of the compound indicating one-half molecule of methanol present before intensive drying. Also, recrystallization of this isomer, m. p. 122–123°, from ethylene glycol gave material melting at 111–113°; one recrystallization from methanol restored the melting point to its former value. The higher-melting isomer, m. p. 168–169°, was also obtained upon reduction of the ketone by aluminum amalgam in moist ether.

Oxidation of the low-melting isomer with lead tetraacetate yielded *p*-methoxyacetophenone, which was isolated quantitatively as the phenylhydrazone.

Several unsuccessful attempts were made to dehydrate this pinacol. Fraser[3] studied the yields obtained upon dehydration of acetophenone pinacol with acetyl chloride in terms of the time of reaction and found seven minutes at reflux with an equal weight of the acid chloride to be the optimum conditions. Such a reaction carried out with *p*-methoxyacetophenone pinacol (with a trace of hydroquinone present to inhibit polymerization) produced 74% of the pinacolone rather than the diene. A crystal of iodine dropped into the melted pinacol at 150° caused vigorous gas-evolution. The oil realized upon cooling did not show positive reactions either for an unsaturated or ketone derivative.

Both isomeric pinacols were treated repeatedly with fused sodium acetate in acetic anhydride, acetic anhydride and dry pyridine, and the high-melting isomer with benzoyl chloride and sodium hydroxide, but in no instance was esterification of the hydroxyl groups achieved. Any attempt to esterify these groups by an acidic reagent resulted in pinacolone rearrangement.

This rearrangement was conveniently carried out at room temperature in acetic anhydride, a trace of sulfuric acid serving as the catalyst. By analogy with 4,4-dianisyl-3-hexanone, which was obtained upon rearrangement of *p*-methoxypropiophenone-pinacol,[6] it was anticipated that this pinacolone should be 3,3-dianisyl-2-butanone.



This pinacolone did not undergo the iodoform reaction as modified by Fuson and Tullock.[7] This was not conclusive evidence for the absence of the acetyl grouping, however, for Poggi[8] has shown that pinacolone itself would not undergo the iodoform reaction when the procedure of Lieben[9] was

(1) Eli Lilly and Company Fellow, 1941–1943.

(2) Allen, Eliot and Bell, *Can. J. Research*, **17B**, 75 (1939).

(3) Fraser, Thesis, University of Illinois, 1939.

(4) Dodds, Golberg, Lawson and Robinson, *Proc. Roy. Soc.* (London), **127B**, 140 (1939).

(5) We are indebted to Professor Sherlock Swann of the Department of Chemistry for the preparation of this pinacol and to Mr. H. D. Marshall and Mr. H. Kerfman, who carried out the electrolytci reductions under his direction.

(6) Wessely, Kerschbaum, Kleedorfer, Prillinger and Zajic, *Monatsh.*, **73**, 127 (1940).

(7) Fuson and Tullock, THIS JOURNAL, **56**, 1638 (1934).

(8) Poggi, *Atti soc. ital. progresso sci.*, XXI Riunione, **2**, 376 (1933)

(9) Lieben, *Ann.*, VII Supplementband, 218 (1870).

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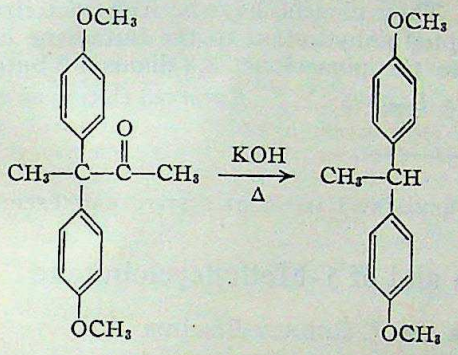
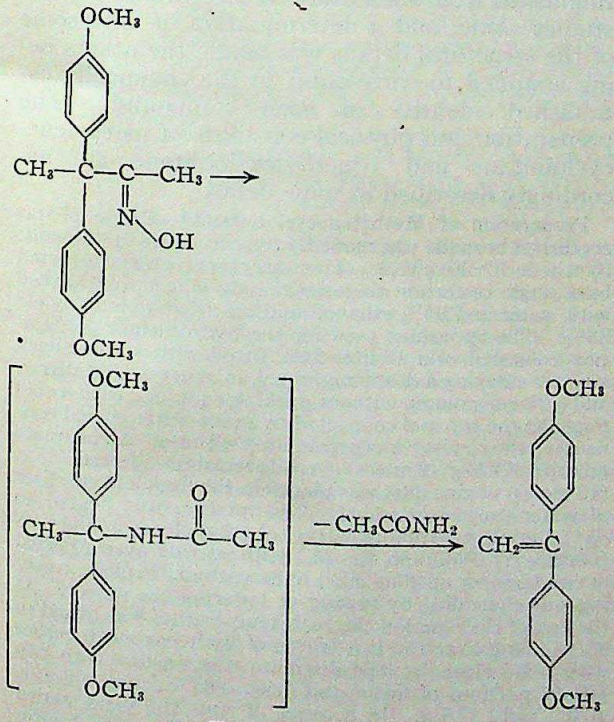
used. Fuson and Tullock observed that pinacolone would undergo the reaction in dioxane solution but that a longer period of heating was necessary.

The ketone was cleaved by molten potassium hydroxide to give a compound having the composition of 1,1-dianisylethane, m. p. 72°. The melting point of this compound has been reported as 59.4° by Lunjak.[10]



The oxime of 3,3-dianisyl-2-butanone was prepared. It proved to be insoluble in alkali. When shaken with phosphorus pentachloride in dry ether this oxime apparently underwent a Beckmann rearrangement. The product, m. p. 141–143°, contained no nitrogen, but showed definite unsaturation. It proved to be 1,1-dianisylethene.[11]



Experimental[12]

2,3-Dianisyl-2,3-dihydroxybutane.—Apparatus for the electrolytic reduction[13] consisted of a 400-cc. beaker, which formed the anode compartment, the anode itself being a sheet of metal bent into a cylinder to fit around an alundum cup which formed the cathode compartment. A rubber stopper fitting into this cup carried the cathodes and an Allihn condenser. In all reductions the area of the cathode was 100 sq. cm. and the total current 2 amp., making the density 0.02 amp. per sq. cm. The combinations of lead anode and cathode or of tin cathode and iron anode were found to be quite satisfactory.

p-Methoxyacetophenone, 20 g., was introduced into a catholyte consisting of 30 g. of potassium acetate, 55 cc. of ethyl alcohol and 25 cc. of water. This mixture was placed in the alundum cup. In some experiments two equivalents of ethyl acetate were added to neutralize the alkali liberated during the reduction. The anolyte consisted of a 40% aqueous solution of potassium carbonate. A current was passed at 110 v. until 120% of the theoretical amount had been used. The entire reduction took place at the refluxing temperature of the catholyte. The catholyte was poured into a liter of cold water and the oil precipitating gradually crystallized and was collected on a filter. The yield of this crude product was 18 g. or 90%. In another experiment where 33 g. of the ketone was reduced in the presence of ethyl acetate the crude product was steam distilled, giving 27 g. of product. The crude material from the first reduction melted at 114–135°.

Repeated recrystallization of the crude product from methyl alcohol gave the low-melting form, m. p. 122–123°. This isomer was quite soluble in glacial acetic acid.

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.34. Found: C, 71.10; H, 7.50.

Similar treatment of the crude pinacol with glacial acetic acid, or even one recrystallization therefrom followed by repeated recrystallization from ethyl alcohol, yielded the high-melting form, m. p. 168–169°.

Anal. Calcd. for $C_{18}H_{22}O_4$: C, 71.50; H, 7.34. Found: C, 71.16; H, 7.22.

Approximately 3 g. of amalgamated, granulated aluminum, 5 g. of *p*-methoxyacetophenone and 30 cc. of moist ether were shaken in a flask for three days, after which the ether was evaporated and the residue warmed with methyl alcohol and filtered. The solution deposited a few crystals of a compound, m. p. 162–165°, which did not depress the melting point of the high-melting isomer obtained above.

Oxidation with Lead Tetraacetate.—The low-melting pinacol, 1.51 g. (0.005 mole), was suspended in 10 cc. of glacial acetic acid and 2.25 g. (0.005 mole) of lead tetraacetate was added to the mixture. After both reactants had dissolved, addition of 1.5 g. of phenylhydrazine in 5 cc. of glacial acetic acid immediately precipitated 2.56 g. of orange *p*-methoxyacetophenone phenylhydrazone. After three recrystallizations from ethyl alcohol it melted at 136–138° (dec.) and did not depress the melting point of an authentic sample of the hydrazone. This derivative decomposed upon standing for three days at room temperature.

Pinacolone Rearrangement: 3,3-Dianisyl-2-butanone.—On addition of one drop of sulfuric acid, 0.5 g. of the low-melting pinacol suspended in 2.5 cc. of acetic anhydride dissolved immediately. Water precipitated the pinacolone which was recrystallized several times from ethyl alcohol, m. p. 69.7–71.5°. The high-melting isomer behaved likewise and yielded the same product. From 7.0 g. of the crude mixture of pinacols, 4.1 g. or 63% of the theoretical amount of the pinacolone was realized.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 76.14; H, 7.27.

The **oxime** was insoluble in strong alkali and was recovered unchanged following two hours of heating in a sealed tube at 100° with concentrated hydrochloric acid. It crystallized from a large volume of ethyl alcohol in fine, colorless needles, m. p. 192–194°.

Anal. Calcd. for $C_{18}H_{21}O_3N$: C, 72.22; H, 7.07. Found: C, 71.75; H, 6.95

(10) Lunjak, *J. Russ. Phys.-Chem. Soc.*, **36**, 301 (1904).
(11) Gattermann, *Ber.*, **22**, 1129 (1889).
(12) The analyses were carried out by Miss Theta Spoor and Miss Dorothy Schneider.
(13) *Cf.* Swann and Nelson, *Trans. Electrochem. Soc.*, **67**, 201 (1935); Swann, Univ. Ill. Eng. Expt. Sta. Bull. 236 (1930).

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Cleavage of the Pinacolone: 1,1-Dianisylethane.—The pinacolone, 1.5 g., was heated for thirty minutes with 20 g. of potassium hydroxide at 170–180°. The cooled melt was dissolved in 100 cc. of water and the insoluble material collected on a filter. This was recrystallized three times from ethyl alcohol, appearing as fine, white platelets, m. p. 70–72°. A 50–50 mixture of this compound with the original ketone melted around 60°.

Anal. Calcd. for $C_{16}H_{18}O_2$: C, 79.31; H, 7.49. Found: C, 79.47; H, 7.80.

Beckmann Rearrangement: 1,1-Dianisylethene.—A suspension of 0.77 g. of 3,3-dianisyl-2-butanone oxime and 0.2 g. of phosphorus pentachloride in 30 cc. of pure, dry ether was shaken for twenty minutes, or until the oxime had dissolved. When the solution was allowed to stand overnight in the cold it deposited large, clear hexagonal plates. Evaporation and recrystallization yielded 0.47 g. of 1,1-dianisylethene, m. p. 141–143°.[11]

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.06; H, 6.16.

Summary

Electrolytic reduction of *p*-methoxyacetophenone has been found to produce a mixture of the two possible diastereoisomeric pinacols in excellent yield. These pinacols have been characterized but attempted dehydration to the butadiene has led only to the pinacolone, 3,3-dianisyl-2-butanone.

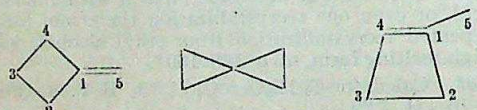
URBANA, ILLINOIS RECEIVED DECEMBER 22, 1943

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, NO. 950]

The Structures of Methylenecyclobutane and of 1-Methylcyclobutene

BY W. SHAND, JR., VERNER SCHOMAKER AND J. RODNEY FISCHER

The hydrocarbon prepared by Gustavson[1] by the action of zinc dust on pentaerythrite tetrabromide has been subjected to an intensive chemical investigation[2] on the basis of which structure (I) has been assigned to this substance. The structure may be regarded as definitely established in spite of the appearance of a recent article by Rogowski,[3] who advocated the spiropentane[3a] structure (II) on the basis of electron diffraction studies. A more recent electron diffraction investigation by Bauer and Beach[4] with results in essentially complete disagreement with those of Rogowski is compatible with structure (I) and eliminates structure (II). The hydrocarbon (III) was also first obtained by Gustavson.[5] It is not as readily accessible as (I) and consequently has received less attention from chemists; its structure, however, is not in doubt.[2]



(I) (II) (III)

The present investigation was undertaken with the aim of isolating methylenecyclobutane and 1-methylcyclobutene in a state as pure as possible and verifying their structures by the electron diffraction method. It was found, however, that the two compounds cannot readily be distinguished from each other by electron diffraction studies alone, and a determination of only some of the structural details was made, the others being assumed to correspond to the chemically established identity of each compound. The preparation and physical constants of methylenecyclobutane and 1-methylcyclobutene are accordingly described in some detail.

Preparation of Methylenecyclobutane.[6]—Crude pentaerythrityl bromide was made by the procedure in "Organic Syntheses."[7] Five moles of pentaerythrytol was converted in a single operation to tetrabromide which was washed with water and 95% ethanol[7] and air-dried, average yield 88%. The apparatus used for the hydrocarbon preparation consisted of a 12-liter flask fitted with a three-neck adapter carrying a dropping funnel, mercury-sealed stirrer, and a 38-cm. column without packing equipped with a cold finger at the top and connected to an ice-water cooled condenser; the receiver was surrounded with ice. An intimate mixture of 776 g. (2 moles) of crude tetrabromide and 785 g. (12 moles) of zinc dust was placed in the flask and one liter of water *cautiously* added. The mixture was heated to 85° on a water-bath and 500 cc. of ethanol was added portionwise (*cf.* Philipow, *loc. cit.*) with stirring over a period of two hours or until no more hydrocarbon distilled; frothing was controlled by raising or lowering the stirrer. At the end of the reaction the bath temperature was raised to 95°, forcing over the last traces of hydrocarbon together with some alcohol. The distillate was washed with two 100-cc. portions of water and dried over calcium chloride at 0°, yield 115 g. In a series of runs the yield varied between 70 and 90%. A quantity of the crude hydrocarbon (1340 g.) was twice fractionated through a 22-mm. inside diameter column, 6.5 ft. long, packed with glass helices and fitted with a total reflux, variable take-off

(1) Gustavson, *J. prakt. Chem.*, [2] **54**, 97 (1896).

(2) More pertinent references: Demjanow, *Ber.*, **41**, 915 (1908); Faworsky and Batalin, *ibid.*, **47**, 1648 (1914); Philipow, *J. prakt. Chem.*, [2] **93**, 162 (1916); Demjanow and Dojarenko, *Ber.*, **55**, 2718, 2727 (1922). The last paper cited demonstrates the identity of the Gustavson hydrocarbon with methylenecyclobutane independently synthesized by a method indicative of structure.

(3) Rogowski, *Ber.*, **72**, 2021 (1939). Structure (II) had previously been advanced in the earlier part of the chemical investigation, but the facts cited in its favor proved on closer examination to be without foundation: Fecht, *Ber.*, **40**, 3883 (1907), *cf.* Mereschkowski, *J. Russ. Phys.-Chem. Soc.*, **46**, 517 (1914) [*Chem. Abst.*, **8**, 3187 (1914); *Chem. Zentr.*, **85**, II, 1266 (1914)]; Zelinsky, *Ber.*, **46**, 160 (1913), *cf.* Philipow, *loc. cit.*, Ingold, *J. Chem. Soc.*, **123**, 1706 (1923).

(3a) A third C_4H_8 hydrocarbon from pentaerythrityl bromide, not identical with either of the Gustavson hydrocarbons discussed in this paper, was recently reported by M. J. Murray and E. H. Stevenson and assigned to formula (II); THIS JOURNAL, **66**, 314 (1944).

(4) S. H. Bauer and J. Y. Beach, THIS JOURNAL, **64**, 1142 (1942).

(5) Gustavson, *J. prakt. Chem.*, [2] **54**, 104 (1896).

(6) The preparations described here were carried out by J. R. F. For details see his Masters' Thesis, California Institute of Technology, 1941.

(7) Schurink in "Organic Syntheses," Vol. 17, p. 73, J. Wiley and Sons, Inc., New York, N. Y., 1937.

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head. About 80% of the distillate[8] boiled at 41.0–41.7° at 750 mm.; this material was refractionated a third time through a 3-foot column packed with helices and a middle portion reserved for electron diffraction study, b. p. 41.39° at 750 mm., n^{10}D 1.4266, n^{15}D 1.4236, n^{20}D 1.4210, d^{20}_4 0.7401, d^{25}_4 0.7349. The product obtained by Whitmore and Williams and used by Bauer and Beach, and identified as methylenecyclobutane by ozonolysis had the constants b. p. 41.3° at 746 mm., n^{20}D 1.4203–6.

Preparation of 1-Methylcyclobutene.—Although Philipow[2] claimed to have fractionated this hydrocarbon from the mixture obtained on treating pentaerythrite tetrabromide with zinc dust, the presence of a constant boiling fraction in this range could not be detected.[9] Several unsuccessful attempts were made to prepare methylcyclobutene by isomerization of methylenecyclobutane over an alumina catalyst at 300°. The greater part of the hydrocarbon was converted to lower boiling material but apparently this consisted almost entirely of products of ring-splitting.[10] Attempts to dehydrate 1-methylcyclobutanol[5,6,11] were also unsuccessful; the use of 60% sulfuric acid and of anhydrous oxalic acid gave polymers while the tertiary alcohol was recovered unchanged after refluxing with iodine.

1-Chloro-1-methylcyclobutane was prepared in 80% yield by treating methylenecyclobutane with excess concentrated aqueous hydrochloric acid at 0°. After shaking for one hour, the lighter phase was washed with sodium carbonate solution, dried over calcium chloride and distilled, b. p. 90–91° at 745 mm., n^{20}D 1.4311, n^{25}D 1.4288, d^{20}_4 0.9495, d^{25}_4 0.9444. The corresponding bromide was prepared in 72% yield from methylenecyclobutane and 62% aqueous hydrogen bromide at 0°, mixing by hand at first and then shaking mechanically for one hour. The bromide layer was worked up in the above manner, b. p. 55–57° at 100 mm., n^{20}D 1.4698, n^{25}D 1.4673, d^{20}_4 1.3179, d^{25}_4 1.3110. 1-Iodo-1-methylcyclobutane was prepared by shaking 68 g. (1 mole) of methylenecyclobutane in a glass-stoppered bottle with a solution of 154 g. (1.2 moles) of hydrogen iodide in 200 g. of glacial acetic acid at 0°.[5] The reaction mixture was poured into one liter of water, the heavy phase separated and washed with bisulfite and carbonate solutions and finally with water, crude yield 94%. At 20 mm. the product boiled at 40–42°, n^{25}D 1.5215, d^{20}_4 1.604, yield 76%.

The chloride, bromide, and iodide were added dropwise under identical conditions to a 100% excess of a boiling solution of potassium hydroxide dissolved in cellosolve (ethylene glycol monoethyl ether). The mixed hydrocarbons produced were collected (yields from chloride 40%, bromide 60%, iodide 60%) and roughly analyzed by comparison[6] of densities and refractive indices with the values found for the pure hydrocarbons. The material obtained from the chloride and from the bromide contained methylenecyclobutane and 1-methylcyclobutene in a ratio of about 2:1, while in the case of the mixture obtained from the iodide, the reverse ratio obtained.

A modification of the original method of Gustavson[5] was therefore employed for the preparation of 1-methylcyclobutene in quantity. Fifty-six grams (1 mole) of potassium hydroxide was dissolved in 250 cc. of cellosolve (cellosolve gave higher yields than ethanol or ethanol–water) and this solution heated to boiling in a 500-cc. flask fitted with dropping funnel and reflux condenser through which water at 45° was circulated. The outlet at the top of the condenser led to another condenser set for downward distillation which was cooled by ice-water and then into a receiver cooled in a dry-ice bath. Ninety-eight grams (0.5 mole) of crude tertiary iodide was added dropwise over a period of two hours to the refluxing alkali solution and the hydrocarbon product washed with ice-water and dried over magnesium perchlorate, yield 20.4 g.

The crude hydrocarbon mixture (233 g.) from several of the above experiments was fractionated twice through the 6.5 ft. column described previously, using, because of the small amount of material available, a higher boiling hydrocarbon still-base. A third fractionation was carried out using a spinning band column similar to the one described by Baker, *et al.*[12] This column had the equivalent of 18 theoretical plates at the reflux rate and throughput used. The considerable portion of material which boiled at 37–38° at 748 mm. in this third fractionation was fractionated again with the spinning band column to obtain material of constant refractive index, b. p. 37.1° at 750 mm., n^{18}D 1.4088, d^{20}_4 0.7244, d^{25}_4 0.7188. This material was used for the electron diffraction investigation.

Electron Diffraction Investigation

Experimental.—The electron diffraction apparatus used in this investigation has been described by Brockway.[13] The camera distance was 10.89 cm., and the wave length of the electrons, determined from transmission photographs of gold foil, was 0.0615 Å. The photographs, made with the samples at about 25°, showed eight maxima and minima extending to s_0 values of about twenty-nine.

Interpretation.—Both the radial distribution method[14] and the correlation method[15] were used in interpreting the electron diffraction photographs. The radial distribution curves were calculated according to the formula where $I(s_k)$

$$rD(r) = \sum_k I(s_k) e^{-as_k^2} \sin s_k r$$

is a visually estimated intensity assuming no falling off of intensity with s_k, and a is chosen so that $e^{-as^2_{max.}} = 0.10$. A plot of the visually estimated intensities was divided into about 50 segments, and the $I(s_k)$'s taken at each endpoint.[16]

Theoretical intensity curves were calculated using the simplified theoretical scattering formula

$$I(s) = \sum_i \sum_j Z_i Z_j \frac{\sin r_{ij} s}{r_{ij}} e^{-a_{ij} s^2}$$

The constant a_{ij} in the exponential temperature factor term was given the value 0.002 for bonded C—H terms, 0.004 for non-bonded C—H terms, and 0.0 for all C—C terms. The contribution of C—H terms is important out to about $s = 20$.

Methylenecyclobutane.—The radial distribution curve shown at the top of Fig. 1 can be interpreted on the basis of a model with structure (I). Peaks occur at 1.09 Å., corresponding to the C—H bond, 1.55 Å., the C—C single-bond distance, 2.20 Å., the cross-ring distance, and 2.61 Å.,

(8) Regarding the composition of the forerun see footnote (5) of reference (4).

(9) Investigators other than Philipow obtained methylcyclobutene by the original Gustavson method, *cf.* for example Dojarenko, ref. (10).

(10) Compare Dojarenko, *Ber.*, **59**, 2933 (1926).

(11) Demjanow and Dojarenko, *J. Russ. Phys.-Chem. Soc.*, **45**, 176 (1913) [*Chem. Abst.*, **7**, 2226 (1913); *Chem. Zentr.*, **84**, I, 2027 (1913)]. The observed constants were b. p. 115–118° at 747 mm., n^{24}D 1.4333, d^{22}_4 0.8971, m. p. −6 to −3°, solubility 1 part in 6.5–7 parts water at 25°, phenylurethan m. p. 139.9° (corr.) [*cf.* Pinkus and Lambert, *Bull. soc. chim.*, [4] **31**, 1312 (1922)].

(12) Baker, Barkenbus and Roswell, *Ind. Eng. Chem., Anal. Ed.*, **12**, 468 (1940).

(13) L. O. Brockway, *Rev. Modern Phys.*, **8**, 231 (1936).

(14) L. Pauling and L. O. Brockway, THIS JOURNAL, **57**, 2684 (1935).

(15) L. Pauling and L. O. Brockway, *J. Chem. Phys.*, **2**, 867 (1934).

(16) R. A. Spurr and V. Schomaker, THIS JOURNAL, **64**, 2693 (1942).

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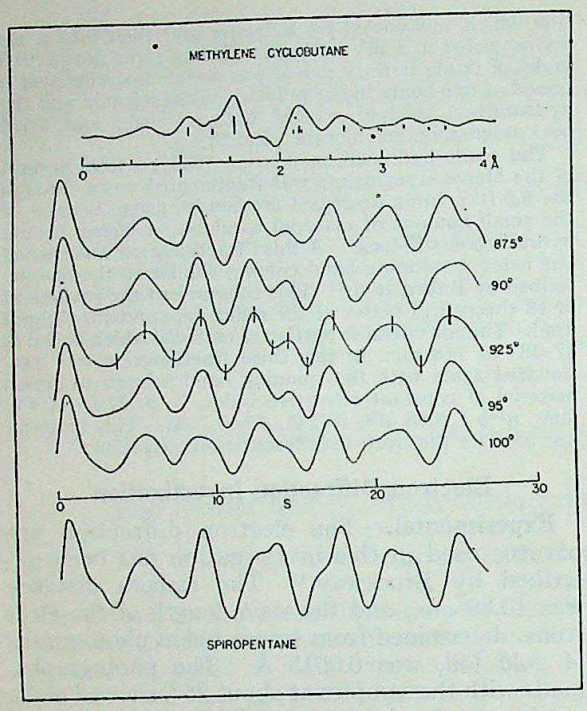

Fig. 1.

the distance between the side-chain carbon and the non-bonded adjacent ring carbon atom. The double-bond distance is not resolved, although a small inflection occurs at 1.33 Å. The spiropentane structure (II) as reported by Rogowski[3] can be ruled out, since it would give only two main peaks, at about 1.54 and 2.87 Å. Other structures differing widely from (I) with respect to their interatomic distances can likewise be ruled out by comparison with the radial distribution function. The chemical identification was accordingly accepted, and theoretical intensity curves calculated for structure (I).

Certain simplifying assumptions were made to reduce the number of structural parameters. The C—H bond distances were taken to be 1.09 Å., and the H—C—H angle on the ring to be 116°. The plane of these H—C—H's was perpendicular to the ring plane and bisecting the ring angles. Moreover, the carbon atoms were assumed to be coplanar and the C—C single-bond distances were taken as being all alike, reducing the problem to one of three parameters, namely, the C—C single-bond distance, the C—C double-bond distance, and an angle of the ring. The single-bond distance was taken from the radial distribution curve to be 1.55 Å., while the double-bond distance and the $\angle C_4C_1C_2$ were varied in calculating the theoretical intensity curves. Curves calculated for values of $\angle C_4C_1C_2$ varying from 87.5° to 100° with a double-bond distance of 1.34 Å. are shown in Fig. 1. The characteristic features of the observed pattern are the roundedness of the first maximum, the shelf-like appearance of the fourth maximum, the roundedness and almost complete

mentary asymmetry of the sixth and seventh maxima. The eighth maximum (not shown) was a sharp peak whose position varied little from curve to curve. Best agreement is given by the curve marked 92.5°. The non-bonded C···C distances in this model are 2.14, 2.24, 2.65 and 3.48 Å.; most of the important C···H distances fall at about 2.20 Å. These distances and their relative weights are shown with the radial distribution curve in Fig. 1. Curves calculated with double bond distances of 1.30 and 1.38 Å. do not give as good agreement with the observed pattern. In general the second minimum is raised, the sixth maximum becomes more symmetrical, and the seventh maximum asymmetrical on the inner side instead of the outer side. Best agreement for these curves is found for $\angle C_4C_1C_2 = 90°$ and C=C = 1.30Å. This is to be expected since for these values of the parameters the distances $C_5\cdots C_2$, $C_5\cdots C_4$, and $C_5\cdots C_3$ are the same as for the 92.5° model with C=C = 1.34 Å. The main difference arises in the cross-ring distances, which are different in the 92.5° model, and alike in the square model.

The effect of removing the restrictions that the ring be coplanar, and that the C—C single-bond distances be all alike was investigated, these variations being made separately. Curves were calculated in which the C_5, C_1, C_2 and C_4 atoms were coplanar (as in ethylene), and the C_3 atom moved perpendicular to this plane. Curves were also calculated for coplanar models with C—C single-bond distances adjacent to the double bond different from those opposite the double bond. Although these theoretical curves showed small but definite points of disagreement with the observed pattern, especially at the second minimum and the sixth and seventh maxima, it became evident that with the available data the complete correlation procedure with the admission of these additional variations could not be made to give more precise information than was already available from the radial distribution function. The final parameter determination was accordingly carried out with the assumptions mentioned in the preceding paragraph.

Quantitative comparison (Table I) of the observed and calculated s values $\left(s = \frac{4\pi}{\lambda}\sin\theta/2\right)$ also shows that the best agreement is for the 92.5° model with C—C single-bond distance 1.55 Å. and C—C double-bond distance 1.34 Å. The 90° model with C—C single-bond distance 1.55 Å. and C—C double-bond distance 1.30 Å. shows a larger average deviation. As discussed above this curve is also considered less satisfactory on the basis of qualitative agreement with the appearance of the observed pattern. The final results are C—C = 1.55 ± 0.02 Å., C=C = 1.34 ± 0.03 Å., and $\angle C_4C_1C_2 = 92.5° \pm 2°$, in fair agreement with Bauer and Beach, who reported C—C = 1.56 ± 0.03 Å., C=C = 1.34 ± 0.02 A., and $\angle C_4C_1C_2 =$ 90°.

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In spite of the exclusion of the spiropentane model by the radial distribution curve, a theoretical intensity curve shown in Fig. 1 was calculated for the spiropentane model of Rogowski[3] for the full s_0 range of our pictures. This curve is in essentially complete disagreement with the observed diffraction pattern, although the positions of the main features are similar.[4]

1-Methylcyclobutene.—The appearance of the diffraction pattern is generally similar to that observed for methylenecyclobutane, but shows numerous distinct points of difference. For 1-methylcyclobutene the first maximum is broader, and higher on the inner side; the shelf-like fourth maximum is less distinctly separated from the third; the fifth minimum is broader and the fifth maximum rises more gradually on the inner side. The sixth maximum is stronger and sharper, and the seventh maximum shows structure on the outer side, which is not too clearly distinguishable. The stronger peaks of the radial distribution curve marked RD in Fig. 2 are at 1.09, 1.54, 2.16 and 2.72 Å. The double-bond distance is not resolved. It was varied from 1.30 to 1.38 Å. in calculating the theoretical intensity curves.

Since the double bond is in the ring in 1-methylcyclobutene there is no doubt that the carbon atoms are coplanar. The same assumptions regarding the hydrogen atoms were made as above. The C—C single-bond distance was taken from the radial distribution curve to be 1.54 Å. The angle $C_5C_1C_2$ was varied from 110 to 140°. About 25 theoretical curves were calculated, of which representative examples are shown in Fig. 2. Curves A to G have double-bond distance 1.34 Å. and the $\angle C_5C_1C_2$ indicated; curves H and I have double-bond distances 1.30 and 1.38 Å., respectively, with $\angle C_5C_1C_2 = 125°$. In all except curves F and G the ring structure was made symmetrical ($\angle C_2C_3C_4 = \angle C_1C_2C_3$; $\angle C_3C_4C_1 = \angle C_4C_1C_2$). For curve F the ring was distorted by increasing the $\angle C_4C_1C_2$ by 5°, and in curve G by decreasing the same angle 5°, changes in other angles being made symmetrically but retaining the same external $\angle C_5C_1C_2$ (= 125° in these curves). On the basis of the features of the observed pattern described above, best agreement was found for the symmetrical ring with double-bond distance 1.34 Å. and 120° < angle $C_5C_1C_2$ < 130°.[17] Curve C (125°) was chosen as best, with calculated non-bonded C···C distances 2.11, 2.71, 2.74 and 3.63 Å. The most important C···H terms are in the neighborhood of 2.20 Å.

(17) The $C_5\cdots C_2$ and $C_5\cdots C_3$ distances and their associated C···H terms, which together are the most important in determining the structure-sensitive features of the theoretical curves, are equal at about $\angle C_5C_1C_2 = 125°$. Consequently a considerable variation of this angle in either direction produces only relatively small differences in the resulting curves, and prevents a close determination of the angle. Similarly curves calculated for distortions of 2 and 5° of the ring in either direction in the manner described above show that distortion of about 5° in either direction is required to produce definite disagreement for the best curve, and does not improve agreement for the other curves.

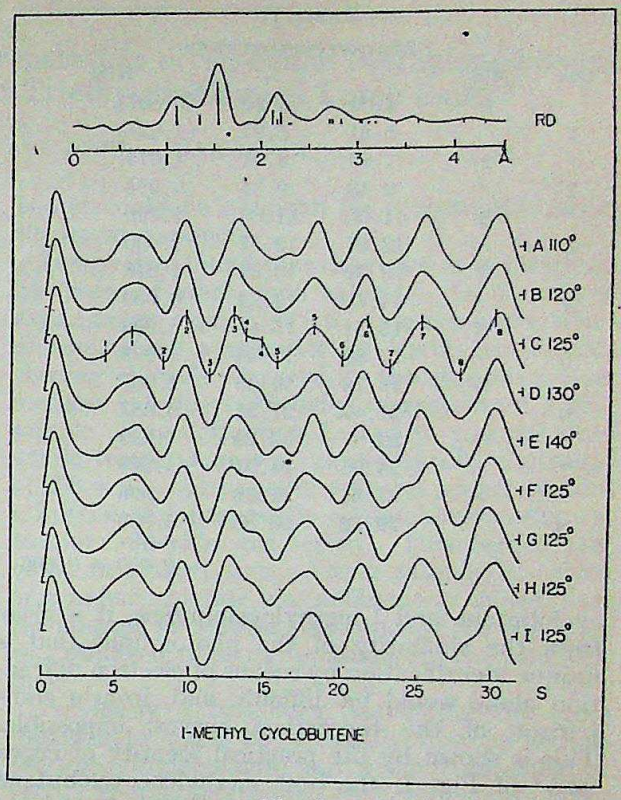

Fig. 2.

These distances with their relative weights are shown on the curve RD of Fig. 2. Quantitative comparison of observed and calculated s values for Curve C (125°) is made in Table II. Our final results are C—C = 1.54 ± 0.03 Å., C=C = 1.34 ± 0.03 Å., $\angle C_5C_1C_2 = 125° \pm 4°$, $\angle C_4C_1C_2 = 93°40' \pm 3°$, etc. (*i. e.*, symmetrical ring structure ±3° distortion).

TABLE I

METHYLENECYCLOBUTANE

Max.	Min.	s_0	s_c (92.5°) 1.34	s_c/s_0	s_c (90°) 1.30	s_c/s_0
	1	4.14	3.61	(0.872)	2.82	(0.688)
1		5.89	5.90	(1.000)	6.06	(1.030)
	2	7.42	7.78	1.048	7.92	1.067
2		9.44	9.35	0.990	9.27	0.982
	3	10.84	11.00	1.014	10.81	1.017
3		12.66	12.66	1.000	12.63	0.998
	4	13.80	14.04	1.017	13.95	1.011
4		14.76	14.83	1.004	14.89	1.009
	5	16.18	16.05	0.992	16.02	0.990
5		17.70	17.36	.980	17.47	.987
	6	19.36	19.10	.987	19.07	.985
6		21.32	21.33	1.000	20.67	.969
	7	23.05	23.03	0.999	22.70	.984
7		24.93	24.91	.999	25.37	1.017
8		29.30	29.31	1.000	29.30	1.000
				1.002 ± 0.011		1.002 ± 0.019

Discussion.—Although the diffraction data for the two substances considered here can be interpreted satisfactorily on the basis of planar cyclic models in agreement with the chemical identification of these substances as methylene-

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TABLE II

1-METHYLCYCLOBUTENE

Max.	Min.	s_0	s_c	s_c/s_0
	1	4.09	3.30	(0.807)
1		5.81	5.97	(1.027)
	2	7.89	8.01	1.014
2		9.43	9.38	0.995
	3	11.00	11.00	1.000
3		12.57	12.57	1.000
	4	13.39	13.57	1.013
4		14.46	14.29	0.989
	5	15.51	15.47	.998
5		17.89	17.84	.998
	6	19.78	19.95	1.008
6		21.49	21.21	0.987
	7	22.97	22.70	.989
7		24.95	24.91	.998
	8	27.51	27.39	.996
8		29.52	29.85	1.009
				0.999 ± 0.006

cyclobutane and 1-methylcyclobutene, it is clear from the similarity of the photographs that a unique identification by means of electron diffraction alone would be difficult, and, from a comparison of the theoretical curves, impossible. This is shown by the practical identity of curve 92.5° of Fig. 1, the best methylenecyclobutane curve, with the 1-methylcyclobutene curves B (120°) and C (125°) of Fig. 2.[18] This is to be expected for molecules whose scattering distances (r_{ij}'s) differ only in what amounts to second order effects: about 70% of the scattering (based on the weight of the coefficients Z_iZ_j/r_{ij}) is due to r_{ij}'s identical for the two models and the remainder is due to r_{ij}'s which are not markedly different. It should be emphasized again that the attempt to differentiate between different chemical structures by the electron diffraction method may not always lead to a unique result, especially when a reasonably great variation of the models representing the various chemical structures is allowed. Where the proposed structures are, however, fundamentally different in geometrical design, the corresponding sets of interatomic distances are usually quite different and a definite choice is made possible.[19] Thus the comparison of the theoretical curves and the diffraction photographs provides definite detailed evidence that neither of our substances is spiropentane.

(18) The similarity of the theoretical curves was overlooked by Bauer and Beach[4] because an error in the cross-ring distance was made in the calculation of their curves E for 1-methylcyclobutene and F for 3-methylcyclobutene. Their model E (private communication from Professor Bauer) was nearly the same as our D (130°).

(19) See for example R. A. Spurr and V. Schomaker, *loc. cit.*; J. Waser and V. Schomaker, THIS JOURNAL, 65, 1451 (1943).

Moreover, a preliminary comparison of the radial distribution curves with the distances to be expected for the models in question at once makes improbable all of the other isomers which contain no four-membered ring, mainly because none of these would give a strong peak at about 2.2 Å. but only a C···H peak, while suggesting the possibility that for 3-methylcyclobutene a reasonable model leading to intensity curves in agreement with the photographs (especially of 1-methylcyclobutene) could be found. It was not thought profitable, however, further to consider these various structures inasmuch as there seemed to be no doubt about the chemical identification and it seemed likely that even after careful consideration by the correlation procedure not all of them could be ruled out with certainty.

The question of the distribution of "strain" in these molecules is of interest. In methylenecyclobutane the strain in the four-membered ring can be taken up by expanding the H—C—H angle to compensate for the compression of the C—C—C angle at the C_2, C_3 and C_4 positions; at C_1 such compensation cannot occur except by increase of the angle $C_4C_1C_2$, as observed. In 1-methylcyclobutene a symmetrical ring structure would be expected if the C_5C_1 single bond were sterically equivalent to the C—H single bond. The angle $C_5C_1C_2$ which distributes equally the distortions from the normal values of the bond angles about the C_1 carbon atom is 125°, in agreement with the angle 125 ± 4° found above. The angle distortion for the system C—C—C is then nearly equal to that for C=C—C, indicating that in this case at least the effective bending constants for the two systems are apparently not markedly different.

The results of Rogowski[3] are not clarified. A radial distribution analysis of his s_0 values leads to the distances 1.55 and 2.88 Å., in agreement with the spiropentane model. In the absence of more details on the preparation and physical constants of the substance used in his investigation no further explanation can be given than was offered by Bauer and Beach.

The authors wish to express their thanks to Dr. E. R. Buchman for suggesting this research, and for his assistance and interest in the work.

Summary

The preparation and physical constants of methylenecyclobutane and 1-methylcyclobutene are described. The electron diffraction investigation of these compounds shows that they are cyclic structures with the expected configurations and distances.

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[CONTRIBUTION FROM NOYES LABORATORY OF CHEMISTRY, UNIVERSITY OF ILLINOIS]

Studies in the Chromammines. III. Preparation of Di-acido Diethylenediamine Salts by Thermal Decomposition of Triethylenediamine Luteo Salts[1,2]

BY CARL L. ROLLINSON[3,4] AND JOHN C. BAILAR, JR.

It has been observed that $[Cr\ en_3]Cl_3 \cdot 3^1/_2H_2O$[5] and $[Cr\ en_3](SCN)_3 \cdot H_2O$ lose one-third of their ethylenediamine (and all their water of crystallization) when heated for several days, the former at 160°,[6] and the latter at 130°.[7,8,9,10] The products of thermal decomposition of the luteo chloride and luteo thiocyanate are, respectively, *cis*-$[Cr\ en_2Cl_2]Cl$[6] and *trans*-$[Cr\ en_2(SCN)_2]SCN$.[8]

These reactions are of practical importance as means for preparing salts of the *cis*- and *trans*-diacido series and as essential steps in *cis–trans* isomerization cycles.[11] The influence of the anion on the configuration of the product is theoretically significant. It is noteworthy that *trans*-$[Cr\ en_2Cl_2]Cl$ is not converted to the *cis* isomer when heated at 160°[12] nor is *cis*-$[Cr\ en_2(SCN)_2]SCN$ converted to the *trans* isomer at 130°.[8]

The order of temperatures at which the two luteo salts decompose, namely, $Cl^- > SCN^-$, is in accord with results reported for other metal ammines. The vapor pressure curves for a series such as $[Ni(NH_3)_6]X_2$ parallel the curves for the corresponding ammonium salts, NH_4X; *i. e.*, the order of temperatures at which a given pressure is reached is $I^- > Br^- > Cl^- > SCN^-$ for both the hexammine salts and the ammonium salts.[13]

The apparent simplicity of these reactions is misleading, however. Preliminary attempts to prepare the *cis*-dichloro salt by thermal decomposition of the luteo chloride were completely unsuccessful. Weighed samples of the latter were heated by various means under a variety of conditions, including temperatures ranging from 160 to 220°, times up to one month, application of vacuum and use of surface extenders such as ground Pyrex or green glass, ground porous plate and glass beads. Although the samples lost weight slowly, the yellow color of the luteo salt never changed to the characteristic red-violet of the *cis*-dichloro salt. None of the desired compound could be obtained by recrystallization of the brown products.

It was then found that the reaction is catalyzed by traces of ammonium chloride. In a series of experiments carried out to determine the effect of impurities, a quantity of triethylenediamine chromic chloride prepared by the chromic sulfate method (1) was repeatedly recrystallized and a sample of each fraction heated in a small oven whose temperature was automatically controlled at 208 ± 3°. The results were disappointing until a fraction unintentionally contaminated with ammonium chloride was tested. This turned red-violet in a short time. Other samples to which ammonium chloride was deliberately added were then heated for several hours and *cis*-$[Cr\ en_2Cl_2]Cl$ was obtained from the products by recrystallization.

Previously it had been found that the luteo thiocyanate could be thermally decomposed to the *trans*-dithiocyanato salt without difficulty at 130°. It was determined that ammonium thiocyanate rather than ammonium chloride is the catalyst in this case.

The preparative methods used account for our success with the thiocyanate and failure with the chloride in the preliminary experiments. Our samples of luteo thiocyanate had been prepared by reaction of the chloride with ammonium thiocyanate as described by Pfeiffer[10] and we found that such samples contain catalytic quantities of ammonium thiocyanate. On the other hand, our original luteo chloride was never in contact with ammonium salts since it was prepared directly from chromous chloride.[14] The luteo chloride which Pfeiffer decomposed was prepared by a method involving reaction of the luteo sulfate with ammonium chloride,[6] a fact whose significance was at first overlooked. Such samples still contain catalytic amounts of ammonium chloride after recrystallization.

To demonstrate conclusively the catalytic nature of these reactions, pure samples of luteo chloride and thiocyanate, to which ammonium chloride and ammonium thiocyanate, respectively, were added in various ways, were heated at controlled temperatures until decomposition was nearly complete as shown by weight loss. To insure freedom from ammonium salts except those intentionally added, the luteo chloride was prepared by the reaction of the sulfate with hydrochloric acid[1] and the luteo thiocyanate from the chloride by means of sodium thiocyanate[1]; the products were recrystallized. Pure samples of the

(1) For the second paper in this series, see Rollinson and Bailar, THIS JOURNAL, **65**, 250 (1943).

(2) Presented at the 99th meeting of the American Chemical Society, Cincinnati, Ohio, April 9, 1940.

(3) Abstracted from a portion of a thesis submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of Illinois, 1939.

(4) University Fellow in Chemistry; present address, Central Research Laboratory, Monsanto Chemical Company, Dayton, Ohio.

(5) The symbol "en" represents one molecule of ethylenediamine.

(6) Pfeiffer, Koch, Lahdo and Trieschmann, *Ber.*, **37**, 4277 (1904).

(7) Pfeiffer, *et al.*, *ibid.*, **37**, 4256 (1904).

(8) Pfeiffer, *et al.*, *ibid.*, **37**, 4269 (1904).

(9) Pfeiffer, *ibid.*, **33**, 2690 (1900); **34**, 4303 (1901).

(10) Pfeiffer, *Z. anorg. Chem.*, **24**, 294 (1900); **29**, 107 (1901).

(11) Ref. 6, p. 4265.

(12) Ref. 6, p. 4264.

(13) Weinland, "Komplex-Verbindungen," Ferdinand Enke, Stuttgart, 1924, p. 485.

(14) Balthis and Bailar, THIS JOURNAL, **58**, 1474 (1936).

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two salts as controls were heated along with those contaminated with ammonium salts. The effect of recrystallization of luteo chloride and thiocyanate contaminated with ammonium salts was also determined.

In all cases the contaminated samples decomposed faster than the controls. The pure luteo chloride turned brown while that to which ammonium chloride had been added turned red-violet. While Pfeiffer reported a temperature of 160° and a time of several days,[6] we found that thermal decomposition of the chloride is nearly complete in a few hours at 210°; this reaction is too slow to be practical even at 180°. Decomposition of the thiocyanate is also complete in a few hours, at 130°, instead of several days as was indicated by Pfeiffer[9]; the discrepancy may be due to difference in ammonium thiocyanate content of Pfeiffer's luteo thiocyanate and that used in the present investigation.

Recrystallization of the luteo thiocyanate containing ammonium thiocyanate greatly decreases the rate of thermal decomposition. Recrystallization of the luteo chloride containing ammonium chloride, on the other hand, causes no change in the rate of thermal decomposition. This may be due to the fact that the luteo thiocyanate is much less soluble than the chloride while ammonium thiocyanate is much more soluble than ammonium chloride. Consequently, recrystallization is more efficient in the case of the thiocyanate.

The specificity of catalyst action seems to indicate that negative ions from the catalyst molecules actually enter the complex nucleus. While ammonium thiocyanate catalyzes the thermal decomposition of the luteo thiocyanate, ammonium chloride does not, even though the luteo thiocyanate crystals obviously contain thiocyanate ions in tremendous excess over the amount required (in the form of ammonium thiocyanate) for catalysis. No attempt was made to test the effect of ammonium thiocyanate on the decomposition of the luteo chloride, since this reaction proceeds at practical rates only at temperatures above that at which ammonium thiocyanate is converted to thiourea.

The water of crystallization of both the luteo chloride and thiocyanate (accounting for 51.2 and 23.1%, respectively, of the total theoretical weight loss) is readily driven off whether or not a catalyst is present. Pure samples decompose rapidly to an extent corresponding approximately to the loss of water of crystallization and thereafter lose weight at a greatly decreased rate. On the other hand, samples contaminated with ammonium salts continue to decompose rapidly even after the weight loss corresponds to the water of crystallization, marked decrease in rate occurring only after considerable ethylenediamine has been driven off.

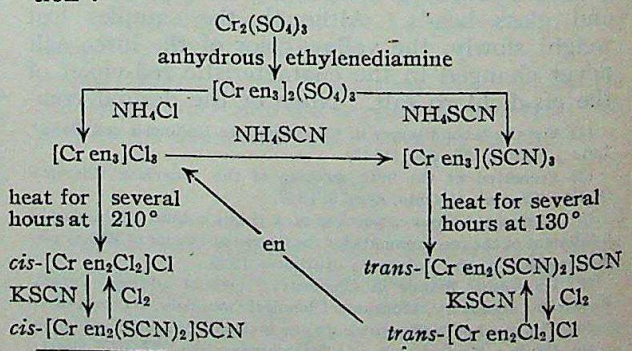
Determination of the conditions on which these reactions depend makes them available as synthetic procedures superior to the usual methods for preparing *cis*-$[Cr\ en_2Cl_2]Cl \cdot H_2O$ and *trans*-$[Cr\ en_2(SCN)_2]SCN \cdot H_2O$. The *cis*-dichloro salt is prepared from pure luteo chloride recrystallized from 1% ammonium chloride solution. The salt, spread in a thin layer, is heated for several hours at 208–212°. The course of the reaction is followed by weighing at intervals. The product may be recrystallized[15] but for most purposes it suffices to wash it with cold concentrated hydrochloric acid. A yield of 50% is easily obtained.

trans-$[Cr\ en_2(SCN)_2]SCN \cdot H_2O$ is prepared in a similar way from the luteo thiocyanate recrystallized from 25% ammonium thiocyanate solution. The salt is heated at about 130°, but not above 134°. The product is recrystallized from warm water. The yield is 60% or better.

These methods are definitely superior in convenience and efficiency to the usual procedures. The *cis*-dichloro salt is ordinarily prepared from potassium chromioxalate by a series of reactions involving synthesis of $[Cr\ en_2C_2O_4][Cr\ en(C_2O_4)_2]$ and $[Cr\ en_2(C_2O_4)]Cl$ as intermediates. Werner[16] reported a yield of only five grams of the *cis*-dichloro salt from one hundred grams of chromioxalate. The *cis*-dichloro salt may also be prepared by repeated evaporation of a solution of the luteo chloride with hydrochloric acid, but the yield is poor.[17]

Pfeiffer prepared *trans*-$[Cr\ en_2(SCN)_2]SCN \cdot H_2O$ by the action of ethylenediamine on $K_3[Cr(SCN)_6]$[8,9] as well as by thermal decomposition of the luteo salt. The yield by the former method is only 22% since separation of the *cis* and *trans* isomers is necessary. Pfeiffer's objection that the method of thermal decomposition is too slow is invalidated by the results of the present investigation.

The importance of these thermal decompositions is indicated by the following cycle based on reactions reported by Pfeiffer and co-workers[11] and those reported here and in a previous communication[1]:



(15) Ferguson (Thesis, University of Illinois, 1934) outlines a suitable procedure. Five grams of the salt is dissolved as quickly as possible in 20 cc. of water at 50–60°. The solution is rapidly filtered and 5 cc. of concentrated hydrochloric acid is added. On cooling in an ice–salt-bath, the solution deposits small red-violet needles of the pure salt.

(16) Werner, *Ber.*, **44**, 3132 (1911).

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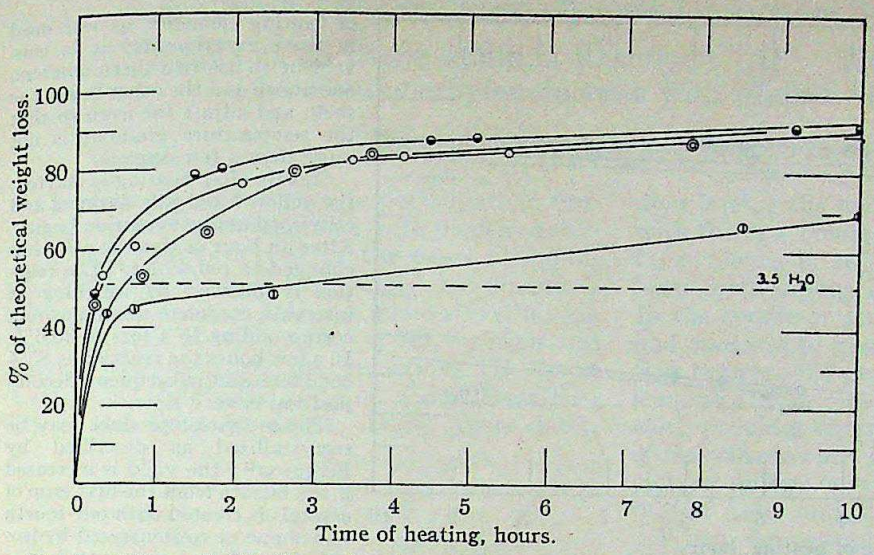

Fig. 1.—Effect of NH_4Cl on the thermal decomposition of $[Cr\ en_3]Cl_3 \cdot 3.5H_2O$ at 210°: ①, pure $[Cr\ en_3]Cl_3 \cdot 3.5H_2O$; ©, pure $[Cr\ en_3]Cl_3 \cdot 3.5H_2O$ ground with 2% solid NH_4Cl; ○, pure $[Cr\ en_3]Cl_3 \cdot 3.5H_2O$ recrystallized from 1% NH_4Cl solution; ◒, pure $[Cr\ en_3]Cl_3 \cdot 3.5H_2O$ recrystallized from 1% NH_4Cl solution, then from H_2O.

Repeated evaporation of the *cis*-dichloro salt with hydrochloric acid and mercuric chloride results in the formation of a mercury *trans*-dichloro double salt, but the yield is poor.[18] This *cis–trans* isomerization may be readily accomplished by use of the above reactions.

Preliminary rate studies indicate that these thermal decompositions are first order reactions, but lack of consistency of results of successive runs precludes a final conclusion. The method used, which evidently requires certain refinements, comprised heating the luteo chloride and thiocyanate (contaminated with ammonium salts) in an apparatus arranged to permit absorption and titration of the ethylenediamine evolved.

Experimental

Apparatus.—In determining the catalytic effect of ammonium salts, a small electric oven whose temperature could be closely controlled was used. This was made from a thin-walled refractory tube, closed at one end, 20 cm. long by 9 cm. inside diameter, wound with chromel wire and covered with alundum cement. The cylinder was enclosed in a transite box and fitted with a door made of transite. A thermometer and mercury thermoregulator were inserted through holes in the closed end of the cylinder. Temperature was controlled by auxiliary resistances which were short-circuited out of the system by a relay except when it was actuated by the thermoregulator.

(18) Ref. 6, p. 4279.

Thermal decomposition of larger quantities of the luteo chloride and thiocyanate, in preparation of the di-acido salts, was carried out in a large electric oven heated by a set of coils at the bottom. A baffle was placed over the coils to minimize the temperature gradient from the bottom to the top of the oven.

Catalytic Effect of NH_4Cl on the Thermal Decomposition of $[Cr\ en_3Cl_3] \cdot 3^1/_2H_2O$.—Pure luteo chloride, prepared by the method previously described,[1] was treated with ammonium chloride in various ways. One-gram samples of the products were heated in the small oven at 208–210° and weighed at intervals. Samples of the following were included for comparison: pure luteo chloride as a control; luteo chloride prepared from the sulfate by reaction with ammonium chloride; a sample prepared by recrystallization of luteo chloride contaminated with ammonium chloride.

The results are shown in Graph 1. It is evident that traces of ammonium chloride profoundly affect the course of the reaction and that the catalytic effect is not nullified by recrystallization of the luteo chloride containing ammonium chloride. It is also apparent that the luteo chloride prepared by action of ammonium chloride on the luteo sulfate contains catalytic amounts of ammonium chloride.

The effect of temperature on the course of the reaction was also determined. A 3-g. sample of pure luteo chloride recrystallized from 1% ammonium chloride solution was heated at 180° and weighed at intervals. The experiment was repeated at 170°. The data are plotted on Graph 2 with a plot of data for 210° for comparison. It is evident that the reaction would be inconveniently slow at 160° as specified by Pfeiffer.

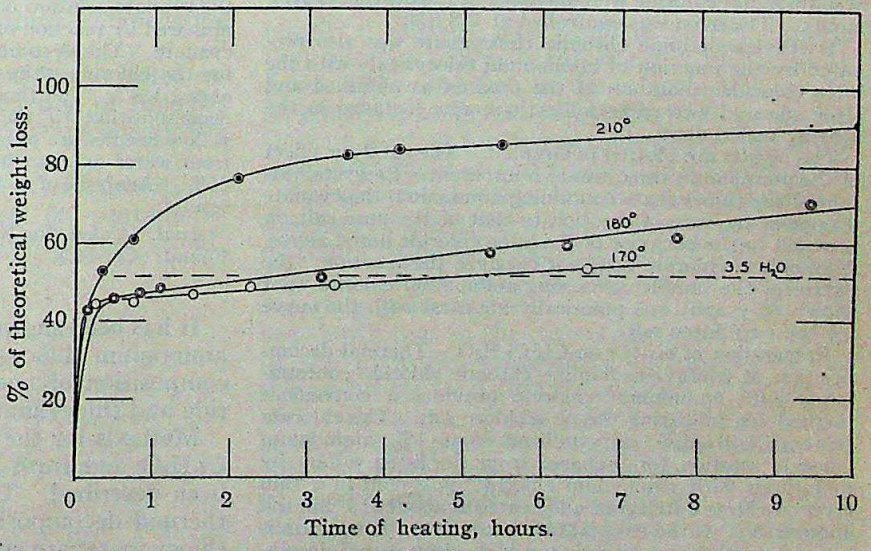

Fig. 2.—Effect of temperature on the thermal decomposition of $[Cr\ en_3]Cl_3 \cdot 3.5H_2O$ recrystallized from 1% NH_4Cl solution.

Catalytic Effect of NH_4SCN on the Thermal Decomposition of $[Cr\ en_3](SCN)_3 \cdot H_2O$.—Similar experiments were carried out with 3-g. samples of luteo thiocyanate containing small amounts of ammonium thiocyanate. To insure

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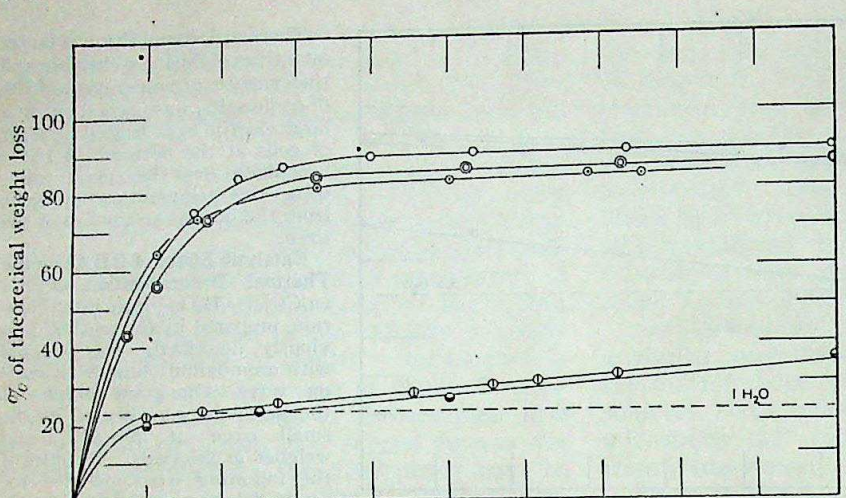

Fig. 3.—Effect of NH_4SCN on the thermal decomposition of [Cr en$_3$]$(SCN)_3$·H_2O at 130°: ⊕, pure [Cr en$_3$]$(SCN)_3$·H_2O; ©, pure [Cr en$_3$]$(SCN)_3$·H_2O ground with 2% solid NH_4SCN; O, pure [Cr en$_3$]$(SCN)_3$·H_2O recrystallized from 25% NH_4SCN solution; ◉, pure [Cr en$_3$]$(SCN)_3$·H_2O washed with saturated NH_4SCN solution; ◒, NH_4SCN-contaminated [Cr en$_3$]$(SCN)_3$·H_2O recrystallized from water.

freedom from ammonium salt except that intentionally added, the luteo thiocyanate was prepared from the pure chloride by means of sodium thiocyanate. Samples for thermal decomposition were prepared by adding ammonium thiocyanate to the triethylenediamine compound in various ways. A sample of the pure luteo thiocyanate, as a control, and a sample of the pure salt ground with 2% of ammonium chloride were included in the heating experiments. The oven was controlled at 128–130°.

Triethylenediamine chromic thiocyanate was also prepared by the reaction of ammonium thiocyanate with the luteo chloride. Samples of the product as obtained and after one and two recrystallizations were included in the heating experiments.

The results are plotted in Graph 3. The catalytic effect of the ammonium thiocyanate is apparent. Recrystallization of the thiocyanate containing ammonium thiocyanate decreases the rate of reaction to that of the pure salt, in contrast to the behavior of the luteo chloride noted above. Ammonium chloride does not catalyze the reaction; the curve for the sample containing ammonium chloride (not shown on graph) was practically identical with the curve for the pure luteo salt.

Preparation of *cis*-[Cr en$_2$Cl$_2$]Cl·H_2O.—Thermal decomposition of triethylenediamine chromic chloride contaminated with ammonium chloride provides a convenient method for preparing the *cis*-dichloro salt. The chloride [Cr en$_3$]Cl_3·$3^1/_2H_2O$ recrystallized from 1% ammonium chloride solution (or prepared from the luteo sulfate by metathesis with ammonium chloride) is spread in a thin layer on a large watch glass and heated at about 210° but not above 215°. If the temperature is too low, the reaction is inconveniently slow; if it is too high, deep-seated decomposition occurs with formation of brown reaction products. Some care must be taken to obtain the right temperature, especially with ovens in which there is a shelf above a set of heating elements, as was used in these experiments; it is convenient to use two thermometers, one above and the other below the shelf, and adjust the oven so that the temperature gradient is not more than a few degrees.

Shortly after heating is started, the yellow luteo salt darkens and ethylenediamine evolution begins. After an hour or two the color has changed to red-violet. The reaction is followed by weighing at intervals, complete decomposition corresponding to a loss of 30.6%. In a few hours the reaction is 85% complete and subsequent decomposition is very slow.

The red-violet product may be recrystallized as described by Ferguson[15]; the yield is increased if the filtrate from the first crop of crystals is treated with one-fourth its volume of concentrated hydrochloric acid and evaporated in a stream of air. However, the salt may be obtained pure enough for resolution and most other purposes by washing the product of thermal decomposition with ice-cold concentrated hydrochloric acid. The yield in either case is 50% or more. Analysis of a typical product by ignition of a sample to Cr_2O_3 gave the following results:

Anal. Calcd. for [Cr en$_2$Cl$_2$]Cl·H_2O: Cr, 17.51. Found: Cr, 17.6.

Preparation of *trans*-[Cr en$_2$(SCN)$_2$]SCN·H_2O.—Excellent yields of the *trans*-dithiocyanato salt may be obtained by a similar procedure. The starting material is pure luteo thiocyanate washed with saturated ammonium thiocyanate solution or unrecrystallized luteo thiocyanate prepared by reaction of the chloride with ammonium thiocyanate. The decomposition is carried out as described for the chloride; the temperature is not allowed to rise above 134°. The theoretical loss in weight for complete decomposition to the di-acido salt is 18.4%. Orange yellow needles are obtained by recrystallizing the product from water as described by Pfeiffer.[10] The yield is 60–65%. Analysis of a typical product gave the following results:

Anal. Calcd. for [Cr en$_2$(SCN)$_2$]SCN·H_2O: Cr, 14.29. Found: Cr, 14.4.

Summary

It has been shown that ammonium chloride and ammonium thiocyanate catalyze the thermal decomposition of triethylenediamine chromic chloride and thiocyanate, respectively.

Methods for the preparation of *cis*-[Cr en$_2$Cl$_2$]Cl·H_2O and *trans*-[Cr en$_2$(SCN)$_2$]SCN·H_2O have been described. These procedures, based on the thermal decomposition of the luteo chloride and thiocyanate, are superior to the usual methods in convenience and efficiency.

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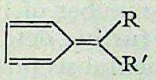
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

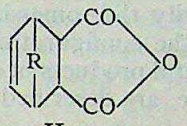
Studies on Diene-addition Reactions. II.[1] The Reaction of 6,6-Pentamethylenefulvene with Maleic Anhydride

BY R. B. WOODWARD AND HAROLD BAER

The capacity of fulvenes to participate in normal diene-addition reactions with maleic anhydride was first observed in the cases of 6,6-diphenylfulvene (I, R = R′ = C_6H_5), 6,6-dimethylfulvene (I, R = R′ = CH_3—), and 6-styrylfulvene (I, R = $C_6H_5CH{=}CH$—, R′ = H), by Diels and Alder,[2] who assigned the structures (II, R = $(C_6H_5)_2C<$ *or* $(CH_3)_2C<$ *or* $C_6H_5CH{=}CH{-}CH<$) to their products. Some years later,

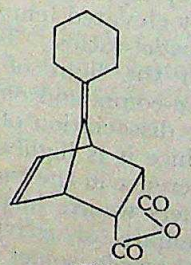


I

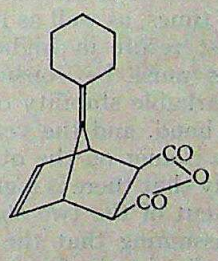


II

Kohler and Kable[3] obtained addition products from 6,6-tetramethylenefulvene (I, R,R′ = —$(CH_2)_4$—) and 6,6-pentamethylenefulvene (I, R,R′ = —$(CH_2)_5$—) with maleic anhydride. These adducts were hydrogenated to dihydroderivatives, from which cyclopentanone and cyclohexanone, respectively, were obtained on ozonization; these facts are in accordance with the formulations (II, R = $(CH_2)_4C{=}C<$ *or* $(CH_2)_5C{=}C<$). These investigators made the further striking observation that their adducts, as well as those obtained earlier by Diels and Alder, had the remarkable property of dissociating readily into their components, even on solution in the cold in a variety of solvents. Subsequently, Alder and Stein[4] called attention to the fact that the reaction of fulvenes with maleic anhydride is not stereochemically homogeneous, but leads in many cases to a mixture of products having different configurations. Thus, according to these workers, 6,6-pentamethylenefulvene gives approximately 40% of an adduct having the *endo-* (III) and 60% of a product with the *exo-* configuration (IV). No experimental evidence in support of these statements has been forthcoming in the intervening six years.[4] In the course of a related investigation, we have had occasion to make a careful study of the reaction between 6,6-pentamethylenefulvene and maleic anhydride. As will appear in the sequel, our work provides *experimental proof of the formation of the stereoisomers III and IV:* beyond this, our picture differs very considerably in detail from that of Alder and Stein.



III



IV

When 6,6-pentamethylenefulvene and maleic anhydride are allowed to react in benzene solution, at room temperature, an *α-adduct*, $C_{15}H_{16}O_3$, m. p. 132°, is obtained.[3] If, however, the mother liquor from the recovery of this product is allowed to stand for several weeks, very large beautiful crystals of a new, *β-adduct*, $C_{15}H_{16}O_3$, m. p. 93°, gradually separate. *Further, as the initial condensation is carried out at higher temperatures, the formation of the β-adduct takes place more rapidly, and less of the α-adduct is obtained.* These isomeric substances exhibit strikingly different behavior on solution in organic solvents. Solutions of the α-adduct, *e. g.*, in ethyl acetate or benzene, develop a deep yellow color, slowly in the cold, and very rapidly if warmed, as a result of partial dissociation into the (colored) fulvene and maleic anhydride. The β-adduct, on the other hand, is stable for relatively long periods, even in boiling solution. Only on heating for long periods above its melting point does the material gradually turn yellow.

Each of the adducts is reduced on shaking in ethyl acetate solution with hydrogen over reduced platinum oxide to a dihydro compound; the α-dihydro adduct melts at 146°, while the corresponding β-derivative has m. p. 104°. Kohler[3] has shown that in the case of the α-adduct, addition of hydrogen takes place exclusively on the ethene bridge, and further addition of hydrogen with saturation of the cyclohexylidene double bond is not possible. Similar phenomena are observed in the case of the new β-adduct. It is worthy of note that these results are concordant with the theory of catalyst hindrance developed *inter alia* by Linstead and his associates,[5] *viz.*, approach of a hydrogen-laden catalyst surface to the ethene bridge (arrows) of the model skeleton (V) would be relatively unhindered, while on the other hand approach to the other double bond would be difficult, if not impossible.

Both dihydro derivatives were stable, and therefore were used to determine the relationships be-

(1) *Cf.* Woodward, THIS JOURNAL, **64**, 3058 (1942).
(2) Diels and Alder, *Ber.*, **62**, 2081 (1929).
(3) Kohler and Kable, THIS JOURNAL, **57**, 917 (1935).
(4) This first suggestion of stereochemical complications in the reaction of fulvenes with maleic anhydride was made briefly by the German authors in a review article on their elegant work on the steric course of diene-addition reactions in general [*Angew. Chem.*, **50**, 514 (1937)]. However, in spite of intimations there and elsewhere [*cf.* Alder and Backendorf, *Ann.*, **535**, 102 (1938), Note 1] that experimental support for the ideas advanced would appear shortly, none has appeared in the considerable interval since 1937.
(5) Linstead, Doering, Davis, Levine and Whetstone, THIS JOURNAL, **64**, 1985 (1942).

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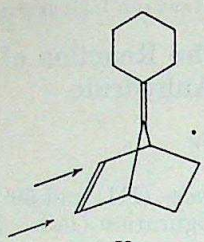
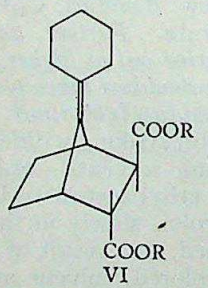


V

tween the isomeric initial adducts, since the dissociation of the latter themselves, at least in the case of the α-adduct, would have precluded their survival in the reactions necessary for configurational determination.

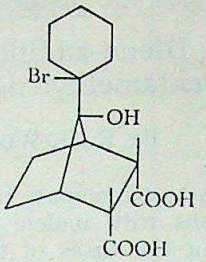
On catalytic esterification with methanol, the α-dihydro adduct was converted to an *oily* α-dihydrodimethyl ester, while the β-dihydro adduct gave a *crystalline* β-dihydrodimethyl ester, m. p. 65°. *Either dimethyl ester on boiling with sodium methoxide in methanol solution was inverted with the formation of the same trans-dihydrodimethyl ester, m. p. 75°.*[6] These facts demonstrate clearly that the latter compound has the structure (VI, R = CH_3), and that the difference



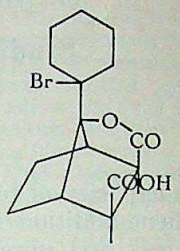
VI

between the initial α- and β-adducts is one of *endo-exo* isomerism. As a further check on the identity of the dimethyl esters, m. p. 75°, from the two sources, hydrolysis by acetic and hydrochloric acids of material prepared in either way gave the same *trans*-dihydrodicarboxylic acid (VI, R = H), m. p. 230–232° (dec.).

We are now in a position to determine which is the *endo*- and which the *exo*-series. On bromination of the α-dihydroanhydride (m. p. 146°) after long boiling in dilute acetic acid solution (to ensure opening of the anhydride ring), *a bromohydroxydicarboxylic acid* (VII), $C_{15}H_{21}O_5Br$, m. p. 153°, neutral equivalent, 179, was obtained. Similar treatment of the β-dihydroanhydride (m. p. 104°) gave a *bromolactone monocarboxylic acid* (VIII), $C_{15}H_{19}O_4Br$, m. p. 147°, neutral equivalent, 332. Since only *exo*-carboxyls are suitably placed for lactonization involving the cyclohexylidene double bond, it is evident that the bromination products have the structures (VII) and (VIII),[7] re-

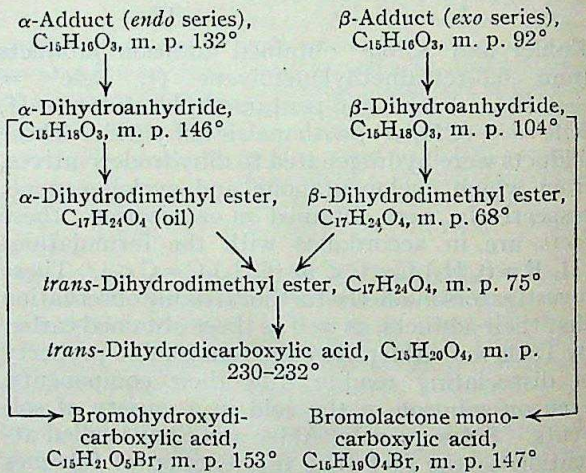


VII



VIII

spectively, and, consequently, *that the α-series has the endo-configuration, while the β-series are exo-derivatives, i. e., the α-adduct (m. p. 132°) has the structure (III), while the β-adduct (m. p. 93°) is to be formulated as (IV).* The accompanying chart will clarify the somewhat involved series of reactions of the configurational proof. A number of incidental products in each series, not further detailed here, are described in the experimental section.



We turn now to a more detailed discussion of the phenomena observed in connection with the formation and stability of the two addition products. We have demonstrated clearly that while the *endo* isomer is formed more rapidly, longer reaction times, as well as relatively elevated temperatures, result in higher *exo*/*endo* ratios. These facts must be considered in the light of the remarkable stability of the *exo*-compound on the one hand, and the very facile dissociation of the *endo* isomer on the other. Since it is highly unlikely that there is a great difference in the energy content of the two stereoisomers we are justified in assuming that the intermediate, or activated complex for the formation of the *endo* isomer is of lower energy than that involved in the *exo* addition. On this basis, the *endo* addition, having the lower energy barrier, will proceed more rapidly, but will compete less favorably as the reaction is carried out at higher temperatures, and the true equilibrium ratio, c_{exo}/c_{endo} will be more rapidly approached. Further, considering the reverse process, the *endo* isomer will pass relatively easily over the same (low) barrier, while the *exo* compound is stabilized by the higher barrier over

(6) For similar inversions, *cf.*, Hückel and Goth, *Ber.*, **58**, 447 (1925); Cook and Linstead, *J. Chem. Soc.*, 946 (1934); Linstead and Doering, THIS JOURNAL, **64**, 1991 (1942).

(7) There is some uncertainty in these formulations, in that the relative positions of the bromine and of the hydroxyl (or lactonic) substituents may be reversed. The point, of course, has no bearing on the configurational argument.

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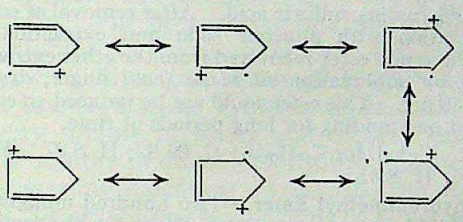
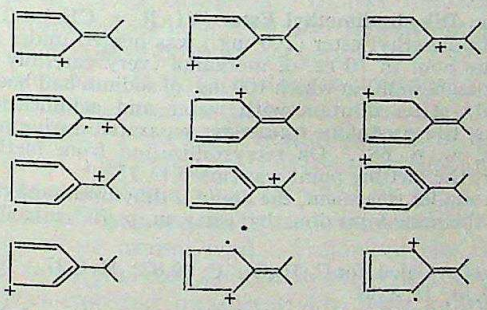
which it must pass during the dissociation process. The situation is symbolized in Fig. 1, and is not an unfamiliar one in organic chemistry.[8] (In the diagram E_{ABexo} is assumed to be somewhat lower than E_{ABendo} since the *exo* isomer apparently preponderates under those conditions under which it is likely that true *exo-endo* equilibrium is most nearly approached.)

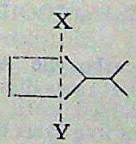
In mechanistic terms we are now faced with the problem of explaining the lower energy of the intermediate for *endo* addition. This may be interpreted in terms of the flat dipolar aggregate, $[A][B] \longleftrightarrow [A.]^+[B.]^- \longleftrightarrow [A]^+:[B]^-$, suggested by one of us as an intermediate in diene-addition reactions of this type.[1] The situation with regard to the distribution of charge over the diene moiety [A] of the intermediates is as follows; in the case of cyclopentadiene the charge will be distributed over the four carbon atoms of the unsaturated system:



In the case of the fulvenes, similar hybridization will likewise result in distribution of charge throughout the (now greater) conjugated system, *viz.*

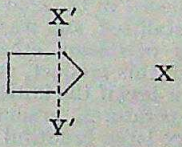


It is clear that in the fulvene case, loss of charge will be distributed over the molecule (IX) on both sides of the line XY



IX

Now when a maleic anhydride molecule adds to a fulvene, the addition takes place at the carbon atoms intersected by the line XY. Further, depending on whether the adding molecule lies to the left or right of the line XY, the *endo* or *exo* isomer will be obtained. It is now evident that in the fulvene case, attractive forces, arising both from exchange and charge overlapping, will be operative between the reacting fragments, whether the maleic anhydride molecule takes one position or the other and, further, that these attractive forces should be greater in the case of the intermediate for *endo* addition, in view of the somewhat greater concentration of charge within the pentacyclic ring. In the cyclopentadiene case it is clear that attractive forces will be operative only in the event that the molecule approaches from the left side of X′Y′ (*cf.* X). These relations will



be apparent from inspection of the space models of Fig. 2. (In these models, the opposite charges on each template, A [or A′] and B, are small, and equal to one another. The signs are intended to represent approximate *distribution*, rather than magnitude of charge.)

It is very likely that similar energetic conditions obtain in the diene-addition reactions of the simple dienes, in which only *endo* products are normally obtained. In this case, E^*_{ABexo} (*cf.* Fig. 1) is so high that none of the *exo* product is obtained under attainable conditions. In this connection it is worthy of note that in one case, that of the dimerization of cyclopentadiene,[9] the observed phemomena are similar to those noted in the case of the fulvenes: *i. e.*, at moderate temperatures, only the *endo* isomer is formed, while heating for long periods at elevated temperatures gives a mixture of *exo* and *endo* products. It is not unlikely that further cases will be found where variation of the experimental conditions will permit isolation of both steroisomers.

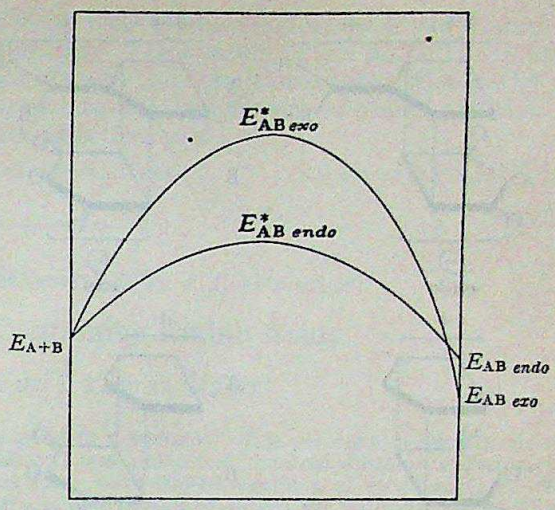


Fig. 1.

(8) Strictly speaking of course these considerations apply rigidly only to the *free* energies of the various processes. Since, however, the two isomers are both relatively rigid structures of equivalent symmetry, their entropies will be comparable, and we are justified in dealing with the absolute heat content of the various species.

(9) Alder and Stein, *Ann.*, **504**, 219 (1933).

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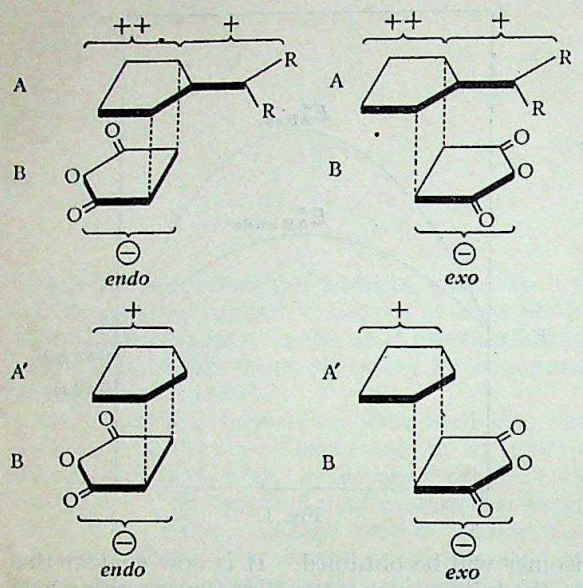

Fig. 2.—Models of intermediate complexes in the addition of maleic anhydride [B] to a fulvene [A] and to a simple diene [A']. Dotted lines indicate points of union in the final products.

Experimental

6,6-Pentamethylenefulvene was prepared according to Kohler's method.[3]

Condensation of 6,6-Pentamethylenefulvene and Maleic Anhydride.—All condensations were carried out with equimolar quantities of the reactants in concentrated benzene solution (fulvene/benzene = 1, by volume.) After standing (with or without heating) for specified times, the reaction mixture was placed in the cold room (5°), where the **α-adduct** (III) crystallized, and was collected and recrystallized from ether–petroleum ether, m. p. 132°. The mother liquors from this product, on standing for periods up to two weeks (or less if the initial reaction was carried out at higher temperatures) gradually deposited the **β-adduct** (IV) in very large beautiful plates, m. p. 87–90°, which on recrystallization from ligroin (b. p. 80–120°) had m. p. 92–93°. A sample recrystallized four times for analysis had m. p. 93.0–93.5°.

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 73.9; H, 6.58. Found: C, 74.07; H, 6.75.

The following figures illustrate the effect of conditions on the yield of the α-adduct: ten minutes at 50°—20.8, 20.5%; 30 minutes at 60°—13.6, 14.5%; 60 minutes at 50°—3.1%.

The α-adduct, on solution in benzene or ethyl acetate, developed a yellow color, slowly in the cold, and rapidly on warming, while the β-adduct was apparently perfectly stable under these conditions.

β-Dihydroadduct.—On shaking with hydrogen over reduced platinum oxide, the β-adduct (3.2 g.) in 30 cc. purified[10] ethyl acetate consumed 315 cc. hydrogen (1 mole = 315 cc.) in *ca.* one-half hour at 26.5°, 776 mm., and the hydrogenation stopped. The residue after removal of solvent was thrice crystallized from ligroin (b. p. 90–120°), and dried *in vacuo* for three hours; needles, m. p. 103–104°.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.1; H, 7.37. Found: C, 73.3; H, 7.73.

Hydrogenation of the α-adduct under similar conditions gave the **α-dihydroadduct,**[3] m. p. 146°. Both dihydro adducts were readily converted into half-methyl esters by dissolving in methanol containing a drop of phenolphthalein solution, and adding 10% aqueous sodium hydroxide until the color persisted after boiling for a few minutes. After adding water to the cooled solution and acidifying with 10% hydrochloric acid, the substances were collected and recrystallized from ligroin. The **α-dihydromonomethyl ester** had m. p. 114°.

Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.05; H, 7.97. Found: C, 69.17; H, 8.39.

The **β-dihydromonomethyl ester had m. p. 118°.**

Anal. Calcd. for $C_{16}H_{22}O_4$: C, 69.05; H, 7.97. Found: C, 68.60; H, 7.92.

That these half-esters are different is evidenced by the mixed m. p., 89–92°.

In similar manner, using ethanol, certain half ethyl esters were prepared, *e. g.*, directly from the β-adduct, the **β-monoethyl ester,** m. p. 137–137.5°, was obtained.

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.5; H, 7.6. Found: C, 70.57; H, 7.72.

From the α-dihydroadduct, an **α-dihydromonoethyl ester,** m. p. 104.5–105°, was prepared.

α-Dihydrodimethyl Ester.—One-half gram of the α-dihydroanhydride (m. p. 146°) was heated fifteen hours under reflux in 10 cc. of absolute methanol containing 0.2 cc. of 30% fuming sulfuric acid. After removal of solvent, neutralization with aqueous soda and extraction with ether, the crude ester recovered from the ether extract was purified by sublimation *in vacuo* (cold finger, dry ice), yield, 330 mg. This ester could not be induced to crystallize even on standing for long periods of time.

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.82; H, 8.27. Found: C, 69.96; H, 8.31.

β-Dihydrodimethyl Ester.—Two hundred milligrams of the β-dihydroadduct (m. p. 104°) treated in the same way, gave 180 mg. of *crystalline* ester, recrystallized from methanol–water, m. p. 65°.

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.82; H, 8.27. Found: C, 69.50; H, 8.59.

***trans*-Dihydrodimethyl Ester** (VI, R = CH_3).—The β-dihydrodimethyl ester (100 mg.) was heated under reflux for one hour in 10 cc. of methanol (very carefully dried over magnesium) in which 100 mg. of sodium had been dissolved. After dilution with water and acidification to litmus, the crystalline *trans*-ester separated during several hours, m. p. 68°. On recrystallization from methanol-water, the melting point was raised to 75°.

On similar treatment, the liquid α-dihydrodimethyl ester gave the same *trans* dimethyl ester, m. p. 75°, mixed m. p. 75°.

Anal. Calcd. for $C_{17}H_{24}O_4$: C, 69.82; H, 8.27. Found: C, 69.43; H, 8.36.

On saponification by heating with acetic and hydrochloric acids, the *trans* ester from either source gave the *trans*-dihydrodicarboxylic acid (VI, R = H), m. p. 230–232° (*dec.*).

Anal. Calcd. for $C_{13}H_{18}(COOH)_2$: neut. eq., 132. Found: neut. eq., 130.

Bromolactone Monocarboxylic Acid (VIII).—The β-dihydro adduct (m. p. 104°) was dissolved in glacial acetic acid, and water was added until the solution became cloudy. After boiling for five to six hours, the solution was rediluted with water until a slight cloudiness appeared. Bromine was then added dropwise until a slight yellow color persisted. After evaporation to very small volume (steam-bath), incipient precipitation was completed by immersion in ice. The collected solid was recrystallized from aqueous acetic acid, m. p. 146.5–147.5° (dec.).

Anal. Calcd. for $C_{15}H_{19}O_4Br$: C, 52.48; H, 5.58. Found: C, 52.41; H, 5.62. Calcd. for $C_{14}H_{18}O_2Br(COOH)$: neut. eq., 343. Found: neut. eq., 332.

Bromohydroxydicarboxylic Acid (VII).—Similar treatment of the α-dihydro adduct (m. p. 146°) gave the dibasic acid, recrystallized from aqueous acetic acid, m. p. 152–153° (dec.).

(10) Fieser, "Experiments in Organic Chemistry," 2nd ed., 1941, p. 364.

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Anal. Calcd. for $C_{16}H_{21}O_5Br$: C, 49.87; H, 5.86. Found: C, 49.75; H, 5.57. Calcd. for $C_{13}H_{19}OBr(COOH)_2$: neut. eq., 181. Found: neut. eq., 179.

Summary

It is shown that in the addition of maleic anhydride to 6,6-pentamethylenefulvene, a dissociable *endo* product and a stable *exo* isomer are obtained. The relation of the properties of these isomers and the conditions under which they are formed to the mechanism of diene-addition reactions is discussed.

CAMBRIDGE, MASS. RECEIVED AUGUST 26, 1943

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, S. M. A. CORPORATION]

Hydantoins of Some Sulfur Containing Amino Acids

BY JOSEPH V. KARABINOS[1] AND J. LESTER SZABO

Introduction

The preparation of a number of hydantoins from amino acids has been described by Boyd.[1a] The hydantoins of the sulfur containing amino acids, cystine[2] and methionine,[1a] have been cited previously. The preparation of a thiol hydantoin in crystalline form, however, has not been described in the literature although Boyd[1a] did mention a non-crystalline cysteine hydantoin which was very soluble in water and alcohol but only slightly soluble in ether, chloroform and benzene.

In this communication we describe the preparation of the crystalline hydantoins of *l*-cysteine, *dl*-homocysteine, homocysteine and S-benzylhomocysteine. *l*-Cysteine hydantoin was obtained in good yield by treating *l*-cystine hydantoin with sodium in liquid ammonia. In like manner we have prepared *dl*-homocysteine hydantoin from the hydantoins of both homocystine and S-benzylhomocysteine. It is interesting to note that under the conditions used in this work, the hydantoin ring is stable to the reduction of sodium in liquid ammonia. The hydantoins of homocystine and S-benzylhomocysteine were obtained by the action of potassium cyanate and hydrochloric acid on the corresponding amino acid. Following the isolation of *l*-cysteine and *dl*-homocysteine hydantoins each was oxidized quantitatively with iodine to yield *l*-cystine- and *dl*-homocystine hydantoins, respectively.

In addition to the many sulfur compounds which have gained attention in therapeutic research certain hydantoins have likewise commanded interest, *e. g.*, in alleviating the symptoms of epilepsy. The fact that the hydantoins of *l*-cysteine and *dl*-homocysteine proved to be water soluble suggested possible practical applications.

Experimental Part

l-Cysteine Hydantoin.—Cystine hydantoin (29 g.) which was prepared according to the directions of Hess[2] was dissolved in 200 cc. of liquid ammonia to which sufficient sodium was added to maintain a blue color for ten minutes. The greater part of the ammonia was allowed to evaporate at room temperature and the last traces were removed in a vacuum. Ten per cent. hydrochloric acid (200 cc.) was added and the acid solution was extracted four times with 200-cc. portions of ethyl acetate. The extracts were combined, dried over sodium sulfate and the solvent was removed *in vacuo*. The white crystalline residue (15 g.) was easily recrystallized from water to give platelets melting at 144–145°.[3]

Anal. Calcd. for $C_4H_6O_2N_2S$: C, 32.87; H, 4.14. Found: C, 33.21; H, 4.14.

S-Benzylhomocysteine Hydantoin.—A mixture of 50 g. of S-benzylhomocysteine[4] and 22 g. of potassium cyanate was heated in 250 cc. of water for thirty minutes until a clear solution was obtained. When 10% hydrochloric acid (620 cc.) was added slowly, a solid precipitated which liquefied on heating. The mixture was heated on the steam-bath for several hours. After cooling the mixture, the crystals were collected on a filter. Following recrystallization from ethanol the material melted at 103–104° and weighed 45 g. (81%).

Anal. Calcd. for $C_{12}H_{14}O_2N_2S$: N, 11.19. Found: N, 11.43.

Homocystine Hydantoin.—Homocystine (10 g.) was suspended in 57 cc. of boiling water with 7.4 g. of potassium cyanate until complete solution was obtained. Ten per cent. hydrochloric acid (110 cc.) was added and the mixture evaporated on the steam-bath to about one-half the original volume. The homocystine hydantoin which crystallized from the cooled solution was collected by filtration, washed with water until chloride free and dried. The yield was 10 g. (82%); the compound melted at 204–205°.

Anal. Calcd. for $C_{10}H_{14}O_4N_4S_2$: N, 17.60. Found: N, 17.70.

***dl*-Homocysteine Hydantoin: (a) From Homocystine Hydantoin.**—To 5.2 g. of homocystine hydantoin in 50 cc. of liquid ammonia was added 1.8 g. of sodium. The ammonia was allowed to evaporate spontaneously. The residue was taken up in water and neutralized to a *p*H of 4 and extracted four times with 50-cc. portions of ethyl acetate. The extracts were combined, dried with sodium sulfate and the solvent removed *in vacuo*. The yield was 3.5 g. (67%) of a product melting at 120°.

(b) From S-Benzylhomocysteine Hydantoin.—To 6 g. of S-benzylhomocysteine hydantoin in 100 cc. of liquid ammonia was added 1 g. of sodium. The residue remaining after the evaporation of the ammonia was evacuated thoroughly, treated with 50 cc. of ice water, acidified with 12 cc. of concentrated hydrochloric acid and filtered. The solution was extracted twice with 10-cc. portions of benzene to remove toluene and dibenzyl and then with four 15-cc. portions of ethyl acetate. The ethyl acetate extracts were combined, dried and evaporated *in vacuo*. The residue weighed 3.5 g. (92%) and melted at 121–122°. Recrystallization from ethyl acetate did not raise the melting point.

(1) Present address, Department of Chemistry, Ohio State University, Columbus (1), Ohio.

(1a) Boyd, *Biochem. J.*, **27**, 1838 (1933).

(2) Hess, THIS JOURNAL, **56**, 1421 (1934).

(3) All melting points were recorded on a microstage and are uncorrected.

(4) Patterson and du Vigneaud, *J. Biol. Chem.*, **111**, 393 (1935).

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Anal. Calcd. for $C_5H_8O_2N_2S$: C, 37.50; H, 5.03. Found: C, 37.83; H, 5.05.

Oxidation of Homocysteine Hydantoin.—Fifty mg. of homocysteine hydantoin was titrated with 2.9 cc. of 0.1 *N* iodine solution which is 93% of the theoretical. The crystals which precipitated were collected by filtration, dried and gave a m. p. of 201–203°. A mixed m. p. with homocystine hydantoin gave no depression.

Oxidation of Cysteine Hydantoin.—Sixty-four and a half mg. of cysteine hydantoin consumed 4.4 cc. of 0.1 *N* iodine solution which is the theoretical quantity. The crystals were collected on a filter and dried. The compound decomposed above 300° and gave a positive disulfide test.

Summary

1. The preparation of the hydantoins of *l*-cysteine, *dl*-homocysteine, S-benzylhomocysteine, and *dl*-homocystine has been described.

2. The hydantoin ring is stable to the reduction of sodium in liquid ammonia.

CHAGRIN FALLS, OHIO RECEIVED JANUARY 6, 1944

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, S. M. A. CORPORATION]

The Dehydration of Hydantoin-5-propionic Acid

BY J. LESTER SZABO AND JOSEPH V. KARABINOS

Introduction

If it is assumed that hydantoins may enolize, three possible structures (II, IV and VI) may be postulated for the compound obtained by the dehydration of hydantoin-5-propionic acid. Dakin[1] has stated that such an enolization (III ⇄ I) is possible since racemization of optically active hydantoins probably occurs through this mechanism.

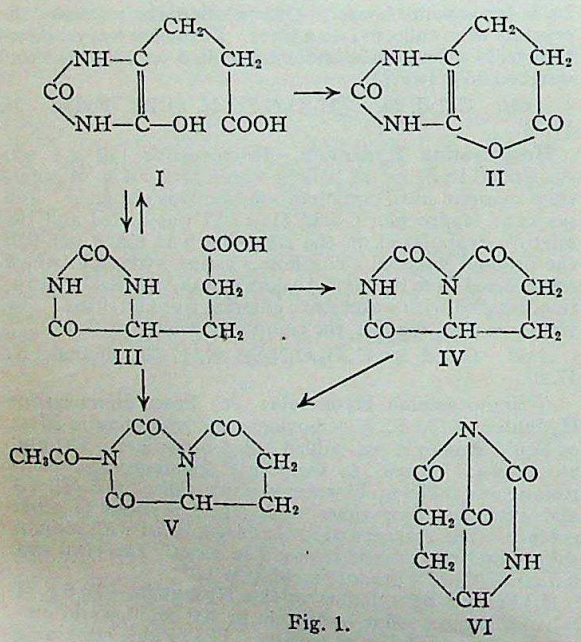

Fig. 1.

By the action of phosphoric anhydride on hydantoin-5-propionic acid (III) a molecule of water was split out and the resulting product obtained in good yield. Theoretically this could be either II, IV or VI. Acetylation of the acid as well as the lactam yielded the same mono-acetyl derivative (V). Neither the dehydration product nor the acetyl derivative reacted with aqueous potassium permanganate or bromine in carbon tetrachloride. The mono-acetyl derivative could not be acetylated further under conditions which yielded diacetyl hydantoin. These facts tend to indicate one of the lactam formulas (IV or VI).

However, the structure of the dehydration product was shown by the following experiment. 2-Thiohydantoin-5-propiolactam-1 (VIII) had been synthesized previously from pyrrolidone carboxylic acid and ammonium or potassium thiocyanate by Johnson and Guest[2] and also by Nicolet and Johnson.[3] By desulfurization of the thiohydantoin with chloroacetic acid they obtained hydantoin-5-propionic acid instead of hydantoin-5-propiolactam-1. Hydrolysis with dilute hydrochloric acid gave 2-thiohydantoin-5-propionic acid (IX). It was obvious, therefore, that if the acid (IX) could be converted back to the lactam (VIII) by dehydration with phosphoric anhydride, we could assume that hydantoin-5-propionic acid undergoes a similar reaction and that our dehydration product is the oxygen analog of VIII, *i. e.*, hydantoin-5-propiolactam-1 (IV). 2-Thiohydantoin-5-propionic acid (IX) was obtained by the hydrolysis of VIII and converted back to VIII by dehydration with phosphoric anhydride. We may assume, therefore, that the dehydration of hydantoin-5-propionic acid yields hydantoin-5-propiolactam-1 (IV) and not hydantoin-5-propiolactam-3 (VI) or the lactone (II).

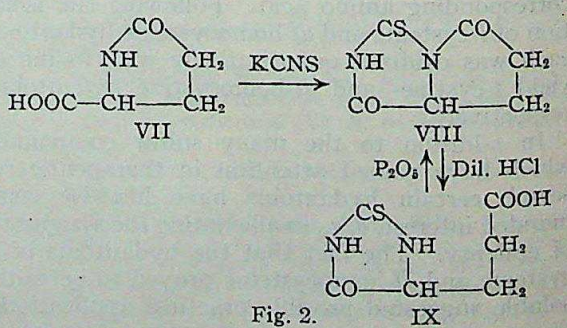

Fig. 2.

(1) Dakin, *Am. Chem. J.*, **44**, 48 (1910).

(2) Johnson and Guest, *ibid.*, **47**, 242 (1912).

(3) Nicolet and Johnson, *ibid.*, **49**, 204 (1913).

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Experimental

dl-**Hydantoin-5-propionic Acid (III).**—Hydantoin-5-propionic acid was prepared in a 62% yield from sodium glutamate and potassium cyanate according to the directions of Dakin.[1] After recrystallization from water, the product melted at 170°.[4]

Hydantoin-5-propiolactam-1 (IV).—Hydantoin-5-propionic acid (1.7 g.) was refluxed for two hours in 15 cc. of xylene containing 0.5 g. of phosphorus pentoxide. The mixture was allowed to stand overnight and crystals separated. The solvent was decanted and the crystals washed with 10 cc. of cold methanol and then recrystallized from 70% methanol. The yield was 1.2 g. (78%) of product melting at 196–198°. After three recrystallizations the substance melted sharply at 201°.

Anal. Calcd. for $C_6H_6O_3N_2$: C, 46.75; H, 3.92; N, 18.18. Found: C, 46.87; H, 4.12; N, 18.25.

1-Acetyl-hydantoin-5-propiolactam-1 (V).—A mixture of hydantoin-5-propionic acid (5 g.) and acetic anhydride (25 cc.) was refluxed for one hour. The excess solvent was removed by distillation *in vacuo* and the residue was crystallized by the addition of alcohol. Recrystallization from alcohol yielded 5 g. (88%) of product melting at 147–148°. One gram of this product was refluxed for four hours with acetic anhydride and recovered unchanged.

Anal. Calcd. for $C_8H_8O_4N_2$: C, 48.98; H, 4.11. Found: C, 48.96; H, 4.31.

Acetylation of Hydantoin-5-propiolactam-1.—Twenty-five mg. of hydantoin-5-propiolactam-1 was acetylated under the same conditions as the hydantoin-5-propionic acid and yielded a product melting at 147–148°. A mixed melting point with the product obtained by the acetylation of hydantoin-5-propionic acid showed no depression.

2-Thiohydantoin-5-propiolactam-1 (VIII).—Pyrrolidone carboxylic acid (VII) (40 g.) (from glutamic acid) and 28 g. of ammonium thiocyanate were warmed on a steam-bath with 180 cc. of acetic anhydride and 20 cc. of glacial acetic acid. A red solution was obtained which yielded 22 g. (43%) of crystals (m. p. 206–207°) after the addition of benzene. The recorded m. p. is 206–207°.

2-Thiohydantoin-5-propionic Acid (IX).—Two grams of (VIII) was refluxed with 25 cc. of 1 *N* hydrochloric acid for one-half hour and cooled. Two grams (90%) of acid (IX) melting at 121.5–122° crystallized out. The recorded m. p. is 122°.

Dehydration of 2-Thiohydantoin-5-propionic Acid (IX).—Two hundred mg. of IX was refluxed for two hours with 15 cc. of toluene containing 100 mg. of phosphorus pentoxide. The solvent was decanted while hot from a small amount of brown residue. On cooling crystals separated from the toluene solution. The yield was 120 mg. (66%) melting at 206–207°. A mixed m. p. with the lactam (VIII) gave no depression.

Acknowledgment.—We wish to thank Mr. John M. Kolbas for his assistance in the preparation of the manuscript.

Summary

The products obtained by the dehydration and the acetylative dehydration of hydantoin-5-propionic acid have been shown to possess the lactam structure IV and V.

CHAGRIN FALLS, OHIO RECEIVED JANUARY 6, 1944

(4) All melting points were recorded on a micro stage and are uncorrected.

NOTES

Synthesis of Bromoacetals

BY PAUL Z. BEDOUKIAN

Of the many syntheses of bromoacetal reported, that of Filachione[1] is the most convenient. It consists of slow addition of bromine to a mixture of vinyl acetate and alcohol at very low temperature (−40°). A recent modification of this method[2] involves very slow addition (ten hours) of bromine in the vapor form to a well-cooled mixture of vinyl acetate and alcohol.

The yields in both procedures are not high, being 46% for dimethyl acetal and 58–68% for diethyl acetal, and the method is rather cumbersome and time-consuming. Its chief disadvantage appeared to be the presence of methyl or ethyl alcohol during the bromination reaction, necessitating slow addition of bromine at low temperatures in order to prevent the bromination of the alcohol.

When bromine is added to a mixture of vinyl acetate and carbon tetrachloride at 0–10°, addition is very rapid and in the theoretical quantities. On adding the mixture to methyl or ethyl alcohol (99.5–100%) with cooling, a rapid reaction takes place with the formation of bromoacetal. This method is applicable to small or large scale preparations and the yields are of the order of 80–85% for dimethyl acetal and 75–80% for diethyl acetal.

Contrary to previous reports, bromoacetal freed from traces of bromoacetaldehyde by means of bisulfite or fractionation is not a lachrymator but does possess a rather pungent odor. On standing for several weeks a slight decomposition takes place with the formation of bromoacetaldehyde.

Experimental

Preparation of Bromoacetaldehyde Dimethyl Acetal.—One mole of vinyl acetate (86 g.) b. p. 71–73° was added to 150 ml. of carbon tetrachloride and cooled in an ice–water mixture. A mixture of 90 ml. of carbon tetrachloride and 160 g. of bromine was added to the vinyl acetate mixture with shaking, care being taken not to allow the temperature to rise above 10°. The addition took about twenty minutes and the end-point was reached when bromine no longer decolorized. The brominated mixture was then added to 350 ml. of methyl alcohol (99.5–100%), and cooled during the first hour to prevent rise in temperature as bromoacetal is formed. It was shaken occasionally and allowed to stand for two days. The mixture which consisted of two layers was diluted with one liter of water and the bromoacetal–carbon tetrachloride layer drawn off. The methyl alcohol–water mixture was further ex-

(1) Filachione, THIS JOURNAL, **61**, 1705 (1939).
(2) "Organic Syntheses," **23**, 8 (1943).

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tracted twice with 150 ml. of carbon tetrachloride to recover the major portion of the dissolved bromoacetal. The carbon tetrachloride solutions were combined and distilled through a Whitmore–Fenske type column. Bromoacetaldehyde dimethyl acetal (124 g. or 83%) distils at 48–49° (14 mm.), n^{20}D 1.4450; d^{20}_4 1.430.

Preparation of Bromoacetaldehyde Diethyl Acetal.—The above procedure was repeated using 500 ml. of ethyl alcohol (99.5–100%) instead of 350 ml. of methyl alcohol. Distillation yielded bromoacetaldehyde diethyl acetal (151 g. or 77%), b. p. 64–65° (16 mm.), n^{20}D 1.4418; d^{20}_4 1.280. On using commercial 95% ethyl alcohol the yield was somewhat lower (142 g. or 72%).

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An Improved Method for the Synthesis of Quinone

BY JOHN H. BILLMAN, BERNARD WOLNAK AND DAVID K. BARNES

In the course of another investigation it was necessary to prepare quinone in relatively large amounts. The procedure described in "Organic Syntheses"[1] requires vanadium pentoxide as a catalyst. Since there was no vanadium pentoxide available, we substituted an equivalent amount of ammonium metavanadate which worked equally well and gave comparable yields. In addition the reaction time was reduced to less than one third the time normally required. Other runs were made using increased amounts of ammonium metavanadate and warming the reaction mixture to 40° before adding the catalyst. It was found that the greater the amount of catalyst used the faster the reaction proceeded. Thus with 1.4 g. of ammonium metavanadate the reaction was complete in less than half an hour or about one-eighth the time normally required. The final procedure which was used is described in the experimental part.

Experimental

Quinone.—In a 2-liter round-bottom three-neck flask equipped with a mechanical stirrer and a thermometer were placed 1 liter of a 2% sulfuric acid solution, 110 g. of hydroquinone, and 60 g. of sodium chlorate. The mixture was vigorously stirred and warmed to 40°. At this temperature 1.4 g. of ammonium metavanadate was added. The flask was cooled from time to time, with tap water, so that the temperature did not rise above 42°. The reaction was over in less than thirty minutes. The mixture was cooled to 10°, then filtered with suction, and the quinone washed once with 100 ml. of cold water. After drying in a desiccator over calcium chloride the product weighed 97–99 g. and melted at 112–113°. Extraction of the filtrate and washings with three 100-ml. portions of warm benzene yielded 3–4 g. more of quinone, bringing the total amount to 101–103 g. (93–95% of the theoretical amount).

The quinone may be dried in about an hour in an oven at 100°. This should be done under a hood. There is about a 15% loss due to sublimation. Over calcium chloride, it takes from one to two days for the quinone to dry.

DEPARTMENT OF CHEMISTRY
INDIANA UNIVERSITY
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(1) "Organic Syntheses," Coll. Vol. II, 1943, p. 553.

Preparation of *o*-Aminobenzyl and β-Aminoethyl Thiazolium Salts

BY HANS T. CLARKE

In view of the interesting observations recorded by Sealock and Goodland,[1] a description becomes necessary of the preparation of the thiazolium amino compounds which inhibit the enzymatic decomposition of the amine. After the recognition of the thiazole ring in thiamine,[2] these substances were synthesized early in 1936 for study as models, but they found useful application only after they had reached Dr. Sealock's Laboratory.

Experimental

3-*o*-Nitrobenzyl-4-methylthiazolium Chloride.—A mixture of 3.5 g. of *o*-nitrobenzyl chloride, 1 cc. of benzene and 2.0 g. of 4-methylthiazole was heated at 95–100° in a sealed tube for eighty to ninety hours. The crystalline product, well washed with ether and recrystallized from absolute alcohol, decomposed at 186.5–187°. The yield was 4.1 g. or 75%.

Anal. Calcd. for $C_{11}H_{11}O_2N_2SCl$: N, 10.4; Cl, 13.1. Found: N, 10.04; Cl, 13.1.

3-*o*-Aminobenzyl-4-methylthiazolium Chloride Hydrochloride.—A hot solution of 1.4 g. of the above nitro compound in 50 cc. of 2 *N* hydrochloric acid was boiled gently for an hour in the presence of 2.4 g. of granulated tin. As very little action had occurred, 3.4 g. of crystallized stannous chloride was added. The precipitate which formed slowly dissolved in the boiling mixture. The clear solution was warmed at 50° overnight, when most of the tin dissolved. The mixture was diluted, freed of tin salts with hydrogen sulfide and evaporated to dryness under reduced pressure. The residue was warmed with 4 cc. of absolute alcohol, when it rapidly became crystalline; it was filtered and washed with absolute alcohol. The product (about 0.9 g.) after recrystallization from aqueous alcohol decomposed over the range 204–212°.

Anal. Calcd. for $C_{11}H_{14}N_2SCl_2 \cdot H_2O$: C, 44.8; H, 5.1; N, 9.5; Cl, 24.1. Found: C, 45.3; H, 4.9; N, 9.2; Cl, 24.4.

3-β-Phthalimidoethyl-4-methylthiazolium Bromide.—Equimolecular quantities of β-bromoethylphthalimide and 4-methylthiazole were heated in a sealed tube at 95–100° for ten days, when the mixture had completely solidified. The product was washed with ether, and recrystallized from water as platelets, m. p. 238° with slight darkening.

Anal. Calcd. for $C_{14}H_{13}O_2N_2SBr$: N, 7.9; Br, 22.7. Found: N, 7.9; Br, 22.4.

3-β-Aminoethyl-4-methylthiazolium Bromide Hydrobromide.—A solution of 2.5 g. of the phthalimide thiazolium bromide in 10 cc. of 48% hydrobromic acid was boiled under reflux for forty hours, and allowed to cool to room temperature. The phthalic acid (1.0 g., 85%) was filtered off and washed with water; the filtrate and washings were combined and evaporated nearly to dryness, the residue treated with absolute alcohol, and the crystalline product well washed with absolute alcohol. It shrank at 218.5–219.5° and melted with decomposition at 222.5–223.5°; yield 2.1 g.

Anal. Calcd. for $C_6H_{12}N_2SBr_2$: N, 9.2; S, 10.5; Br, 52.7. Found: N, 9.1; S, 10.7; Br, 52.8.

DEPARTMENT OF BIOCHEMISTRY
COLUMBIA UNIVERSITY
NEW YORK, NEW YORK RECEIVED DECEMBER 30, 1943

(1) Sealock and Goodland, THIS JOURNAL, 66, 507 (1944).
(2) Clarke and Gurin, *ibid.*, 57, 1876 (1935).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NATIONAL SOUTHWEST ASSOCIATED UNIVERSITY AND THE INSTITUTE OF CHEMISTRY, NATIONAL ACADEMY OF PEIPING]

Syntheses of Compounds Related to Vitamin K. II. *p*-(3-Alkyl-4-hydroxynaphthylazo)-benzenesulfonamides

BY EDITH JU-HWA CHU, ZOE-ING SHEN, TSUI-LIN CHIEN AND T. S. TUAN

In continuation of our work on compounds related to vitamin K[1] a number of 2-alkyl-1-naphthols have been synthesized and coupled with the diazotized sulfanilamide to yield the corresponding *p*-(3-alkyl-4-hydroxynaphthylazo)-benzenesulfonamides in which the alkyl groups are ethyl, *n*-propyl, *n*-butyl, isobutyl, *n*-amyl and *β*-phenylethyl, respectively. The parent substance, *p*-(4-hydroxynaphthylazo)-benzenesulfonamide was mentioned in the literature.[2]

All the *p*-(3-alkyl-4-hydroxynaphthylazo)-benzenesulfonamides were obtained in colored crystals except *p*-(3-isobutyl-4-hydroxynaphthylazo)-benzenesulfonamide which was a viscous mass and was difficultly purified. They possess no inhibitory effect on the growth of *Bacillus coli*, *Staphylococcus aureus* or *Streptococcus pyrogenes*.[3] The antihemorrhagic activity of these compounds and *p*-(3-methyl-4-hydroxynaphthylazo)-benzenesulfonamide will be reported later on. They behave as indicators, red in alkaline solution and yellow in acid solution.

TABLE I

2-ACYL-1-NAPHTHOLS

-1-naphthol	% yield $AlCl_3$	% yield $ZnCl_2(SnCl_4)$
2-Acetyl-	67	89
4-Acetyl-	6	0
2-Propionyl-	40	100
4-Propionyl-	4	0
2-*n*-Butyryl-	37	100
4-*n*-Butyryl-	3	0
2-Isobutyryl-	53	75
4-Isobutyryl-	34	0
2-*n*-Valeryl-	73	83
4-*n*-Valeryl-	2	0
2-*β*-Phenylacetyl-	..	91

Experimental

2-Alkyl-1-naphthols.—They were synthesized by Clemmensen reduction of 2-acyl-1-naphthols. Although the Stoughton method[4] of preparing 2-acyl-1-naphthols gave better result than other methods[5-9] described in the literature, the Fries rearrangement of *α*-naphthyl ester by means of aluminum chloride always gave the *p*-isomer and other by-products besides the desired 2-acyl-1-naphthol. Then the procedure was thus modified: A mixture of equal amounts of the *α*-naphthyl ester and freshly fused and powdered zinc chloride was heated on an oil-bath at 140–50° for an hour. The cold mass was treated with water to remove zinc chloride and the precipitate was recrystallized from a mixture of alcohol and acetone. The yields of 2-acyl-1-naphthols were much more satisfactory as shown in Table I. The use of anhydrous stannic chloride gave the same good results.

The 4-isobutyryl- and 4-*n*-valeryl-1-naphthols were quantitatively rearranged to the 2-isomers, respectively, by refluxing with 35% sodium hydroxide solution for two hours. However, the 4-acetyl-1-naphthol was not isomerized by the same treatment.

Among the 2-alkyl-1-naphthols prepared, the 2-*β*-phenylethyl-1-naphthol was not previously reported. It was obtained in colorless crystals from alcohol; yield, 23% and m. p. 77–78° (dec.). The reddish-orange needles of its picrate melt at 179–180 (dec.).

Anal. Calcd. for $C_{18}H_{16}O \cdot C_6H_3N_3O_7$: N, 8.81.[10] Found: N, 9.20.

***p*-(3-Alkyl-4-hydroxynaphthylazo)-benzenesulfonamides.**—An acetic acid solution of 0.01 g. mole of 2-alkyl-1-naphthol was gradually added to a diazotized solution prepared from 0.01 g. mole of sulfanilamide. The colored precipitate was filtered and then purified either by recrystallization from a suitable solvent or by dissolving in dilute sodium hydroxide and reprecipitating with dilute hydrochloric acid. The yields and properties are listed in Table II.

TABLE II

p-(3-ALKYL-4-HYDROXYNAPHTHYLAZO)-BENZENESULFONAMIDES

Alkyl group	Solvent for recrystn.	Color[11]	Cryst. form	Yield, %	M. p., °C.	N Analyses,[11] % Calcd.	Found
Ethyl	Acetone	Yellowish-orange	Fine needles	73	249	11.83	12.13
n-Propyl	Alc.	Yellowish-orange	Fine needles	69	251	11.38	11.39
n-Butyl	Alc.	Orange-yellow	Fine needles	66	280	10.96	10.70
Isobutyl	Alc.	Dark red	Viscous mass	..	...	...	...
n-Amyl	Acetone	Yellowish-orange	Fine needles	56	260	10.57	10.04
β-Phenylethyl	NaOH + HCl	Red	Prisms	51	261	9.74	9.40

(1) Chu and Shen, *J. Chinese Chem. Soc.*, **10** (in press) (1943).

(2) Tutiva and Kawamura, *Arch. Dermatol. Syphilis*, **182**, 598 (1941).

(3) The authors are indebted to Dr. Tang Fei-Fen and his collaborators in the Central Epidemics Prevention Bureau of China for the test.

(4) Stoughton, THIS JOURNAL, **57**, 202 (1935).

(5) Nencki and Sieber, *J. prakt. Chem.*, **23**, 147 (1881).

(6) Akram, Desai and Kamal, *Proc. Indian Acad Sci.*, **11A**, 139 (1940).

(7) Goldzweig and Kaiser, *J. prakt. Chem.*, **43**, 95 (1891).

(8) Hantzsch, *Ber.*, **39**, 3096 (1906).

(9) Brewster and Watters, THIS JOURNAL, **64**, 2578 (1942).

(10) We wish to thank Dr. R. J. Williams for his generosity in permitting us to use the micro-Dumas Apparatus in the Biochemical Institute of University of Texas for some of the analyses.

(11) Compared with Mulliken's color standards.

KUNMING, YUNNAN, CHINA RECEIVED JANUARY 22, 1944

The Second Ionization Constant of Deuterocarbonic Acid

BY JAMES CURRY AND Z. ZIMMERMAN HUGUS, JR.

Introduction.—We have measured the e. m. f. of the following cells at 25°

H_2, $KHCO_3$, K_2CO_3, KCl, AgCl, Ag (I)

D_2, $KDCO_3$, K_2CO_3, KCl, AgCl, Ag (II)

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The potential of cell I is given by

$$E = E_0 - \frac{RT}{F} \ln m_H m_{Cl} - \frac{RT}{F} \ln f_H f_{Cl} \quad (1)$$

where E_0 is the standard electrode potential of the silver–silver chloride electrode in water referred to hydrogen, m is the concentration in molal terms and f is the activity coefficient of the quantities indicated by the subscripts.

The second thermodynamic ionization constant for proto-carbonic acid is

$$K_H = \frac{m_H m_{CO_3}}{m_{HCO_3}} \frac{f_H f_{CO_3}}{f_{HCO_3}} \quad (2)$$

Replacing m_H in (1) by its value from (2) and solving for the negative logarithm of the ionization constant we obtain

$$pK_H = \frac{E - E_0}{0.0591} + \log \frac{m_{HCO_3} m_{Cl}}{m_{CO_3}} + \log \frac{f_{HCO_3} f_{Cl}}{f_{CO_3}} \quad (3)$$

If we define pK_H as the sum of the first two terms on the right-hand side of (3) we then get

$$pK_H = pK_H^* + \log \frac{f_{HCO_3} f_{Cl}}{f_{CO_3}} \quad (4)$$

The analogous equations for cell II are

$$pK_D = \frac{E - E_0'}{0.0591} + \log \frac{m'_{DCO_3} m'_{Cl}}{m'_{CO_3}} + \log \frac{f'_{DCO_3} f'_{Cl}}{f'_{CO_3}} \quad (5)$$

$$pK_D = pK_D^* + \log \frac{f'_{DCO_3} f'_{Cl}}{f'_{CO_3}} \quad (6)$$

where K_D is the second ionization constant of deutero-carbonic acid and the primes refer to the values for D_2O. E_0' includes the standard electrode potential of the deuterium electrode and the silver–silver chloride electrode in D_2O.

Experimental.—The purification of the salts and deuterium oxide, the preparation of the silver–silver chloride electrode, the cell and the potentiometer have been described previously.[1] A detailed description of the hydrogen (deuterium) electrode will be given in another article. In order to avoid loss of carbon dioxide and consequent change in the carbonate-bicarbonate concentrations a device was developed which circulated the hydrogen in a closed system. This also allowed the use of macro quantities of deuterium but at the same time avoided the necessity of using a large quantity of this gas.

This device consisted of a short endless system of tubing which was fastened to the end of the cell containing the hydrogen electrode. One portion of the system was enlarged and contained a Bunsen valve. The pressure in part of the system could be increased by raising a column of mercury. This caused the hydrogen to bubble through the solution around the platinum electrode. The mercury was then lowered and the cycle repeated. A motor and eccentric raised and lowered the mercury column at a rate of fifteen times per minute. The electrode, itself was spiral in shape and was platinized in a conventional manner.

The hydrogen was obtained from a commercial tank and was purified by passing it through alkaline pyrogallol, sulfuric acid and distilled water. The deuterium was prepared by electrolyzing 98.9% D_2O. For one determination about 100 cc. of deuterium was used. The circulation system, including the cell, had a volume of 35 cc. and the excess gas was used for flushing purposes.

Constant readings were obtained with no great difficulty, the e. m. f. of the cell usually varied no more than 0.1 mv. over a period of an hour or two. Before measurements were made on cells (I) and (II) the reliability of the circulating device was tested on the cell H_2, HCl, AgCl, Ag. These measurements were found to be quite satisfactory.

Results.—The results obtained are summarized in the following table.

$E_0 = 0.2224$				$E_0' = 0.2190$	
Molality					
KCl	bicarbonate	K_2CO_3	$X \times 10^4$	E	pK^*
		H_2O			
0.01356	0.01572	0.01234	1.7	0.9263	10.158
.02841	.02976	.03055	2.4	.9129	10.133
		98.9% D_2O			
.01111	.01286	.01169	1.2	.9663	10.740
.02444	.02883	.02887	1.5	.9468	10.707
		$K_H/K_D = 3.95$			

Discussion.—The fourth column gives the amount of potassium carbonate hydrolyzed. This was calculated according to the method of MacInnes and Belcher[2] and was taken into account in calculating pK^*. The value of K_w for D_2O was taken as 0.16×10^{-14}. As is customary, the values of E have been corrected to a hydrogen (deuterium) pressure of one atmosphere.

The values obtained for pK_H^* agree well with those of MacInnes and Belcher at similar ionic strengths. The first agrees within 0.04%; the second within 0.3%.

E_0' is made up of the standard electrode potential of the silver–silver chloride electrode in D_2O and the deuterium ion–deuterium electrode. As in previous work[1] the standard electrode potential for the silver–silver chloride electrode was taken to be the same in D_2O as in H_2O. For the deuterium electrode the value obtained by Abel, Bratu and Redlich,[3] namely, 0.0034 volt, was used. These authors used a micro method to measure this value and it had been our original intention to redetermine it using our macro method but events precluded this.

In a comparative method, such as the present one, the quantity desired is K_H/K_D. This can be obtained through a knowledge of the ratio pK_H/pK_D and the value of K_H. Because the solutions used were quite dilute a close approximation to this latter ratio can be obtained by finding pK_H^*/pK_D^*, the numerator and denominator being taken at the same ionic strengths. The reason for this is that the logarithmic term of the ratio of activities in both (4) and (6) is small compared to pK^*.

Using the values of pK_D^* in the table and finding pK_H^* for the same ionic strengths from the work of MacInnes and Belcher, we calculate from the first measurement in D_2O that pK_H^*/pK_D^* is equal to 0.94590 and from the second a value of 0.94415. Thus, for the reasons given above, we can take the average of these to be equal to pK_H/pK_D. Using this average and MacInnes and Belchers' value of K_H, namely, 5.61×10^{-11},

(1) Curry and Hazelton, THIS JOURNAL, 60, 2773 (1938).

(2) MacInnes and Belcher, *ibid.*, 55, 2630 (1933).

(3) Abel, Bratu and Redlich, *Z. physik. Chem.*, A173, 353 (1935).

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the second ionization constant for deutero-carbonic acid may be calculated to be 1.42×10^{-11}. Thus K_H/K_D is equal to 3.95.

It should be pointed out that this value of K_H/K_D for the second ionization constant of carbonic acid agrees within 4% of that predicted by the curve of Rule and LaMer[4] and confirmed by Martin and Butler.[5]

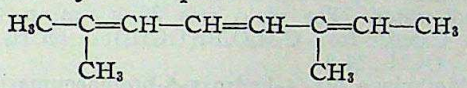
(4) Rule and LaMer, THIS JOURNAL, **60**, 1974 (1938).
(5) Martin and Butler, *J. Chem. Soc.*, 1366 (1939).

DEPARTMENT OF CHEMISTRY
WILLIAMS COLLEGE
WILLIAMSTOWN, MASS. RECEIVED JANUARY 19, 1944

The Production of α- and β-Pyronene from *allo*-Ocimene

BY L. A. GOLDBLATT AND S. PALKIN[1]

Among the products obtained in the pyrolysis of α-pinene in the vapor phase,[2,3,4] at about 375°, the acyclic terpene



(2,6-dimethyl-2,4,6-octatriene) is of the greatest interest, both from a practical and theoretical point of view. The simultaneous formation of the monocyclic hydrocarbons α- and β-pyronene was first observed by Dupont and Dulou, who postulated[3] that they were obtained from α-pinene by a simultaneous and independent reaction, namely, rupture of the four-membered ring in α-pinene, and not by further isomerization of either *allo*-ocimene or dipentene, other products of the pyrolysis. They later reported[5] that this hypothesis had been confirmed.

In the course of the work of the Naval Stores Research Division on the vapor phase thermal isomerization of terpene hydrocarbons, it was found that the pyronenes are in fact obtained by the recyclization of *allo*-ocimene.[6]

The apparatus used for the pyrolysis is shown in Fig. 1. This consists essentially of a pyrolysis tube, together with a suitable condensing and receiving system. Heat for the pyrolysis tube is supplied by means of a bath of "HTS" (a commercial mixture of sodium and potassium nitrate and nitrite). This in turn is heated by passage of an electric current through 25 feet (resistance, 16 ohms) of no. 20 Nichrome wire wound on asbestos-paper covering a suitable length of ordinary 1.5-inch iron pipe. Temperature was controlled by a variable voltage transformer and measured by a movable thermocouple in a glass well placed vertically in the center of the reaction tube. In normal operation the temperature generally did not vary more than 5° for about half the length of the pyrolysis tube, although the temperature was materially lower at both ends. *allo*-Ocimene was supplied to the pyrolysis tube by a Tropsch and Mattox pump[7] capable of supplying *allo*-ocimene at a definite rate varying from about 50 to 750 cc. per hour with a precision of 1%. Flow of *allo*-ocimene supplied by the pump was made more uniform by inserting a coil of glass tape just inside the spherical joint.

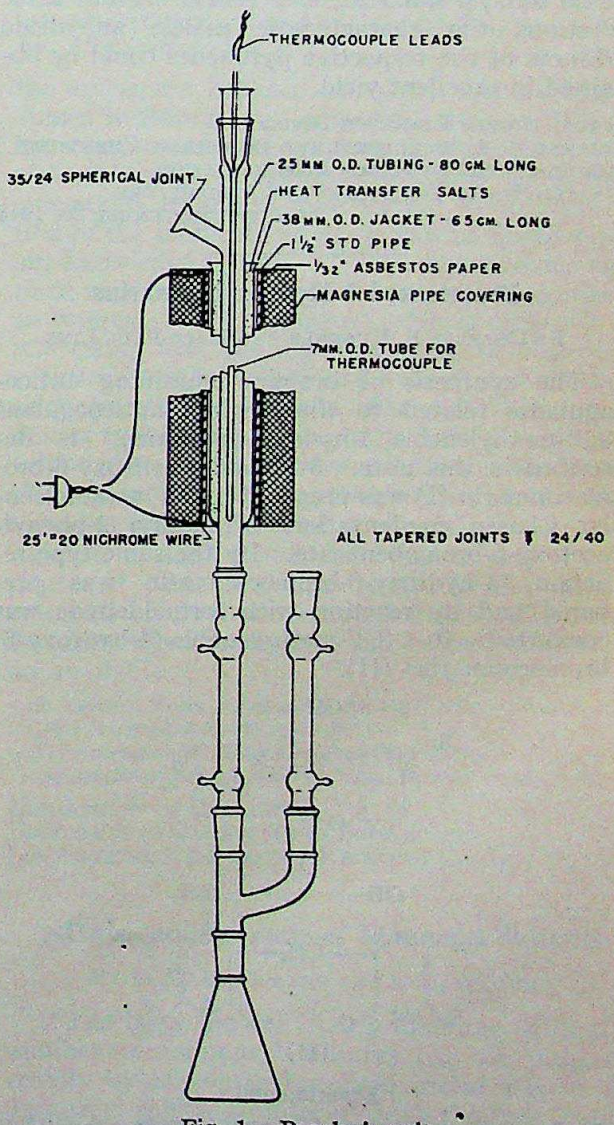


Fig. 1.—Pyrolysis unit.

Change in refractive index provides a convenient guide to the extent of isomerization. A sample of *allo*-ocimene having the characteristics

(1) Died May 2, 1943.
(2) Arbuzov, *J. Gen. Chem.* (U. S. S. R.), **3**, 21 (1933); *Ber.*, **67B**, 563 (1934).
(3) Dupont and Dulou, *Compt. rend.*, **201**, 219 (1935).
(4) Goldblatt and Palkin, THIS JOURNAL, **63**, 3517 (1941).
(5) Dupont and Dulou, *Atti. X° Congr. Intern. Chim.*, **3**, 127 (1939).
(6) Work of the Naval Stores Research Division on the vapor phase cyclization of *allo*-ocimene has been temporarily discontinued owing to preoccupation with problems more closely related to the war effort. Reporting of these preliminary results at this time is prompted by a communication from Dr. J. E. Hawkins and R. E. Fuguitt of the University of Florida, who have confirmed this observation from information obtained in the study of the thermal isomerization of α-pinene in the liquid phase, and who have generously undertaken to remove any question as to priority of this discovery in a forthcoming publication.
(7) Tropsch and Mattox, *Ind. Eng. Chem.*, **26**, 1338 (1934).

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$n^{20}D$ 1.5449 and d^{20}_4 0.8083, when pyrolyzed under optimum conditions (a temperature of 400° and a through-put of 250 g. per hour) gave a product of $n^{20}D$ 1.4790. Considerable variations in through-put rate or pyrolysis temperature may be made without materially altering the extent of isomerization (as judged by change in refractive index).

A portion of the pyrolyzate obtained in this way ($n^{20}D$ 1.4795; d^{20}_4 0.8358) when fractionally distilled *in vacuo* was found to contain about 30% of α-pyronene and about 45% of β-pyronene, together with some unchanged *allo*-ocimene, dimer, and other unidentified hydrocarbons. The fractions containing the highest concentrations of α- and β-pyronene had the following characteristics: α-pyronene, b. p. 54–56° at 20 mm., d^{20}_4 0.8272, $n^{20}D$ 1.4672; β-pyronene, b. p. 62–64° at 20 mm., d^{20}_4 0.8481, $n^{20}D$ 1.4800. From these fractions the characteristic maleic anhydride adducts of the respective pyronenes could be obtained in excellent yield.

NAVAL STORES RESEARCH DIVISION
BUREAU OF AGRICULTURAL AND INDUSTRIAL CHEMISTRY
AGRICULTURAL RESEARCH ADMINISTRATION
UNITED STATES DEPARTMENT OF AGRICULTURE
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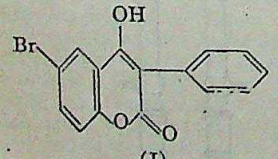
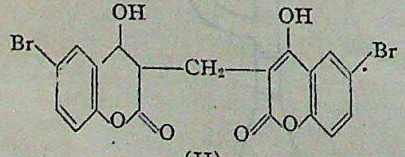
Brominated 4-Hydroxycoumarins

BY CHARLES F. HUEBNER AND KARL PAUL LINK

The synthesis of bromine-containing anticoagulants related to the original anticoagulant 3,3′-methylenebis-(4-hydroxycoumarin),[1] is described in this note. 3-Phenyl-4-hydroxy-6-bromocoumarin (I) was prepared by an intramolecular Claisen condensation[2] of methyl 2-phenylacetoxy-5-bromobenzoate. By the same type reaction, 4-hydroxy-6-bromocoumarin was prepared and by reaction with formaldehyde was converted to 3,3′-methylenebis-(4-hydroxy-6-bromocoumarin) (II).



(I)



(II)

Experimental

Methyl 2-Phenylacetoxy-5-bromobenzoate.—A mixture of 60 g. of phenylacetyl chloride and 90 g. of methyl 5-bromosalicylate[3] was heated under reflux on a steam-bath for four hours. Pyridine (30 ml.) was added and the heating was continued for four hours longer. The resulting oil was dissolved in ether and extracted successively with water, hydrochloric acid solution, and sodium carbonate solution. The ether solution was dried and the ester was crystallized by the addition of petroleum ether. After two recrystallizations from ethanol the product weighed 56 g., m. p. 68–70°. *Anal.* Calcd. for $C_{15}H_{10}O_3Br(OCH_3)$: OCH_3, 8.9. Found: OCH_3, 8.8.

3-Phenyl-4-hydroxy-6-bromocoumarin (I).—To a well-stirred melt of 20 g. of methyl 2-phenylacetoxy-5-bromobenzoate contained in a round bottom flask, 1.3 g. of sodium was added and the temperature was raised to 200°, at which point a spontaneous reaction occurred. External heating was discontinued and after thirty minutes the glassy mass was cooled and dissolved in water. The aqueous solution was acidified to *p*H 6, extracted with ether, and further acidified to *p*H 5. The product crystallizing between these two *p*H's was filtered and recrystallized twice from acetic acid. The yield was 8 g., m. p. 252–254°. *Anal.* Calcd. for $C_{15}H_9O_3Br$: C, 56.8; H, 2.8. Found: C, 57.0; H, 2.9.

Methyl 2-Acetoxy-5-bromobenzoate.—To 30 g. of methyl 5-bromosalicylate was added 80 ml. of acetic anhydride and 1 ml. of sulfuric acid. After thirty minutes the mixture was poured into ice water, the oil was washed with sodium carbonate solution, and crystallized from methanol–water. The yield was 20 g., m. p. 33–35°. *Anal.* Calcd. for $C_9H_6O_3Br(OCH_3)$: OCH_3, 11.4. Found: OCH_3, 11.3.

3,3′-Methylene bis-(4-hydroxy-6-bromocoumarin) (II).—4-Hydroxy-6-bromocoumarin was prepared in a manner similar to that described for 3-phenyl-4-hydroxy-6-bromocoumarin except that the reaction was run in kerosene and the final product was collected between *p*H 5.6 and 2.5. From 176 g. of ester, and 14.8 g. of sodium in 300 ml. of kerosene, 92 g. of crude 4-hydroxy-6-bromocoumarin was obtained. This crude product was refluxed in ethanol with an excess of formaldehyde. The methylenebis product which was extremely insoluble in alcohol crystallized after one hour. This product was filtered and recrystallized from cyclohexanone, yield 40 g., m. p. 326–327°. *Anal.* Calcd. for $C_{19}H_{10}O_6Br_2$: C, 46.2; H, 2.0. Found: C, 46.3; H, 2.3.

3,3′-Methylene bis-(4-hydroxy-6-bromocoumarin) dimethyl ether was prepared by the diazomethane technique. The ether was recrystallized from β-dichloroethyl ether, m. p. 218–220°. *Anal.* Calcd. for $C_{19}H_8O_6Br_2(OCH_3)_2$: OCH_3, 11.8. Found: OCH_3, 12.0.

DEPARTMENT OF BIOCHEMISTRY
UNIVERSITY OF WISCONSIN
MADISON 6, WISCONSIN
RECEIVED DECEMBER 14, 1943

The Dielectric Constants and Dipole Moments of Acetylenic Ethers

BY THOMAS L. JACOBS, JOHN D. ROBERTS AND W. G. MACMILLAN

The dielectric constants of pure samples of ethoxy-, butoxy- and phenoxy-acetylene[1] were measured at 25° by the heterodyne beat method as described by Wood and Dickinson.[2]

The frequency of the standard circuit was adjusted to that of the carrier wave of radio station KFAC which broadcasts on a frequency of 1300 kilocycles,[3] and the increment of capacity was

(1) Stahmann, Huebner and Link, *J. Biol. Chem.*, **138**, 513 (1941).
(2) Stahmann, Wolff and Link, THIS JOURNAL, **65**, 2285 (1943).
(3) Peratoner, *Gazz. chim. ital.*, **16**, 405 (1886).

(1) The acetylenic ethers were carefully refractionated samples prepared in connection with other investigations: Jacobs, Cramer and Hanson, THIS JOURNAL, **64**, 223 (1942); Jacobs, Cramer and Weiss, *ibid.*, **62**, 1849 (1940). The phenoxyacetylene was prepared by Dr. Wm. Penn Tuttle, Jr.
(2) Wood and Dickinson, *ibid.*, **61**, 3259 (1939).
(3) Stations Committee, *Ind. Eng. Chem., Anal. Ed.*, **6**, 187 (1934).

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measured with a variable condenser which was carefully calibrated against a General Radio Precision Condenser (calibrated by the manufacturer at 1000 cycles per second). The cell was of the type described by Doborzynski[4] and the cell constant was obtained by measurements on purified samples of chlorobenzene, ethylene dichloride and benzene whose dielectric constants are known accurately (5.612, 10.36, 2.272 at 25°). Table I summarizes the results.

TABLE I

DIELECTRIC CONSTANTS AND DIPOLE MOMENTS OF ACETYLENIC ETHERS AND PHENYLACETYLENE

Compound, -acetylene	ϵ	M	d^{25}_4	$n^{25}D$	MR_D obs.	$(n^2_\infty)^{25°}$	μ
Ethoxy-	8.05	70.1	0.7874	1.3785	20.53	1.853	1.98
Butoxy-	6.62	98.2	0.8078	1.4033	29.66	1.925	2.03
Phenoxy-	4.76	118.1	1.0088	1.5143	35.27	2.216	1.41
Phenyl-	2.98	102.1	0.9243	1.5461	34.99	2.231	0.78

Dipole moments were calculated by the Onsager equation[5,6] and phenylacetylene was included for comparison. The value is in reasonable agreement with 0.77–0.87 found by measurements in benzene solution.[7] The values of n^2_∞ were obtained by extrapolating the molecular refraction to infinite wave length as was done by Böttcher.[8] The observed molecular refractions for the acetyleneic ethers are in close agreement with the calculated values so that no error was introduced by using the latter. Phenylacetylene shows a rather large exaltation, but even here the values for the dipole moment obtained using calculated or observed molecular refractions were not greatly different (0.78 instead of 0.75).

Böttcher[8] has calculated the dipole moments of a number of compounds from the dielectric constants of the pure liquids using Onsager's equation. His results for unassociated substances are in excellent agreement with dipole moments obtained from measurements in solution or in the vapor state except for anisole and diethyl ether, and for these he believed that the equation failed. His calculations appear to be in error for anisole, and the corrected figure lies between values obtained in solution and in the vapor. We have calculated the moments for phenetole and diphenyl ether and found fairly close agreement, so that Onsager's equation appears to give reasonable results with simple aromatic ethers. The values for diethyl ether from the Onsager equation are high as Böttcher reported, but better agreement is found for di-*n*-propyl ether. Table II compares the calculated values for these ethers with values from measurements in solution or in the vapor.

Despite the simplifying assumptions of symmetrical dipole configurations and non-association made in the derivation of the Onsager equation,

(4) Doborzynski, *Z. Physik*, **66**, 657 (1930).
(5) Onsager, THIS JOURNAL, **58**, 1486 (1936).
(6) Wilson, *Chem. Rev.*, **25**, 377 (1939).
(7) Smyth and Dornte, THIS JOURNAL, **53**, 1296 (1931).
(8) Böttcher, *Physica*, **6**, 59 (1939); see ref. 6.

TABLE II[a]

DIPOLE MOMENTS OF ETHERS

Compound	n^2	ϵ	Ref.	μ Calcd.	μ_v	μ_s
Diethyl ether	1.798	4.376	9	1.47	1.18	1.2–1.3
Di-*n*-propyl ether	1.873	3.394[b]	10	1.31	1.18	1.16
Anisole	2.214	4.41	11	1.28	1.35	1.2
Phenetole	2.187	4.22	11	1.34	1.4	1.0
Diphenyl ether	2.388	3.686	11	1.17	1.14	1.13–1.17

[a] The values are at 20° unless otherwise stated. The calculated *MR*'s were used, but the exaltations are low with these compounds and μ is lowered but slightly by using *MR* obs. for the calculation. $\mu_{calcd.}$, μ_v and μ_s designate the dipole moments in Debye units from the calculations and from measurements in the vapor and in solution respectively. All μ_s values are in benzene except di-*n*-propyl ether which is in hexane. The values for the dipole moments in solution were taken from Landolt–Börnstein, "Physikalisch-chemische Tabellen," the second and third supplementary volumes, Julius Springer, 1931–1936. The values from measurements in the vapor phase are from Groves and Sugden, *J. Chem. Soc.*, 1779, 1782 (1937), except for diphenyl ether where their value of 1.35 appears less reliable than that found by Coop and Sutton, *J. Chem. Soc.*, 1869 (1938). [b] At 25.7°.

the agreement between calculated and measured values is satisfactory in general and, as Wilson[6] has commented, the equation appears to be empirically useful. Certainly the values for acetylenic ethers are not in gross error. No interpretation of the moments of ethers can be made without knowledge of the —C—O— bond angles and these may be quite different in unsaturated ethers as compared with saturated. Nevertheless it is interesting that the dipole moment of phenoxyacetylene is only slightly larger than those of other aromatic ethers while the alkoxyacetylenes give figures which are significantly higher. One interpretation of this difference is that in the latter there is a considerable contribution from resonance forms of the type $R—\overset{+}{O}=C=\bar{C}H$, an idea which is in accord with their greater rate of hydration.[12] An extended study of the dipole moments of vinyl and ethynyl ethers will be undertaken when more time and better equipment are available.

(9) LeFèvre, *Trans. Faraday Soc.*, **34**, 1127 (1938).
(10) Pyle, *Phys. Rev.*, **38**, 1057 (1931).
(11) Estermann, *Z. physik. Chem.*, **1B**, 134 (1928).
(12) Jacobs and Searles, THIS JOURNAL, **66**, May (1944).

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA AT LOS ANGELES
LOS ANGELES, CALIFORNIA RECEIVED JANUARY 11, 1944

p-Bromoaniline Salts of Monoaryl Sulfates

BY D. H. LAUGHLAND AND LESLIE YOUNG

It has been shown[1] that *p*-toluidine salts of a number of monoaryl sulfates can be prepared readily by allowing the alkali metal salt of the monoaryl sulfate to interact with the base hydrochloride in an aqueous medium. With bases which yield relatively insoluble salts of monoaryl sulfates, this reaction is of value in the isolation of monoaryl sulfates from the urine of animals dosed

(1) A. D. Barton and Leslie Young, THIS JOURNAL, **65**, 294 (1943)

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p-BROMOANILINE SALTS OF MONOARYL SULFATES

Monoaryl sulfate	Crystalline form	Solubility[a] at 8°	Solubility[a] at 25°	Formula	Analytical data[b] Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfate, % Calcd.	Sulfate, % Found	Equiv. wt. Calcd.	Equiv. wt. Found
Phenyl	Plates	1.04	2.21	$C_{12}H_{12}NO_4SBr$	41.63	41.78	3.50	3.67	4.05	4.15	27.8	27.4	346	343
o-Methoxyphenyl	Needles	1.92	3.26	$C_{13}H_{14}NO_5SBr$	41.50	41.57	3.75	3.79	3.72	3.95	25.5	24.5	376	376
p-Bromophenyl	Plates	0.37	0.77	$C_{12}H_{11}NO_4SBr_2$	33.90	34.01	2.61	2.53	3.30	3.49	22.6	22.0	425	421
p-Cresyl	Plates	.24	.62	$C_{13}H_{14}NO_4SBr$	43.35	43.60	3.92	4.05	3.89	3.79	26.7	26.6	360	360
α-Naphthyl	Plates	.60	.89	$C_{16}H_{14}NO_4SBr$	48.49	48.45	3.56	3.73	3.53	3.82	24.2	24.0	396	394

[a] Grams of derivative per 100 ml. of solution. [b] The micro-analyses were performed by Mr. Michael Edson.

with phenols.[2] Experiments with *p*-bromoaniline suggested that this base might serve as a useful precipitant for monoaryl sulfates. For example, at 8° the solubility of potassium phenyl sulfate is 12.85 g. per 100 ml. of solution, whereas the solubility of *p*-bromoaniline phenyl sulfate is 1.04 g. per 100 ml. of solution. Several potassium monoaryl sulfates were prepared by the method of Burkhardt and Wood,[3] and were converted to their *p*-bromoaniline salts (see table) by the above method.[1] Although these derivatives are fairly insoluble, they are somewhat unstable, and their melting points are ill-defined.

(2) D. H. Laughland and Leslie Young, *Trans. Roy. Soc., Can.*, Series III, **36**, 166 (1942).

(3) G. N. Burkhardt and H. Wood, *J. Chem. Soc.*, 141 (1929).

DEPARTMENT OF BIOCHEMISTRY
UNIVERSITY OF TORONTO
TORONTO, ONTARIO, CANADA

RECEIVED DECEMBER 3, 1943

The Action of Ammonia on Allophanic Azide

BY WERNER L. LIPSCHITZ

In contrast to Thiele and Uhlfelder[1] we were not able to prepare tetruret by the action of ammonia on allophanic azide, but, under the varied reaction conditions herein described, always obtained the normal amide, biuret, and in no experiment was a significantly different product formed which could be claimed to be tetruret.

(1) **Concentrated Ammonia.**—A suspension of allophanic azide (prepared from 41 g. of aminobiuret hydrochloride and 18.3 g. of sodium nitrite. *Anal.* Calcd. for $C_2H_3N_5O_2$: C, 18.6; H, 2.32. Found: C, 18.55; H, 2.34) in 30 cc. of water was treated with 250 cc. of 28% aqueous ammonia and, after the initial spontaneous reaction subsided, the mixture was maintained at 55–60° until a clear solution was obtained. The product (21 g.) separated from the concentrated and cooled solution was recrystallized from 100 cc. of boiling water and yielded 18 g. of pure biuret, which melted at 192° and did not depress the melting point of an authentic specimen. *Anal.* Calcd. for $C_2H_5N_3O_2$: C, 23.3; H, 4.86; N, 40.78. Found: C, 23.43; H, 4.45; N, 39.9.

(2) **Dilute Ammonia.**—The azide (3 g.) was added, during an hour and a quarter, to 31 cc. of 2% ammonia at 0° and stirring was continued for a half hour at room temperature. More 2% ammonia (15 cc.) was added, the mixture was shaken overnight at room temperature and, when heated to 70°, gave a clear solution which, when cooled, deposited 1.48 g. of crystalline product and, after concentration, yielded 0.87 g. more of the same material. The combined solids were recrystallized three times from ethanol and yielded pure biuret. *Anal.* Calcd. for $C_2H_5N_3O_2$: C, 23.3; H, 4.86. Found: C, 23.16; H, 4.76.

(3) **Liquid Ammonia.**—The azide (3 g. *Anal.* Calcd. for $C_2H_3N_5O_2$: C, 18.6; H, 2.32; N, 54.26. Found: C, 18.1; H, 2.84; N, 53.87) was dissolved in 125 cc. of liquid ammonia and, after one hour, the solvent was evaporated. The residue (3.84 g.), twice recrystallized from ethanol, gave 1.02 g. of pure biuret. *Anal.* Calcd. for $C_2H_5N_3O_2$: C, 23.3; H, 4.86; N, 40.78. Found: C, 22.78, 23.33; H, 4.53, 4.16; N, 40.0, 41.2.

(1) J. Thiele and E. Uhlfelder, *Ann.*, **303**, 93 (1898).

LEDERLE LABORATORIES
PEARL RIVER, N. Y.

RECEIVED JANUARY 13, 1944

On the Cryoscopic Constant of Camphor

BY JOHN E. RICCI

If the heat of fusion of camphor is 10.74 ± 0.40 cal. per g., then the limiting molecular freezing point depression for solutions in equilibrium with pure solid camphor must be $K_f = RT^2/1000\ l_f = 37.7 \pm 1.4$ deg. per mole as calculated by Frandsen,[1] who also measured the heat of fusion. Meldrum, Saxer and Jones[2] have reported, in some careful and well-planned experiments, that a cryoscopic constant of 39.7 (in sufficiently close agreement with the calculated value) is actually obtained in solutions of four different solutes in camphor; but that the molecular depression apparently increases, in every case, as the concentration of the solute decreases (below ~ 0.2 *m*) and approaches zero.

This would constitute a serious anomaly, if the facts are real. Deviations from the calculated depression are caused either by (A) deviation of the liquid solution from ideality in the positive or in the negative sense, or by (B) precipitation of a solid solution of camphor rather than of pure camphor.

(A) The deviations from ideality, in either direction, must vanish to zero with increasing dilution. Hence the observations cannot be the result either of repulsion, since the molecular depression should in that case start as the theoretical and then fall short of it, or of attraction, which should again give the theoretical depression in limiting dilution, with subsequent increase above the calculated value.

Solid solution would lead always to values lower than the theoretical (even to negative values) but never to values higher than the theoretical cryoscopic constant. For, in the ideal and limiting case, the apparent molecular depression then becomes

$$K_f' = K_f(1 - k)$$

where *k* is the distribution constant of the solute

(1) B. S. Frandsen, *J. Res.*, **7**, 477 (1931).

(2) Meldrum, Saxer and Jones, THIS JOURNAL, **65**, 2023 (1943).

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between solid and liquid phases.[3] Since k cannot be negative, the limiting value of K_f' must be smaller than K_f. The unexpected behavior of camphor therefore cannot be caused by solid solution.

Since the theory cannot be satisfied, it seems that the experimental data must be at fault somewhere. The experimental values involved in the calculation of the ideal constant, K_f, are the melting point and the heat of fusion. The melting point, though somewhat uncertain, can hardly be so incorrect, especially as an absolute temperature, as to account for an almost 50% change in K_f. The fusion heat seems to have been measured with great care, and it similarly does not seem possible for it to be wrong by such a factor; Frandsen reports it as 10.74 ± 0.40 cal., and his data seem to justify this estimate.

There are, however, two points in Frandsen's report which indicate that the camphor under observation near its melting point was not absolutely pure; it appears that it may have been slightly impure at the outset or that it underwent some slight decomposition at temperatures at or near its melting point. Thus: (1) the cooling curve for the determination of the melting point shows a degree of rounding-off hardly consistent with purity; and (2) the agreement in the duplicate determinations of heat content for liquid camphor was not very close. Incidentally, the above suggestions about the impurity or the instability of the camphor used are made by Frandsen himself.

Now, while a slight degree of impurity or instability would hardly affect the measured melting point and heat of fusion to the extent here in question, it is possible to account, on such a basis, for the apparently anomalous molecular freezing point depressions reported by Meldrum. Even with initially pure camphor, it may be that the melting, mixing and grinding required in the preparation of the binary mixtures for melting point determinations, caused in each case a small and approximately constant extent of decomposition of the camphor. If this decomposition amounts to m' moles of foreign species per 1000 g. of camphor, then the true molecular depression would be $K_f = \Delta T_f/(m + m')$. If m' is very small, its neglect would have a negligible effect on K_f measured in high concentration, but would cause the apparent K_f' to rise higher and higher as the concentration decreases.

It is sufficient to assume m' equal to only 0.005, in Meldrum's experiments, to derive a molecular depression approximately constant throughout, within the probable experimental error (as shown in Fig. 1), and with an average value of 39.2° per mole, which is sufficiently close to the calculated limiting or ideal value. The constancy is even better than it seems, when it is remembered that

(3) Thus in Glasstone, "Text-Book of Physical Chemistry," D. Van Nostrand Co., New York, 1940, p. 641.

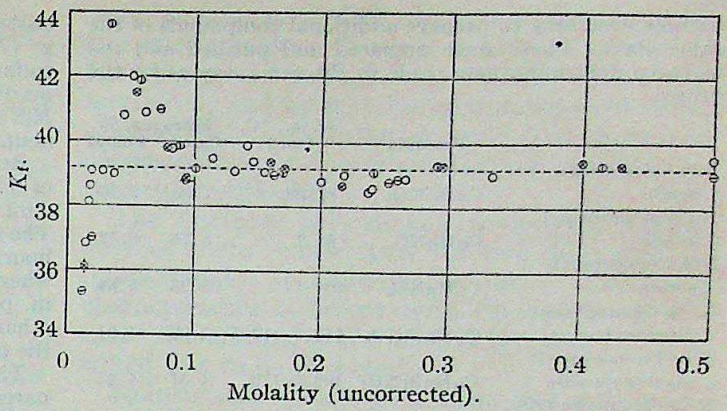

Fig. 1.—Solute key: ○, naphthalene; ⊕, *p*-bromodiphenyl; ⊖, phenylacetic acid; ⊗, ethylacetanilide.

the points at lowest concentration are likely to be experimentally the most uncertain (as pointed out by Meldrum himself). Since the temperatures in Meldrum's experiments seem to have been measured to a precision of only 0.05°, ΔT is probably dependable only within 0.05 to 0.10°. It follows then that at small values of m, even relatively large variations in the value of the ratio $\Delta T/m$ must be considered insignificant; for example, ±2 or 3 at m = 0.05, and as high as ± 8 at m (uncorrected) = 0.012. It is significant that the values of K_f now calculated from all the measurements with $\Delta T > 3°$, lie, with one exception, within one unit of the mean, 39.2, the average deviation being only 0.3 unit.

It should be pointed out that, depending on the molecular weight of the impurity, this value of m' would represent about 0.02 to 0.06% (for molecular weights of 50 to 150) by weight of the camphor used. Such contamination or decomposition would hardly be detectable in the melting point or in the heat of fusion of the substance, but would have the actual effect on the determination of K_f at very low concentrations which was observed by Meldrum.

We have here, in other words, another and very sensitive method for the determination of the purity (or the stability) of a substance. In the absence of solid solution, the molecular depression of the freezing point should approach the value calculated from its melting point and heat of fusion, in limiting dilution.

DEPARTMENT OF CHEMISTRY
NEW YORK UNIVERSITY
NEW YORK, N. Y. RECEIVED DECEMBER 17, 1943

NEW COMPOUNDS

N-Substituted Piperonylamides

In a previous communication[1] several new N-substituted piperonylamides have been recorded. Since then, it has

(1) Gertler and Haller, THIS JOURNAL, 64, 1741 (1942).

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become necessary to prepare additional compounds of the same class. These were prepared and purified and the nitrogen determinations made in the same way as for the others.

Name	Formula	M. p., °C. (cor.)	Nitrogen, % Calcd.	Found
N Ethylpiperonyl-amide	$C_{10}H_{11}NO_3$	87–88	7.25	7.29
N-Propylpiperonyl-amide	$C_{11}H_{13}NO_3$	86–7	6.76	6.57
N-Amylpiperonyl-amide	$C_{13}H_{17}NO_3$	104–5	5.95	5.84
N-(*m*-Chlorophenyl)-piperonylamide	$C_{14}H_{10}ClNO_3$	110.5–112.5	5.08	4.94
N-(*o*-Bromophenyl)-piperonylamide	$C_{14}H_{10}BrNO_3$	109.5–110	4.37	4.35
N-(*m*-Bromophenyl)-piperonylamide	$C_{14}H_{10}BrNO_3$	116–117	4.37	4.30
N-(*p*-Bromophenyl)-piperonylamide	$C_{14}H_{10}BrNO_3$	222–222.5	4.37	4.34

BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE
AGRICULTURAL RESEARCH ADMINISTRATION
U. S. DEPT. OF AGRICULTURE S. I. GERTLER
WASHINGTON, D. C. W. F. BARTHEL

RECEIVED JANUARY 19, 1944

N^1-Acetyl-N^4-benzoyl-sulfanilamide

N^1-Acetyl-N^4-benzoyl-sulfanilamide, the simplest N^1-acyl-N^4-aracylsulfanilamide, has been prepared both by acetylation of N^4-benzoyl-sulfanilamide and by benzoylation of N^1-acetyl-sulfanilamide.

Acetylation of N^4-Benzoyl-sulfanilamide.—A solution of N^4-benzoyl-sulfanilamide (m. p. 285–286°[1]) (1.4 g.) in acetic anhydride (11 ml.) and anhydrous pyridine (6 ml.) was refluxed in a boiling water-bath for one hour, and then cooled. The solid was collected and dried; it weighed 1.14 g. (70%), m. p. 261–263°. The N^1-acetyl-N^4-benzoyl-sulfanilamide was recrystallized from ethanol; it formed needles melting at 262–263°. *Anal.* Calcd. for $C_{15}H_{14}O_4N_2S$: N, 8.80; neut. equiv., 318. Found: N, 9.01; neut. equiv., 317.

Benzoylation of N^1-Acetyl-sulfanilamide.—To a solution of 0.21 g. of N^1-acetyl-sulfanilamide[2] (m. p. 181–182°) in 2 ml. of pyridine, five drops of benzoyl chloride was added. The solution was refluxed in a boiling water-bath for one hour. It was then diluted with water and acidified, whereupon 0.29 g. of N^1-acetyl-N^4-benzoyl-sulfanilamide, m. p. 255–257°, precipitated. After crystallization from ethanol, it melted at 261–262° alone or when mixed with the product obtained by the first method.

The N^1,N^4-dibenzoyl-sulfanilamide has also been prepared by refluxing either sulfanilamide or N^4-benzoyl-sulfanilamide with excess of benzoyl chloride in the presence of pyridine for one hour. The mixture was then diluted with about ten times its volume of ethanol and allowed to stand in the icebox. The solid was recrystallized from ethanol in which it is only slightly soluble. The m. p. of the pure product was found to be 260° (with decomposition).[3] Yields in both cases were 70%. *Anal.* Calcd. for $C_{20}H_{16}O_4N_2S$: N, 7.37. Found: N, 7.57.

Thanks are due to Dr. T. S. Ma, University of Chicago, for the micro-analyses.

NATIONAL RESEARCH INSTITUTE OF CHEMISTRY
ACADEMIA SINICA, KUNMING, CHINA CHIEN-PEN LO[4]
LUCY JU-YUNG CHU

RECEIVED JANUARY 11, 1944

(1) Miller, Rock and Moore, THIS JOURNAL, **61**, 1199 (1939), reported the m. p. as 280°.

(2) Crossley, Northey and Hultquist, *ibid.*, **61**, 2591 (1939); Huang, Lo and Chu, *J. Chinese Chem. Soc.*, **9**, 63 (1942).

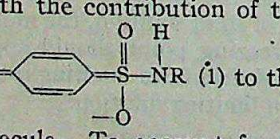
(3) The m. p. of N^1,N^4-dibenzoyl-sulfanilamide has been reported as 268–270° by Dewing, Gray, Platt and Stephenson, *J. Chem. Soc.*, 239 (1942), and as 252° (dec.) by Siebenmann and Schnitzer, THIS JOURNAL, **65**, 2126 (1943).

(4) Present address: School of Chemistry, University of Minnesota, Minneapolis, Minnesota.

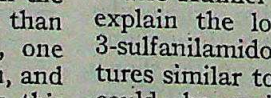
COMMUNICATIONS TO THE EDITOR

STRUCTURE AND ACTIVITY OF SULFANILAMIDES

Sir:

In a recent paper, Kumler and Daniels[1] have suggested that the activity of sulfonamides may be correlated with the contribution of the resonance form,  (I) to the structure of the molecule. To account for the fact that the sulfonamide anion seems to be the active form of the drug, they have postulated that the contribution of the resonance structure with the separation of charge is greater in the anion than in the undissociated molecule. *A priori*, one would be inclined to the contrary conclusion, and we believe the spectral evidence[2] confirms this interpretation.

High intensity ultraviolet absorption spectra are due to transitions from the neutral ground state of the molecule to an ionic excited state.[3] An increase in the number or contribution of ionic resonance structures stabilizes the excited state, *i. e.*, decreases its energy relative to that of the ground state, and hence shifts the maximum of the absorption toward larger wave lengths. Consequently, the fact that the maximum absorption of sulfanilamide in neutral solution is at 2600 Å., whereas that in basic solution is at 2500 Å., indicates that ionic resonance forms contribute *less* to the anion than they do to the undissociated molecule.

The Kumler and Daniels theory also does not explain the low activity of sulfanilylurea and 3-sulfanilamido-1,2,4-triazole. Resonance structures similar to those written for these molecules could be written for N^1-acetylsulfanilamide,  , for sulfadiazine,

(1) Kumler and Daniels, THIS JOURNAL, **65**, 2190 (1943).

(2) Kumler and Strait, *ibid.*, **65**, 2349 (1943).

(3) Mulliken, *J. Chem. Phys.*, **7**, 20 (1939); **7**, 121 (1939); **7**, 339 (1939); O'Shaughnessy and Rodebush, THIS JOURNAL, **62**, 2906 (1940).

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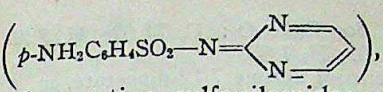
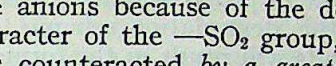
 , and for many other active sulfanilamides. It should be observed that Bell and Roblin[4] originally suggested that the *individual anions* in more acidic sulfanilamides such as sulfadiazine, *sulfanilylurea*, and *3-sulfanilamido-1,2,4-triazole* are less active than sulfanilamide anions because of the decrease in negative character of the $-SO_2$ group, but that this effect is counteracted *by a greater number* of anions.[5]

Simple vinylogs of sulfanilamide such as p-$NH_2C_6H_4CH{=}CH{-}SO_2NHR$ have occupied the attention of one of us for some time. These compounds are now of especial interest since the contribution of resonance structures with a coplanar amino group should be appreciable due to the possibility of a contribution from structures of the type  , in addition to those attributed to sulfanilamides by Kumler and Daniels. If, as Kumler and Daniels suggest, the sulfonamide group is significant for activity only insofar as it affects the amino group, these vinylogs should be active. Up to now only one compound of this type has been tested. 2-p-Aminophenylethene-1-sulfonamide (R = H) appears to be practically inactive *in vitro*.

(4) Bell and Roblin, THIS JOURNAL, **64**, 2905 (1942).

(5) Kumler and Daniels attribute the low activity of very acidic sulfanilamides to the impenetrability of the cell wall toward anions, as originally suggested by Cowles, *Yale J. Biol. Med.*, **14**, 599 (1942), rather than to the concentration effects postulated by Bell and Roblin.

DEPARTMENT OF CHEMISTRY
NORTHWESTERN UNIVERSITY FREDERICK G. BORDWELL
EVANSTON, ILLINOIS IRVING M. KLOTZ

RECEIVED JANUARY 3, 1944

AN AZEOTROPE IN THE SYSTEM *n*-BUTANE–METHYL BROMIDE

Sir:

In analyzing the products of reactions of mixtures containing butanes, methyl bromide, and aluminum bromide,[1] a successful procedure has been to remove excess methyl bromide from the volatile fraction by reaction with ethanolamine and to determine the paraffin hydrocarbons remaining by low temperature micro-fractionation. In one such experiment, where there was poor contact between the halide and amine, the distillation showed no *n*-butane (b. p. −0.6°), but did give a methyl bromide flat (b. p. 3.5°[2]), and in addition a puzzling fraction boiling at approximately −5° (atm. pressure).

The only possibilities for this −5° fraction would be unsaturates (butadiene, b. p. −4.8°; isobutene, b. p. −6.6°; butene-1, b. p. −6.1°) and methylamine (b. p. −6.5°), although the former are very unlikely because they all are polymerized by and form stable complexes with aluminum bromide, and the latter could come only from decomposition of the ethanolamine, which is extremely improbable.

The distillate was shaken with 96% sulfuric acid at room temperature for two days and refractionated. It showed the same distillation characteristics as before, with the exception of a slight diminution of the methyl bromide fraction, which was to be expected.

Sulfuric acid will absorb unsaturates and amines readily, and these possibilities are therefore eliminated. The only hypothesis that will fit the facts is that *n*-butane and methyl bromide form a minimum boiling mixture. Indeed, when the product reacted with excess fresh ethanolamine and was refractionated, the flat at −5° disappeared and the expected *n*-butane fraction appeared, in accord with the hypothesis.

To determine the properties of the azeotrope, a synthetic mixture of 49.1 mole % of *n*-butane and 50.9 mole % of methyl bromide was prepared and fractionated in a Podbielniak micro-precision type R column[3] with 3.0 mm. unpacked inner bore, manually operated, the pressure being regulated at 760 mm. (cor.). The distillation curve is shown below. Each mm. of distillate corresponds to 1.85×10^{-4} mole at 26°, the temperature of the vapor receiving bulb in this case, and the thermocouple-galvanometer system gives a deflection of almost exactly 2 per deg. (R, $t < 0°$; L, $t > 0°$) in the range −15 to 15°.

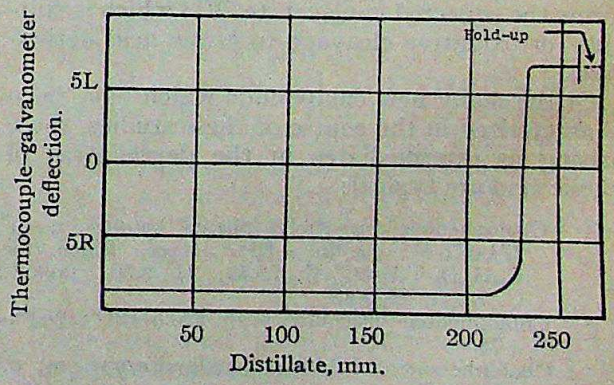


Fig. 1.

From the distillation plot, it is apparent that the azeotrope boils at −4.4°. A material balance suffices to fix its composition at 58.1 ± 0.5 mole % *n*-butane.

A detailed study of the vapor–liquid equilibrium in the above system is now in progress.

CHEMICAL LABORATORY
UNIVERSITY OF CALIFORNIA
BERKELEY, CALIFORNIA JULIUS D. HELDMAN

RECEIVED MARCH 6, 1944

(1) These experiments are to be presented shortly for publication in THIS JOURNAL.

(2) The value 4.6° in the "Handbook of Chemistry and Physics," 25th Edition, Chemical Rubber Publishing Co., Cleveland, Ohio, p. 880, is in error. See Egan and Kemp, THIS JOURNAL, **60**, 2097 (1938).

(3) Podbielniak, *Ind. Eng. Chem., Anal. Ed.*, **3**, 177 (1931); **5**, 119 (1933).

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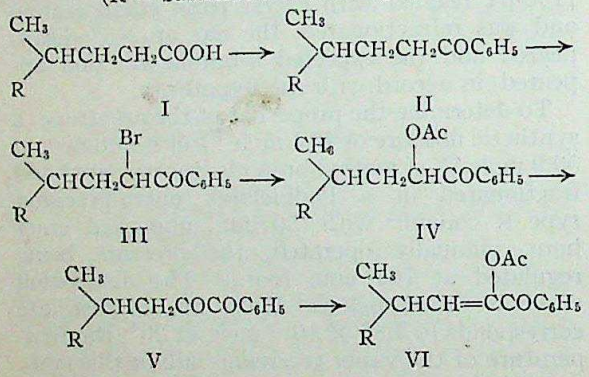
A NEW METHOD FOR THE DEGRADATION OF BILE ACID DERIVATIVES

Sir:

I wish to report in outline form a promising new procedure for degrading the characteristic γ-substituted *n*-valeric acid side chain (I) of the bile acids and their derivatives in the preparation of suitable starting materials for steroid hormone partial syntheses.

The excellent method of Gilman and Nelson[1] when applied to the acid chloride of I provides the phenyl ketone (II) in 70 to 75% yield if diphenylcadmium is used. Bromination of the ketone yields a mixture of isomeric 23-bromo compounds (III) which upon acetolysis forms the corresponding 23-acetoxy derivatives (IV). The latter, after hydrolysis to the α-ketols, can be oxidized

(R = Substituted steroid ring system)



with copper sulfate in aqueous pyridine to the α-diketone (V) in 65 to 70% over-all yield from the monoketone. Acetylation of the diketone then forms the expected enolacetate (VI) which is suitable for oxidative cleavage to *bisnor*-acid derivatives.

Of the many new compounds which have been characterized in the course of these studies, those arising as intermediates in the degradation of cholic acid are typical:

(II) Cholophenone (*nor*-cholyl phenyl ketone), m. p. 174–176.5°; $[\alpha]^{20}D$ +26°.[2] *Anal.* Calcd. for $C_{30}H_{44}O_4 \cdot {}^1/_2H_2O$: C, 75.43; H, 9.50. Found: C, 75.35; H, 9.48.
Cholophenone triacetate, m. p. 120.3–121°; $[\alpha]^{20}D$ +79°
Cholophenone 2,4-dinitrophenylhydrazone, m. p. 221–222.5°
Cholophenone oxime, m. p. 214–217° dec.

(III) 23(β)[3]-Bromo-cholophenone triacetate, m. p. 108.5–111.5°; $[\alpha]^{20}D$ +95°. *Anal.* Calcd. for $C_{36}H_{49}O_7Br \cdot H_2O$: C, 62.51; H, 7.43. Found: C, 62.86; H, 7.19. Calcd. for $C_{36}H_{49}O_7Br$: C, 64.18; H, 7.33. Found: (sintered *in vacuo*), C, 64.05; H, 7.35.

(IV) 23(α)[3]-Acetoxy-cholophenone triacetate, m. p. 180–182°; $[\alpha]^{20}D$ −10°. *Anal.* Calcd. for $C_{33}H_{52}O_9 \cdot {}^1/_2H_2O$: C, 68.96; H, 8.07. Found: C, 69.15; H, 8.09.

(V) *bisnor*-Cholyl benzoyl ketone triacetate, m. p. 166–169° (after drying, 161.5–166°); $[\alpha]^{20}D$ +92°. *Anal.* Calcd. for $C_{36}H_{48}O_8$: C, 71.02; H, 7.95. Found: C, 70.92; H, 7.88.

bisnor-Cholyl benzoyl ketone 7,12-diacetate, m. p. 201–203.5°; $[\alpha]^{20}D$ +80°. *Anal.* Calcd. for $C_{34}H_{46}O_7$: C, 72.05; H, 8.18. Found: C, 72.16; H, 8.34.

2-*bisnor*-Cholyl-3-phenyl-quinoxaline triacetate, m. p. 217–218.5°.

Work now in progress indicates that the application of this degradation scheme to substituted *nor*-bile acids will result in the formation of pregnane-20-one derivatives in much higher yields than heretofore obtainable.

National Institute of Health
Bethesda, Maryland
Robert P. Jacobsen

Received March 21, 1944

(1) Gilman and Nelson, *Rec. trav. chim.*, **55**, 518 (1936).
(2) Rotations measured in chloroform.
(3) Configuration tentatively assigned.

DESTRUCTION OF RIBOFLAVIN IN MILK BY SUNLIGHT[1]

Sir:

The phenomenon of photochemical destruction of riboflavin has been adequately demonstrated by György and coworkers[2] and Roscoe,[3] and more recently by Williams and Cheldelin.[4] The latter workers demonstrated that as much as 26% of the riboflavin of milk was destroyed by light when the milk was exposed for as short a time as five minutes at 100°. These findings suggested that in all probability appreciable amounts of riboflavin would be lost in milk bottled in the standard type retail glass milk bottle when exposed to sunlight at ordinary temperatures.

Experiments were conducted from mid-morning until mid-afternoon on sunny days. Fresh milk obtained the same day was bottled in pint milk bottles with the usual type cap and exposed to direct sunlight on an open porch. Riboflavin concentrations were determined fluorometrically with the Coleman electronic photometer (Model 12), using essentially the technic of Hand[5] except that 10 cc.

Table I

Destruction of Riboflavin in Milk by Sunlight

Series	Original riboflavin content, γ/cc.	Riboflavin content after 1 hr. exposure, γ/cc.	Destruction %
I	1.86	1.13	39
	1.51	0.97	36
II	1.98	1.13	43
	2.29	1.40	39
	2.29	1.60	30
III	0.83	0.38	54
	1.94	1.30	33
IV	2.43	1.65	32
	2.60	1.90	27
	1.28	0.66	48

(1) Published with the approval of the Director of the North Carolina Agricultural Experiment Station as Paper No. 182 of the Journal series.
(2) P. György, R. Kuhn and T. Wagner-Jauregg, *Naturwissenschaft*, **21**, 560 (1933).
(3) M. H. Roscoe, *Biochem. J.*, **27**, 1540 (1933).
(4) R. R. Williams and V. H. Cheldelin, *Science*, **96**, 22 (1942).
(5) D. B. Hand, *Ind. Eng. Chem., Anal. Ed.*, **11**, 306 (1939).

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of acetone was added to 5 cc. of well-mixed whole milk to obtain the filtrate. The results of four studies conducted on separate days are summarized in Table I. All samples were from different cows. Atmospheric temperatures at which the samples were exposed were never less than 60°F. nor higher than 72°F.

The mean loss of riboflavin in sixty minutes was 0.69 γ. The standard error of this loss based on the variation in loss from series to series was 0.055 γ. Observed losses of riboflavin at exposure intervals of 30, 90, 120 and 210 minutes were, respectively, 28, 50, 66 and 72%.

Control samples of milks used in the study showed no loss of riboflavin when stored in the dark at room temperature for twenty-four hours, nor did any loss occur when they were stored in a refrigerator for seven days. In order to determine whether an initial exposure to sunlight would stimulate a more rapid decrease when samples were subsequently placed in the dark under refrigeration, three samples (1.54 γ/cc.) were placed in the refrigerator after one-half, one, three and five hours of exposure. After forty-eight hours, the additional loss which had taken place was extremely small, averaging 0.016 γ, and in no case exceeding 0.07 γ.

It is evident that the destruction of riboflavin in milk by sunlight proceeds at a very rapid rate, even at ordinary temperatures.

DEPARTMENT OF ANIMAL INDUSTRY WALTER J. PETERSON
NORTH CAROLINA STATE COLLEGE F. M. HAIG
RALEIGH, N. C. A. O. SHAW

RECEIVED MARCH 13, 1944

THE LINKAGE OF CORPUSCULAR PROTEIN MOLECULES. I. A FIBROUS MODIFICATION OF INSULIN

Sir:

When 1.5 to 2.0% solutions of insulin hydrochloride (Lilly, amorphous) at *p*H 2.0 to 2.5 are heated for thirty minutes at 100°, thixotropic gels are formed which exhibit static double refraction.[1,2] Dilution to 0.5% produces a viscous solution showing intense flow double refraction.

Electron micrographs of this material reveal the presence of uniform fibrils several microns in length, having uniform widths of approximately 200 Å. (an asymmetry well above 100).

Insulin gels, containing 2% protein, have been frozen and thawed many times in a solid carbon dioxide-alcohol mixture. During this treatment the viscosity gradually decreases to low values. Flow double refraction replaces static double refraction and after 10 cycles even the former decreases greatly in magnitude. A second heat treatment produces a thixotropic gel showing static double refraction. This indicates that segments of fibrils produced by the freezing-thawing treatment unite in a directional manner.

After standing for twenty-four to forty-eight hours at *p*H 11.0–11.5 and 0°, a dispersion of insulin fibrils loses its characteristic double refraction and viscosity. The solution thus produced resembles an equivalent solution of native insulin so far as the methods mentioned have demonstrated.[3] Protein may be recovered after such a "reversal" and dissolved to form a 2% solution at *p*H 2.0. Heat treatment again produces a thixotropic gel showing static double refraction. This cycle has been repeated several times.

Prolonged heating of insulin in acid solution or at reactions well below *p*H 2.0 produces sphaerocrystalline aggregations of insulin fibrils termed the "heat precipitate of insulin" by du Vigneaud, Geiling and Eddy.[4] These authors have shown that this material, dissolved in dilute alkali and immediately acidified, exhibits 80% of the biological activity of the original insulin. Since the heat precipitate of insulin is now shown to consist of aggregations of insulin fibrils, it is considered that insulin fibrils show such activity after reversal by alkali whether or not they have formed the "heat precipitate."

Insulin fibrils are considered to be constructed of corpuscular molecules which have been deformed only slightly in the process. Jensen[5] has suggested that the insulin molecules present in the heat precipitate are linked by covalent bonds. Unpublished chemical evidence shows that insulin fibrils may be formed after the sulfur has been split off by alkali and after ammonia has been liberated by heat. This type of evidence indicates that fibril formation may take place after the removal of those groupings which are expected to take part in covalent bond formation. Therefore it is proposed that insulin molecules are linked mainly through the secondary valence forces resulting from the approximation of nonpolar side chains. Two surface concentrations of these chains on opposite portions of the insulin molecule would account for the bifunctional nature exhibited in fiber formation.

DEPARTMENT OF BIOLOGY AND BIOLOGICAL ENGINEERING
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE, MASS. DAVID F. WAUGH

RECEIVED MARCH 1, 1944

(1) I. Langmuir and D. F. Waugh, THIS JOURNAL, **62**, 2771 (1940).

(2) D. F. Waugh, *Jour. Phys.*, **133**, p. 484 (1941).

(3) More refined methods are being applied.

(4) Vincent du Vigneaud, E. M. K. Geiling and C. A. Eddy, *J. Pharm. Exp. Therapy*, **33**, 497 (1928).

(5) H. Jensen, *Science*, **75**, 614 (1932).

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NEW BOOKS

Optical Crystallography. By ERNEST E. WAHLSTROM, Department of Geology and Mineralogy, University of Colorado, Boulder. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y., 1943. v + 206 pp. 209 figs. 14.5 × 22 cm. Price, $3.00.

This book is a welcome addition to the rather small number of optical crystallographic texts accessible to chemists. The simple, concise presentation of the theory of crystal optics in a form already familiar to mineralogists and petrographers accents the sound physical foundation underlying this subject in a way not as readily achieved in the typical laboratory treatments. Both in the more advanced petrographic manuals and in experimental texts on chemical microscopy the details of microscopic technique tend to obscure the well integrated treatment of the propagation light in crystalline solids upon which the individual methods depend.

After brief chapters on geometric crystallography, physical properties, elementary optics, and the polarizing microscope, the author begins a systematic development of the behavior of light in non-opaque crystals. Isotropic materials are discussed first and after a timely digression to describe fundamental methods of refractive index measurement, the treatment goes on to cover uniaxial and finally biaxial crystals. Extensive use is made of the indicatrix and the related ellipsoidal diagrams in correlating optical phenomena. This treatment is essential to a clear understanding of the relationships of the individual optical constants both among themselves and to the crystal lattice. A commendable feature is the large amount of space (including illustrations) given to the description of interference figures and their use in discovering the principal ellipsoidal axes and in determining optical sign. Much attention is given to off-center interference figures which in practice greatly predominate.

The author confines his treatment to those optical properties of unquestioned value in mineralogical studies and leaves to the chemist the problem of discovering and developing for himself other optical criteria which may assume importance because of the greater variety of chemical compounds at his disposal. It is believed that insufficient emphasis has been placed upon the value of interference figures in locating the principal refractive indices, greater attention having been given the less exact statistical methods based on the selection of high and low interference colors in an aggregate of crystalline particles. While there is evident some tendency toward over-simplification, the simple, direct treatment employed gives this book unquestioned pedagogical value.

W. M. D. BRYANT

The Biochemistry of Malignant Tumors. By KURT STERN, M.D., Formerly Research Associate of University of Vienna, New York, N. Y., and ROBERT WILHELM, M.D., Professor, University of Philippines, Manila. Reference Press, Brooklyn, N. Y. (The Chemical Publishing Co., Inc., 234 King Street, Brooklyn, N. Y.), 1943. xiv + 951 pp. 14.5 × 22.5 cm. Price, $12.00.

The etiology of cancer has commanded the attention of specialists in widely different fields of scientific research, and valuable contributions have already been made by investigators whose background experiences lie outside the boundaries of morphological pathology and clinical medicine. There has been a tendency, unfortunate but probably unavoidable, for investigators of the cancer problem to become segregated into small specialist groups of biochemists, organic chemists, geneticists, endocrinologists, and the like, each following its own highly specialized line of attack. Under these conditions it is not easy to obtain an integrated picture of the progress of cancer research as a whole, or to gain an insight into possible inter-relationships between the findings of the various specialist groups.

The book has yet to be written in which such a complete coördination is attempted, and must probably await further advances in our understanding of the nature of the disease. In "The Biochemistry of Malignant Tumors" Dr. Stern and Dr. Willheim have achieved the lesser, but still formidable, task of coördinating the contributions of the chemist and bio-chemist to this subject, and the range of the material actually covered is much broader than the title suggests. The text was developed from an earlier German monograph, published by the authors in Vienna in 1936. Coöperation between Dr. Stern and Dr. Willheim was unfortunately interrupted in December, 1941, when Dr. Willheim was in Manila, and the greater share of the responsibility for the later stages of the preparation of the book was borne by Dr. Stern.

The book is divided into ten chapters. The first three are concerned with the contributions of inorganic, organic and physical chemistry, and are followed by chapters on enzymes, nutrition and vitamins, metabolism, endocrine glands and their hormones, immunology, biochemical aspects of tumor origin and tumor growth, and, finally, chemical and biological tumor diagnostics. The literature has been covered systematically to the end of 1941; yet, in spite of the considerable amount of detail included, the authors have succeeded in avoiding the tedious style common to many specialist monographs in which a more or less complete literature coverage is attempted. This can be attributed mainly to their plan of omitting authors' names from the text, where possible, but providing extensive references to original publications as footnotes to each page.

Drs. Stern and Willheim make no attempt to advance any particular "cancer theory" of their own. They draw attention to discrepancies between the observations of different workers, where they occur, try to reconcile these, or to suggest factors which may account for the differences. It is somewhat discouraging to observe how frequently some line of attack has yielded promising results in the hands of one group of workers while other investigators obtained contradictory results under apparently comparable circumstances. It would seem there must still be many uncontrolled factors which influence the initiation, growth and degeneration of malignant tumor tissue.

As a result of the war, the number of investigators active in the field of cancer research has been very materially reduced, but it is to be expected that a search for the cause and cure of cancer will become one of the foremost objectives of post-war science. In summarizing the present state of our knowledge of the bio-chemistry of cancer, Dr. Stern and Dr. Willheim have made a real contribution to that post-war objective; their book should be read both by those at present engaged in the study of cancer and by those contemplating taking up such work in the future.

R. NORMAN JONES

BOOKS RECEIVED

February 10, 1944–March 10, 1944

C. H. BAILEY. "The Constituents of Wheat and Wheat Products." (A. C. S. Monograph Series.) Reinhold Publishing Corporation, 330 West Forty-second Street, New York, N. Y. 332 pp. $6.50.

HERBERT S. HARNED and BENTON B. OWEN. "The Physical Chemistry of Electrolytic Solutions." (A. C. S. Monograph Series.) Reinhold Publishing Corporation, 330 West 42nd Street, New York, N. Y. 611 pp. $10.00.

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Manuscripts for THIS JOURNAL should be submitted to the Editor ready for publication, typewritten (double space), with 2–3 cm. margins, on a good quality, durable paper, preferably of 8.5″ × 11″ size. In addition to the original typewritten copy, one or more carbon copies should be submitted so that the time required for examination by the Editorial Board may thus be considerably shortened. Care should be taken that all pages in a manuscript, including tables (but not the diagrams) be numbered consecutively. In preparing manuscripts authors are requested to observe, for reasons of economy, the utmost conciseness consistent with clarity of presentation. The manuscripts should be addressed to specialists in their particular field rather than to the general reader. Extensive reviews of the literature cannot be accepted. When well-known or previously published procedures have been followed in the experimental work they should only be designated or referred to.

Form of Presentation.—There should be one or more introductory paragraphs setting forth the occasion, significance and main objectives of the investigation and the method of attack. This should be followed by the experimental results and a discussion of them, either *seriatim* or at their conclusion. Finally, there should be a brief summary of the main achievements of the investigation. Sometimes, particularly when the subject matter is involved and there are many details which, though essential for a successful repetition of the experiments, are unnecessary for the main account of the investigation, these details can with advantage be relegated to an appendix or supplement, just preceding the Summary. In intermediate cases it is often advisable to retain a single, straightforward presentation but to intercalate sections in fine print giving the experimental details of procedure. This has the great advantage of keeping the experimental details close to the more general statements based upon them and yet at the same time permitting the reader if he wishes to pass over this section without inconvenience.

It will be of great assistance to the Editor's Office if the style, arrangement and orthography of the manuscripts are made to conform to the usages of the JOURNAL as exemplified in its recent issues and as set forth in the following paragraphs.

Center headings should be employed sparingly; side headings should be indented and run into the text to which they apply, using period and dash. References to the literature and all footnotes regardless of their nature (except those in tables) should be numbered in one consecutive series, repetition of notes being avoided by using simply the superscript number corresponding to the original reference. They should follow immediately in separate lines the line of text containing the text words to which they refer, and may be set off by short rules above and below. The items in the references to the literature should conform to the uniform usages of the Journal as regards order and punctuation, and to the abbreviations as given by *Chemical Abstracts* in its "List of Periodicals Abstracted." The names of all simple compounds rather than their formulas should be used whenever they occur in the text. Periods of time (unless fractional) should be written in words and quantities of material in Arabic numerals, unless occurring at the beginning of a sentence. Letters used to represent quantities in mathematical expressions should be underscored to indicate that they are to be printed in italics, and Greek or other unusual characters should be written plainly or should be explained by annotations. Simple fractional expressions should be written with a slant line rather than in the conventional manner, so that only a single line of type is required. All subscripts and superscripts should be carefully made and placed (the degree sign ° or a small o should not be used to represent zero). For economy, except in unusual circumstances the abbreviations %, °A., cm., cc., ml., g., Å., m. p., f. p., b. p., cal., kcal., expt. and Fig., should be used rather than the words.

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New Compounds.—This department is for brief accounts of new substances which do not appear of sufficient importance to justify separate publication and cannot be described appropriately as part of any other Article or Note. These accounts should report the preparation of the new compound succinctly, yet fully enough so that the operations can be duplicated. Significant properties, formulas and analytical data to establish the identity and purity of the substance should be given. Material appearing in this classification will not be accepted for subsequent publication.

Communications to the Editor are designed to afford prompt, brief, preliminary publication in our Journal of new and significant observations or discoveries. Their total length may in no case exceed 500 words or the equivalent. They will be given as rapid editorial consideration as possible, but at best it will usually be out of the question to include them in a given issue of the Journal if they arrive at the Editor's office later than the 20th of the preceding month. Communications like other contributions should be self-sustaining; that is, they should present experimental or other evidence adequate to establish the *prima facie* credibility of the results or conclusions stated or to permit their appraisal by an expert in the field although because of the 500-word limit a complete presentation cannot usually be expected. These requirements make Communications on many subjects impracticable, particularly those of an involved or theoretical nature.

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The Acetolysis of Trimethylene-D-sorbitol. 2,4-Methylene-D-sorbitol and 1,3:2,4-Dimethylene-D-sorbitol

BY A. T. NESS, RAYMOND M. HANN AND C. S. HUDSON

Recently[1] we have shown that the limited acetolysis of the trimethylene-D-mannitol of Schulz and Tollens yields a compound to which has been tentatively assigned the structure 1,6-diacetyl-3,4-di-(acetoxymethyl) - 2,5 - methylene - D - mannitol. This structure seems highly probable since the saponification of the acetolysis product yields a 2,5-methylene-D-mannitol, a fact which we take to indicate that the acetal linkages of trimethylene - D - mannitol which are formed through secondary hydroxyl groups are relatively more stable to acetolysis than those formed through primary hydroxyl groups. The acetolysis apparently proceeds with rapid rupture of the acetal linkages at positions one and six and the 3,4-di-(hydroxymethyl) - 2,5 - methylene - D - mannitol which is assumed to be formed is immediately acetylated to produce 1,6-diacetyl-3,4-di-(acetoxymethyl)-2,5-methylene-D-mannitol. In view of the unusual nature of the acetolysis reaction, and particularly since the acetolysis product and the 2,5-methylene-D-mannitol derived from it contain the rare C_5O_2 dioxepane ring as an integral part of their structures, it seemed of interest to study the acetolysis of the known trimethylene-D-sorbitol.[2] In the course of preparation of a supply of this material we isolated from the mother liquor a dimethylene-D-sorbitol, a new substance, which melted at 174–175° and rotated $[\alpha]^{20}D$ −29.6° in water, and the investigation was extended to include the acetolysis and proof of structure of this diacetal.

Considering first the trimethylene-D-sorbitol, it is obvious that its acetal linkages must be formed through four secondary and two primary hydroxyl groups. From our previous experience it was anticipated that upon limited acetolysis it would yield a diacetyl-di-(acetoxymethyl)-monomethylene-D-sorbitol; it was found that the acetolysis of trimethylene-D-sorbitol by an ice-cold 1% sulfuric acid acetylating solution for five minutes gave a 51% yield of a crystalline reaction product (m. p. 111–112°; $[\alpha]^{20}D$ +29.8° in chloroform), the composition of which agreed with that of the expected substance. The compound was saponified by the method of Kunz[3] with the consumption of four molecular equivalents of sodium hydroxide, and the saponification product proved to be a crystalline monomethylene-D-sorbitol (m. p. 163–164°; $[\alpha]^{20}D$ −9.8° in water). Oxidation of this product with sodium periodate (and other glycol-splitting reagents) reduced one molecular equivalent of the oxidant and proved that only a single glycol grouping is present in the monomethylene-D-sorbitol. At this stage of the study the experimental results in the case of trimethylene-D-sorbitol are thus closely parallel with those previously reported for the isomeric trimethylene-D-mannitol. However, the periodate oxidation of the 2,5-methylene-D-mannitol proceeded without the production of acid or formaldehyde, thereby confirming the structure assigned to it, whereas 0.86 of a molecular equivalent of formaldehyde was isolated as the crystalline dimethone derivative from the oxidized solution of the monomethylene-D-sorbitol. One hydroxyl group of the glycol grouping of methylene-D-sorbitol is therefore primary in character and the structure of the acetal cannot be 2,5 but is limited to that of 2,4 or 3,5-methylene-D-sorbitol. A choice between these two possibilities could be readily made; the oxidation of 2,4-methylene-D-sorbitol (III) with glycol-splitting reagents would yield 2,4-methylene-L-xylose, which upon reduction would be converted to 2,4-methylene-xylitol (IV) of *meso* con-

(1) Ness, Hann and Hudson, THIS JOURNAL, 65, 2215 (1943).
(2) Schulz and Tollens, *Ann.*, 289, 23 (1896).
(3) Kunz, THIS JOURNAL, 48, 1982 (1926).

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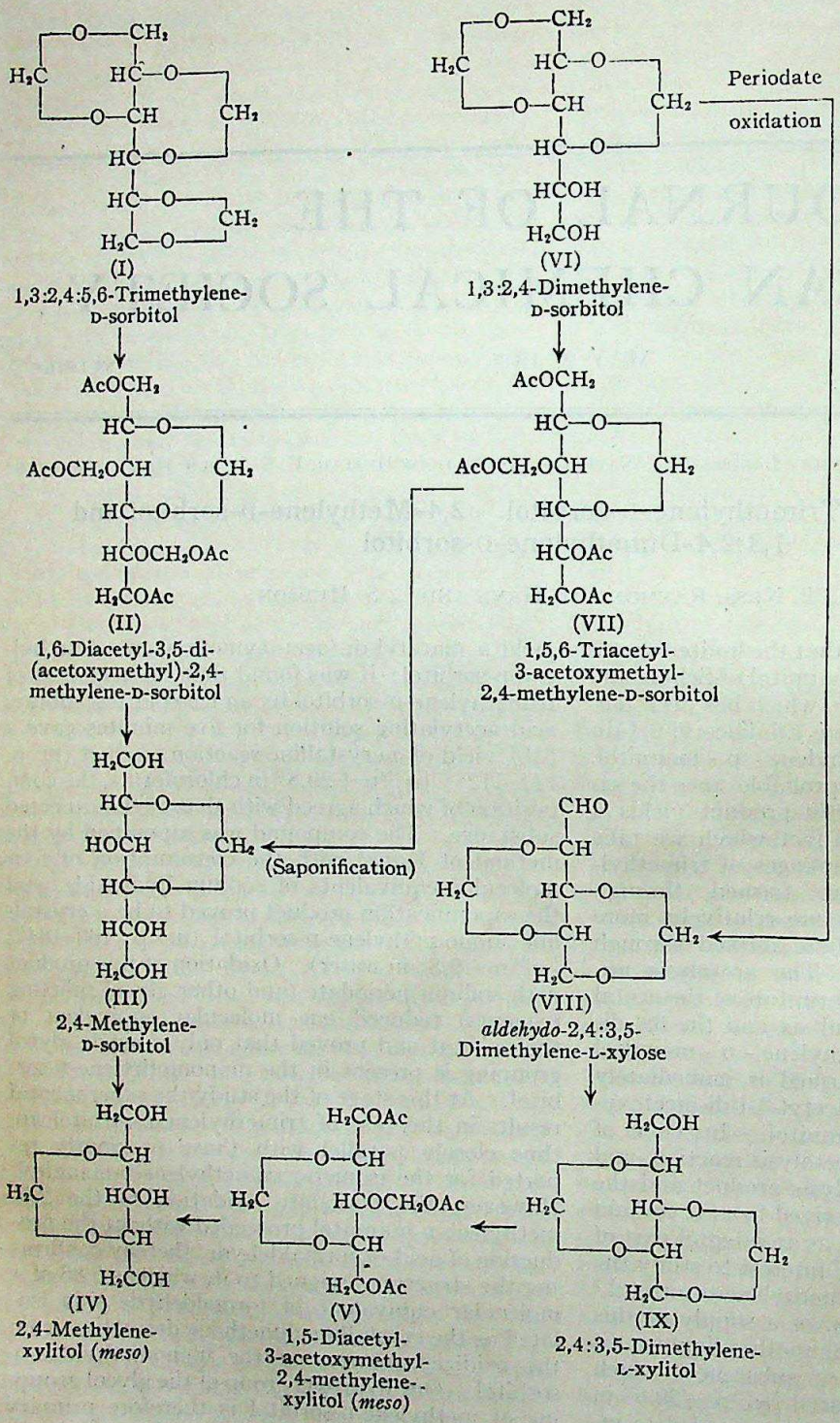

solution, which had changed in rotation $[\alpha]^{20}D$ from an original value of $-9.8°$ (calculated as 2,4-methylene-D-sorbitol) to $-17.6°$ (calculated as 2,4-methylene-pentose), was found to be strongly reducing to Fehling solution; removal of the acids and the solvent left the colorless sirupy oxidation product, which did not crystallize; this sirup was reduced in aqueous solution at 100° for six hours with Raney nickel and hydrogen under a pressure of 133 atmospheres. The crystalline reduction product (m. p. 108–109°), which did not reduce Fehling solution and had the composition of a monomethylene-pentitol, was optically inactive in aqueous solution, from which fact the conclusion was drawn that it is the *meso* 2,4-methylenexylitol rather than the 2,4-methylene-D-arabitol. Exact proof of this conclusion was obtained through the preparation of authentic 2,4-methylene-xylitol from xylitol, as described in the accompanying article[4]; the substances from the two sources are identical. The production of 2,4-methylene-xylitol (IV) from the monomethylenesorbitol limits the structure of the latter to 2,4-methylene-D-sorbitol (III) and this conclusion makes it probable that trimethylene-D-sorbitol is 1,3:2,4:5,6-trimethylene-D-sorbitol (I) (since a 1,5- or 1,6-acetal ring is highly improbable) and that the intermediate product obtained by the acetolysis of trimethylene-D-sorbitol is 1,6-diacetyl-3,5-di-(acetoxymethyl)-2,4-methylene-D-sorbitol (II).

Considering next the dimethylene-D-sorbitol of m. p. 174–175° and rotation $[\alpha]^{20}D$ $-29.6°$ in water, it was found that upon oxidation in dilute

figuration and therefore optically inactive; on the other hand, the oxidation of 3,5-methylene-D-sorbitol would produce 2,4-methylene-D-arabinose, reducible to 2,4-methylene-D-arabitol, the formula of which represents an optically-active system. To decide the question, methylene-D-sorbitol was oxidized by aqueous per-iodic acid; the oxidation was complete in fifteen minutes and the oxidized

(4) Hann, Ness and Hudson, THIS JOURNAL, 66, 670 (1944).

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aqueous solution with sodium periodate, only slightly more than one molecular equivalent of oxidant was consumed, and the yield of crystalline formal-dimethone from the oxidized solution corresponded to 0.98 molecular equivalent of formaldehyde. In further experiments, the other oxidation product, which proved to be an *aldehydo*-dimethylene-pentose monohydrate, crystallized spontaneously from the oxidation mixture; the compound, which rotated $[\alpha]^{20}D$ −33.9° in water and melted at 175–180° after previous sintering at 150°, was converted upon sublimation to the anhydrous dimethylene-pentose, which melted at 189–192° and rotated −38.7° in aqueous solution; it was characterized as the crystalline oxime, a substance which melted with decomposition at 227–228° and showed the unusually high rotations $[\alpha]^{20}D$ −272° in pyridine and −215° in water. The structure of the *aldehydo*-dimethylene-pentose is limited by reason of the genesis of the substance from dimethylene-D-sorbitol to *aldehydo*-2,3,4,5-dimethylene-L-xylose or *aldehydo*-2,3,4,5-dimethylene-D-arabinose. Conclusive proof that it is the former compound was obtained in the following manner: upon reduction with hydrogen and Raney nickel it is converted to a crystalline dimethylene-pentitol melting at 217–219° and rotating $[\alpha]^{20}D$ −25.3° in aqueous solution; this pentitol diacetal is transformed by limited acetolysis to the 1,5-diacetyl-3-acetoxymethyl-2,4-methylene-xylitol (*meso*) (V) that is obtained by the limited acetolysis of the 2,4:3,5-dimethylene-D,L-xylitol which is described in the accompanying communication.[4] This result is definitive proof that the optically active pentitol diacetal ($[\alpha]^{20}D$ −25.3°) is 2,4:3,5-dimethylene-L-xylitol (IX); it follows that the *aldehydo*-dimethylene-pentose and the dimethylene-D-sorbitol from which it is derived must be *aldehydo*-2,4:3,5-dimethylene-L-xylose (VIII) and 1,3:2,4-dimethylene-D-sorbitol (VI), respectively.

The formation of an optically inactive acetolysis product (1,5-diacetyl-3-acetoxymethyl-2,4-methylene-xylitol, *meso* structure (V)) from the optically active 2,4:3,5-dimethylene-L-xylitol (IX) is additional evidence supporting our previously expressed view that the limited acetolysis of methylene sugar alcohol acetals takes place initially through a rupture of the acetal linkage at a primary hydroxyl group; had the acetal rupture of (IX) occurred at any other position than carbon five the acetolysis product would be expected to possess optical rotatory power.

Confirmatory evidence for the assigned structure of 1,3:2,4-dimethylene-D-sorbitol (VI) was also obtained through its acetolysis to form the expected 1,5,6-triacetyl-3-acetoxymethyl-2,4-methylene-D-sorbitol (VII), a compound which is saponified by sodium methylate with the production of the previously isolated 2,4-methylene-D-sorbitol (III).

The fact that 1,3:2,4-dimethylene-D-sorbitol (VI) is obtained from the reaction mixture employed for the preparation of trimethylene-D-sorbitol, suggests that it is a precursor of the latter compound; support for this inference was attained when it was found that upon treatment with formaldehyde and hydrochloric acid the crystalline diacetal was converted in 85% yield into the triacetal; this experimental result also offers further support for the previously expressed view that the triacetal is 1,3:2,4:5,6-trimethylene-D-sorbitol (I). Apparently the rare C_5O_2 dioxepane ring that is present in 1,3:2,5:4,6-trimethylene-D-mannitol is absent from the structure of the isomeric trimethylene-D-sorbitol. The two substances are structural rather than stereoisomers, and in view of this result it seems obvious that the methylene derivatives of the other hexitols should be investigated similarly.

Experimental

I. Substances Derived from Trimethylene-D-sorbitol

1,3:2,4:5,6-Trimethylene-D-sorbitol (I) and 1,3:2,4-Dimethylene-D-sorbitol (VI) from D-Sorbitol, Formaldehyde and Concentrated Hydrochloric Acid.—A solution of 200 g. of D-sorbitol in a mixture of 300 cc. of 37% aqueous formaldehyde and 200 cc. of concentrated hydrochloric acid was heated at 50° for four days; after cooling the reaction mixture to 5° for several hours the trimethylene-D-sorbitol which had crystallized was separated by filtration and the filtrate was again heated at 50° for several days; no further deposition of triacetal occurred and the solution was employed for the isolation of 1,3:2,4-dimethylene-D-sorbitol as described in the following paragraph. The trimethylene-D-sorbitol, which was obtained in a yield of 162 g. (68%), was recrystallized from 20 parts of water or 50% alcohol as long rods which melted at 212–216° and rotated $[\alpha]^{20}D$ −30.8° in chloroform (*c*, 1.2).[5] Schulz and Tollens[3] record a melting point of 206° and rotations $[\alpha]^{20}D$ −30.3° (*c*, 2.58) and −29.3° (*c*, 4.578) in chloroform.

The mother liquor of the triacetal preparation was neutralized with sodium carbonate, the sodium chloride which precipitated was separated by filtration, and the filtrate was concentrated *in vacuo* to dryness; the dry residue was extracted with two 200-cc. portions of hot absolute alcohol and the extract upon cooling deposited 35 g. of fine needles (m. p. 150–168°) which after several recrystallizations from 40 parts of acetone yielded 19.0 g. of pure 1,3:2,4-dimethylene-D-sorbitol melting at 174–175° and rotating $[\alpha]^{20}D$ −29.6° in water (*c*, 1.47). The yield was 8% based on the D-sorbitol used or 26% based on the D-sorbitol which did not form trimethylene-D-sorbitol. The diacetal is soluble in cold water, dioxane, pyridine and acetic acid, in warm methyl and ethyl alcohols and practically insoluble in ether, carbon tetrachloride and chloroform.

Anal. Calcd. for $C_8H_{14}O_6$: C, 46.60; H, 6.84. Found: C, 46.66; H, 6.92.

1,6-Diacetyl-3,5-di-(acetoxymethyl)-2,4-methylene-D-sorbitol (II).—Eighty grams of dried and powdered trimethylene-D-sorbitol was added to a rapidly stirred ice-cold mixture of 175 cc. of acetic anhydride, 75 cc. of glacial acetic acid and 2.5 cc. of concentrated sulfuric acid; solution of the triacetal was rapid and after five minutes the reaction mixture was poured into 3 liters of vigorously stirred ice water. The acetolysis product crystallized and after two hours the crystalline product was separated by

(5) All the crystalline compounds described in the experimental part were recrystallized to constant melting point and specific rotation; *c* is the concentration in grams in 100 cc. of solution; the tube length was 4 dm.; all melting points were determined with the stem of the calibrated thermometer immersed in the rapidly stirred bath.

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filtration, washed with cold water and air dried. The yield was 80 g. (52%). The compound was recrystallized from 12 parts of alcohol as long needles which melted at 111–112° and rotated $[\alpha]^{20}D$ +29.8° in chloroform (*c*, 1.20). It is soluble in acetone, chloroform, benzene, acetic acid and pyridine and practically insoluble in water, ether and cold methyl and ethyl alcohols.

Anal. Calcd. for $C_{17}H_{26}O_{12}$: C, 48.34; H, 6.20; saponification, 0.1452 g. substance requires 13.75 cc. 0.1 *N* NaOH (4 saponifiable groups). Found: C, 48.41; H, 6.10; saponification, 0.1452 g. substance consumed 13.75 cc. 0.1 *N* NaOH.

2,4-Methylene-D-sorbitol (III).—A solution of 10 g. of 1,6 - diacetyl - 3,5 - di - (acetoxymethyl) - 2,4 - methylene-D-sorbitol in 100 cc. of chloroform was cooled in an ice-bath and 10 cc. of 0.2 *N* sodium methylate solution was added; upon standing at 5° for eighteen hours, 4.6 g. (quantitative) of 2,4-methylene-D-sorbitol crystallized from the reaction mixture. The acetal was recrystallized from 20 parts of alcohol in the form of fine needles which melted at 163–164° and rotated $[\alpha]^{20}D$ −9.8° in aqueous solution (*c*, 1.30). It is readily soluble in water, hot methyl and ethyl alcohols and practically insoluble in chloroform, acetone and ether.

Anal. Calcd. for $C_7H_{14}O_6$: C, 43.29; H, 7.27. Found: C, 43.27; H, 7.25.

1,3,5,6-Tetraacetyl-2,4-methylene-D-sorbitol.—A solution of 2.0 g. of 2,4-methylene-D-sorbitol in a mixture of 15 cc. of acetic anhydride and 10 cc. of pyridine was allowed to stand for forty-eight hours at 25° and then poured into ice-water; the precipitated tetraacetyl derivative, which is soluble in chloroform, acetone, acetic acid, pyridine and benzene and practically insoluble in water and cold methyl and ethyl alcohols, was recrystallized from 10 parts of alcohol as prismatic needles melting at 150–151° and rotating $[\alpha]^{20}D$ −1.5° in chloroform (*c*, 1.40). The yield was 3.6 g. (94%).

Anal. Calcd. for $C_{15}H_{22}O_{10}$: C, 49.72; H, 6.12; CH_3CO, 47.5. Found: C, 49.80; H, 6.03; CH_3CO, 47.3.

Lead Tetraacetate Oxidation of 2,4-Methylene-D-sorbitol.—To a solution of 0.1018 g. of 2,4-methylene-D-sorbitol in 15 cc. of glacial acetic acid, 30 cc. (3.32 molecular equivalents) of 0.0581 *M* lead tetraacetate glacial acetic acid solution was added and the volume was adjusted to 50 cc. with glacial acetic acid, all operations being conducted at 25°. Analysis of 5 cc. subsamples at one, three and nineteen hours indicated that 0.67, 1.00 and 1.04 molecular equivalents, respectively, of oxidant had been consumed. The analytical data indicate that 2,4-methylene-D-sorbitol contains a single glycol grouping as a portion of its structure.

Per-iodic Acid Oxidation of 2,4-Methylene-D-sorbitol.—A solution of 1.0036 g. of 2,4-methylene-D-sorbitol in 25 cc. of water was cooled to 5° and 15 cc. (1.79 molecular equivalents) of 0.616 *M* per-iodic acid was added; the solution was allowed to warm to 20° and the volume was adjusted to 50 cc. with water. Analysis of 5 cc. aliquots at twenty, forty and sixty minutes showed that 1.04 molecular equivalents of oxidant had been consumed and no further oxidation was noted after twenty and two hundred sixty hours. After titration, the first three aliquots were combined and poured into 200 cc. of 0.4% dimethone solution; the precipitate of formal-dimethone (m. p. 189–190°) which deposited on keeping the mixture at 5° for eighteen hours, weighed 0.387 g. and represented 85% of that expected from the production of one molecular equivalent of formaldehyde as an oxidation product. The results of the oxidation show that the glycol grouping of 2,4-methylene-D-sorbitol must contain a primary alcohol group since the analytical findings agree with the reaction course $C_5H_9O_4{\cdot}CHOH{\cdot}CH_2OH + HIO_4 = C_5H_9O_4{\cdot}CHO + HCHO + H_2O + HIO_3$. Although the analyses mentioned above show that the oxidation was complete within twenty minutes under the experimental conditions, the specific rotation $[\alpha]^{20}D$ of the solution (calculated on its presumed content of methylene-pentose) showed values of −17.6, −14.5, −6.2, −3.1° and a constant value of −2.6° at the expiration of fifteen and sixty minutes, four, twenty and ninety-two hours, respectively; these changes in rotatory power are presumably due to the change of the *aldehydo* form of the methylene-pentose to the equilibrium mixture of its α and β cyclic forms (probably α- and β-2,4-methylene-L-xylopyranose).

Sodium Periodate Oxidation of 2,4-Methylene-D-sorbitol.—The oxidation of 1.0045 g. of 2,4-methylene-D-sorbitol with 15 cc. (1.65 molecular equivalents) of 0.570 *M* sodium periodate was conducted by the same procedure employed in the per-iodic acid oxidation. The analytical results showed that 1.01, 1.03 and 1.02 molecular equivalents of oxidant had been consumed at the end of twenty, forty and sixty minutes, respectively, and the formal-dimethone recovered was 86% of that expected for the production of one molecular equivalent of formaldehyde. The specific rotation $[\alpha]^{20}D$ of the oxidized solution remained constant at −18.4° for three hours and thereafter showed values of −15.3, −11.9, −4.1, −3.6 and −2.6° at the expiration of nineteen, forty-three, one hundred eighty-seven, two hundred twelve and two hundred eighty-three hours, respectively, the reduced rate of mutarotation in this case being probably due to the lower hydrogen-ion concentration.

2,4-Methylene-xylitol (IV) from 2,4-Methylene-D-sorbitol (III).—A solution of 5.0 g. of 2,4-methylene-D-sorbitol in 50 cc. of water was cooled to 5° and 50 cc. (1.20 molecular equivalents) of 0.616 *M* aqueous per-iodic acid was added; the reaction mixture was allowed to stand at 25° for eighteen hours, cold saturated barium hydroxide solution was added in slight excess, the precipitated barium iodate and periodate were separated by filtration and the filtrate was concentrated *in vacuo* to a dry sirup in the presence of barium carbonate. The sirup was extracted with 50 cc. of warm water and the extract, which was reducing to Fehling solution, was transferred to a bomb and agitated at 100° for six hours with Raney nickel and hydrogen under a pressure of 133 atmospheres. The catalyst was separated by filtration and the filtrate, upon concentration *in vacuo*, deposited a crystalline residue (4.2 g.; quantitative) which was recrystallized from 5 parts of alcohol and yielded 2.9 g. of the 2,4-methylene-xylitol (m. p. 108–109°) which is described in the accompanying communication.[4] The isolation and identification of this methylene-pentitol is a definitive proof that the methylene-D-sorbitol from which it is derived is 2,4-methylene-D-sorbitol.

Anal. Calcd. for $C_6H_{12}O_5$: C, 43.90; H, 7.37. Found: C, 43.82; H, 7.35.

II. Substances Derived from 1,3:2,4-Dimethylene-D-sorbitol

5,6-Diacetyl-1,3:2,4-dimethylene-D-sorbitol.—A solution of 1.0 g. of the previously described 1,3:2,4-dimethylene-D-sorbitol in a mixture of 10 cc. of acetic anhydride and 10 cc. of pyridine was allowed to stand at 25° for seventy-two hours and then poured into 600 cc. of ice water; the solution was extracted with chloroform and the washed and dried extract was concentrated *in vacuo* to a crystalline residue which upon crystallization from 10 parts of alcohol formed plates melting at 135–136° and rotating $[\alpha]^{20}D$ −12.8° in chloroform (*c*, 1.08). The compound is soluble in acetone, benzene, chloroform, acetic acid and ethyl acetate and insoluble in water. The yield was 1.2 g. (86%).

Anal. Calcd. for $C_{12}H_{18}O_6$: C, 49.65; H, 6.25; CH_3CO, 29.7. Found: C, 49.60; H, 6.27; CH_3CO, 29.8.

5,6-Dibenzoyl-1,3:2,4-dimethylene-D-sorbitol.—The dibenzoate was obtained by the action of benzoyl chloride on 1,3:2,4-dimethylene-D-sorbitol in pyridine solution. The yield was 2.1 g. (quantitative). The compound deposited from its solution in 10 parts of alcohol in the form of needles melting at 134–135° and rotating $[\alpha]^{20}D$ −54.8° in chloroform (*c*, 1.08); it is soluble in pyridine, acetic acid, acetone and ethyl acetate and insoluble in water.

Anal. Calcd. for $C_{22}H_{22}O_8$: C, 63.76; H, 5.35; C_6H_5CO, 50.7. Found: C, 63.61; H, 5.37; C_6H_5CO, 50.8.

Sodium Periodate Oxidation of 1,3:2,4-Dimethylene-D-sorbitol (VI).—A solution of 1.0619 g. of 1,3:2,4-dimethyl-

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ene-D-sorbitol in 20 cc. of water was cooled to 5° and 25 cc. (2.10 molecular equivalents) of 0.432 *M* aqueous sodium periodate was added; the mixture was allowed to warm to 25° and the volume was adjusted to 50 cc. with water. Analysis of 5-cc. aliquots at the expiration of twenty minutes, two and twenty hours indicated that 1.00, 1.03 and 1.04 molecular equivalents, respectively, of sodium periodate had been reduced. After titration, the first two aliquots were poured into 200 cc. of 0.4% dimethone solution and the mixture, upon preservation at 5° for forty-eight hours, deposited 0.2124 g. of formal-dimethone, which is 98% of that expected if one molecular equivalent of formaldehyde was produced as a product of the oxidation. These analyses prove that the dimethylene-D-sorbitol contains a terminal glycol grouping as a part of its structure. They indicate that the dimethylene-acetal was oxidized with the formation of formaldehyde and an *aldehydo*-dimethylene-pentose. Support for this assumption was obtained when it was noted that the specific rotation, $[\alpha]^{20}D$ −37.1° (calculated as *aldehydo*-dimethylene-pentose), of the oxidized solution did not change in value even on standing for one-hundred twenty hours, an observation which would be expected only in the absence of a ring form of the sugar (compare the rotation changes of the oxidized solution of 2,4-methylene-D-sorbitol which presumably contains 2,4-methylene-L-xylose, a sugar capable of existing in α and β cyclic forms).

aldehydo-2,4:3,5-Dimethylene-L-xylose Monohydrate from 1,3:2,4-Dimethylene-D-sorbitol (VI).—A solution of 5.0 g. of 1,3:2,4-dimethylene-D-sorbitol in 50 cc. of water was cooled to 5° and 75 cc. (1.3 molecular equivalents) of 0.432 *M* aqueous sodium periodate was added. Within thirty minutes small needles started to deposit in the solution and after the mixture had been allowed to stand in the refrigerator for eighteen hours they were separated by filtration. The yield was 2.6 g. (56%). The product was recrystallized from 10 parts of water as needles which rotated $[\alpha]^{20}D$ −33.9° in aqueous solution (*c*, 0.82) and melted at 175–180° after prior sintering at 150°. The substance is soluble in warm water and acetic acid and practically insoluble in warm methyl and ethyl alcohols, chloroform, acetone and dioxane.

Anal. Calcd. for $C_7H_{10}O_5 \cdot H_2O$: C, 43.75; H, 6.30. Found: C, 43.78; H, 6.34.

aldehydo-2,4:3,5-Dimethylene-L-xylose (VIII).—A sample of 0.5 g. of *aldehydo*-2,4:3,5-dimethylene-L-xylose monohydrate was sublimed in a vacuum at 140–145°; the sublimate of fine needles showed a melting point of 189–192° and a specific rotation $[\alpha]^{20}D$ −38.7° in water (*c*, 0.44); no mutarotation was observed in twenty-four hours.

Anal. Calcd. for $C_7H_{10}O_5$: C, 48.27; H, 5.79. Found: C, 48.02; H, 5.92.

Oxime of *aldehydo*-2,4:3,5-Dimethylene-L-xylose.—A mixture of 1.0 g. *aldehydo*-2,4:3,5-dimethylene-L-xylose monohydrate, 1.0 g. of hydroxylamine hydrochloride, 1.0 g. of fused sodium acetate, 25 cc. of methyl alcohol and 5 cc. of water was refluxed for twenty minutes. Upon standing at 5° for several days the solution deposited 0.8 g. (80%) of product, which upon recrystallization from 100 parts of alcohol yielded small lath-like crystals which melted at 227–228° and rotated $[\alpha]^{20}D$ −272° in pyridine (*c*, 0.50). Because the magnitude of this rotation is unusual for this type of compound, its rotation was also determined in aqueous solution (*c*, 0.31); it was found to be $[\alpha]^{20}D$ −215.0°. The oxime is soluble in pyridine, hot water and hot alcohol and practically insoluble in cold alcohol, acetone and chloroform.

Anal. Calcd. for $C_7H_{11}O_5N$: C, 44.44; H, 5.86; N, 7.40. Found: C, 44.43; H, 5.86; N, 7.45.

2,4:3,5-Dimethylene-L-xylitol (IX) from *aldehydo*-2,4:3,5-Dimethylene-L-xylose Monohydrate.—A solution of 6.0 g. of 2,4:3,5-dimethylene-L-xylose monohydrate in 200 cc. of water was agitated in a bomb at 25° for eighteen hours with Raney nickel and hydrogen at a pressure of 133 atmospheres; the catalyst was separated by filtration and the filtrate was concentrated *in vacuo* to a crystalline mass (5.0 g.; 91%) which was recrystallized from 50 parts of alcohol; the 2,4:3,5-dimethylene-L-xylitol crystallized in needles which melted at 217–219° and rotated $[\alpha]^{20}D$ −25.3° in aqueous solution (*c*, 1.09). The compound is one component of the crystalline 2,4:3,5-dimethylene-D,L-xylitol which is described in the accompanying communication.[4] A more detailed comparison of these two substances is made in that article.

Anal. Calcd. for $C_7H_{12}O_5$: C, 47.72; H, 6.87. Found: C, 47.64; H, 6.83.

1-Acetyl-2,4:3,5-dimethylene-L-xylitol.—This compound was prepared by the acetylation of 2,4:3,5-dimethylene-L-xylitol (1.0 g.) in pyridine solution (10 cc.) by acetic anhydride (10 cc.). The yield was 1.0 g. (83%). It was recrystallized from 12 parts of alcohol in the form of rods which melted at 153–154° and rotated $[\alpha]^{20}D$ +2.8° in chloroform (*c*, 0.96); it is soluble in acetone, ethyl acetate, carbon tetrachloride and acetic acid and practically insoluble in water. A microscopic optical crystallographic examination by Mr. George L. Keenan, of the Food and Drug Administration, Federal Security Agency, showed that in parallel polarized light (crossed nicols) the extinction was parallel and the elongation negative, the refractive indices being $n_\alpha = 1.484$, $n_\beta = 1.504$ and $n_\gamma = 1.524$, all ±0.002.

Anal. Calcd. for $C_9H_{14}O_6$: C, 49.54; H, 6.47; CH_3CO, 19.7. Found: C, 49.58; H, 6.48; CH_3CO, 19.7.

1,5-Diacetyl-3-acetoxymethyl-2,4-methylene-xylitol (V) from 2,4:3,5-Dimethylene-L-xylitol (IX).—A suspension of 1.0 g. of 2,4:3,5-dimethylene-L-xylitol in a mixture of 7.0 cc. of acetic anhydride and 3.0 cc. of glacial acetic acid was cooled to 0° and 10 cc. of an acetylating solution (prepared as described for the acetolysis of trimethylene-D-sorbitol) cooled to 0° was added; the mixture was agitated until solution of the alcohol diacetal was complete (ten minutes) and after a further five minutes it was poured into 400 cc. of ice water. The solution was nearly neutralized by the addition of 35 g. of sodium bicarbonate and extracted with three 50 cc. portions of chloroform; the washed and dried extract was concentrated to a crystalline residue (1.4 g.; 78%; m.p. 138–145°) which was recrystallized from 30 parts of hot water and yielded 0.8 g. of pure 1,5-diacetyl-3-acetoxymethyl-2,4-methylene-xylitol melting at 139–140° and devoid of rotation in aqueous solution (*c*, 0.92). A mixed melting point with the compound prepared by the acetolysis of 2,4:3,5-dimethylene-D,L-xylitol[4] also showed 139–140°, a result which was anticipated since the acetolysis of either the optically active (IX) or racemic form of the diacetal according to the acetolysis mechanism which has been proposed should yield the *meso* 1,5-diacetyl-3-acetoxymethyl-2,4-methylene-xylitol (V).

1,5,6-Triacetyl-3-acetoxymethyl-2,4-methylene-D-sorbitol (VII) from 1,3:2,4-Dimethylene-D-sorbitol (VI).—A solution of 1.0 g. of 1,3:2,4-dimethylene-D-sorbitol in 5 cc. of an ice-cold 1% sulfuric acid acetylating mixture was allowed to stand at 0° for five minutes and then poured into 200 cc. of ice-water; the flocculent precipitate which formed (0.6 g.; 32%) was separated by filtration and recrystallized from 7 parts of alcohol. The compound, which crystallized as fine needles, melted at 94–95° and rotated $[\alpha]^{20}D$ +11.0° in chloroform (*c*, 1.04); it is readily soluble in acetone, ethyl acetate, acetic acid, pyridine and warm methyl and ethyl alcohols and practically insoluble in water.

Anal. Calcd. for $C_{16}H_{24}O_{11}$: C, 48.98; H, 6.16; saponification, 0.1139 g. substance requires 11.61 cc. 0.1 *N* NaOH (4 saponifiable groups). Found: C, 49.05; H, 6.21; saponification, 0.1139 g. substance consumed 11.58 cc. 0.1 *N* NaOH.

2,4-Methylene-D-sorbitol (III) from 1,5,6-Triacetyl-3-acetoxymethyl-2,4-methylene-D-sorbitol (VII).—To an ice-cold solution of 2.0 g. of 1,5,6-triacetyl-3-acetoxymethyl-2,4-methylene-D-sorbitol in 30 cc. of chloroform, 5 cc. of 0.2 *N* sodium methylate solution was added and the reaction mixture was allowed to stand at 5° for seventy-two hours; the precipitate which had deposited was separated by filtration and recrystallized from 20 parts of alcohol; the needles which formed showed a melting point of 163–

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164° and a specific rotation $[\alpha]^{20}D$ −9.7° in aqueous solution, these data being in agreement with those previously found for the 2,4-methylene-D-sorbitol obtained by the saponification of 1,6-diacetyl-3,5-di-(acetoxymethyl)-2,4-methylene-D-sorbitol (II). A mixed melting point determination with 2,4-methylene-D-sorbitol from this source showed no depression.

1,3:2,4:5,6-Trimethylene-D-sorbitol (I) from 1,3:2,4-Dimethylene-D-sorbitol (VI).—A solution of 1.0 g. of 1,3:2,4-dimethylene-D-sorbitol (VI) in a mixture of 1.0 cc. of concentrated hydrochloric acid and 1.0 cc. of 37% aqueous formaldehyde was warmed to 50°; within thirty minutes crystallization of needles was noted and after forty-eight hours the mixture was cooled to 5°, the needles were separated by filtration, washed with ice-cold 50% alcohol, and dried. The yield was 0.90 g. (85%). The product, after recrystallization from 20 parts of 50% alcohol, showed a melting point of 210–214° and a mixed melting point determination with authentic trimethylene-D-sorbitol showed no depression.

Summary

The condensation of D-sorbitol with formaldehyde under the influence of concentrated hydrochloric acid yields, in addition to the known trimethylene-D-sorbitol of Schulz and Tollens, a new crystalline dimethylene-D-sorbitol. The limited acetolysis of the known trimethylene-D-sorbitol yields a diacetyl-di-(acetoxymethyl)-methylene-hexitol, which upon saponification is transformed into a crystalline methylene-D-sorbitol that can be only 2,4-methylene-D-sorbitol since it is converted by periodate oxidation and subsequent reduction to 2,4-methylene-xylitol of proved structure.

The new dimethylene-D-sorbitol can be only 1,3:2,4-dimethylene-D-sorbitol since upon periodate oxidation it yields an *aldehydo*-2,4:3,5-dimethylene-L-xylose which is successively converted to 2,4:3,5-dimethylene-L-xylitol, 1,5-diacetyl-3-acetoxymethyl-2,4-methylene-xylitol and 2,4-methylene-xylitol by known reactions.

The fact that the limited acetolysis of 2,4:3,5-dimethylene-L-xylitol forms a compound of *meso* structure rather than one possessing optical activity is cited as evidence supporting the previously proposed acetolysis mechanism based on the hypothesis that the acetal linkages of methylene acetals which are formed through primary alcoholic groups are more easily ruptured than those formed through secondary alcoholic groups; this experimental corroboration allows assignment of the structures of 1,6-diacetyl-3,5-di-(acetoxymethyl)-2,4-methylene-D-sorbitol and 1,-5,6-triacetyl-3-(acetoxymethyl)-2,4-methylene-D-sorbitol, respectively, to the acetolysis products of trimethylene-D-sorbitol and 1,3:2,4-dimethylene-D-sorbitol.

In view of the present experimental results, and particularly the conclusive establishment of the presence of the 2,4-acetal linkage, it seems highly probable that the trimethylene-D-sorbitol of Schulz and Tollens is 1,3:2,4:5,6-trimethylene-D-sorbitol, the rare C_5O_2 dioxepane ring that is present in 1,3:2,5:4,6-trimethylene-D-mannitol being absent from the structure of the isomeric trimethylene-D-sorbitol.

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2,4:3,5-Dimethylene-D,L-xylitol and 2,4-Methylene-xylitol

BY RAYMOND M. HANN, A. T. NESS AND C. S. HUDSON

In the course of the study of the acetolysis of trimethylene-D-sorbitol that is described in the accompanying article[1] there was obtained by degradative reactions a monomethylene-pentitol (m. p. 108–109°) the structure and configuration of which needed to be established. In configuration it is limited to a monomethylene derivative of xylitol or D-arabitol by reason of its origin. In aqueous solution no optical rotation was detected, which indicated the probability that the compound is a monomethylene-xylitol of *meso* structure since all structures for a monomethylene-D-arabitol represent optically active systems. The direct identification of its constituent pentitol through acid hydrolysis seemed of little attraction because of the experimental difficulties that are often encountered in attempts to hydrolyze methylene cyclic acetals. Accordingly, it was sought to produce the substance by condensing formaldehyde with xylitol, a procedure which, if successful, would establish the identity of its constituent pentitol and might also lead to a less laborious method for obtaining it.

There appears to be no recorded combination of formaldehyde with xylitol, although dibenzylidene[2] and di-isopropylidene xylitols[3] are known. A crystalline dimethylene-xylitol (m. p. 201–202°) was obtained in 91% yield by the reaction of xylitol with 37% aqueous formaldehyde and concentrated hydrochloric acid for two hours at 50°. One of the methylene groups in this dimethylene-xylitol is readily removable, as will be described, and the resulting monomethylene-xylitol proved to be identical with the monomethylene-pentitol (m. p. 108–109°) which was obtained from trimethylene-D-sorbitol. This monomethylene-xylitol does not react with sodium periodate and thus it contains no α-glycol group;

(1) Ness, Hann and Hudson, THIS JOURNAL, 66, 665 (1944).

(2) (a) L. de Bruyn and van Ekenstein, *Rec. trav. chim.*, 18, 151 (1899); (b) Wolfrom and Kohn, THIS JOURNAL, 64, 1739 (1942).

(3) (a) Tipson and Cretcher, *J. Org. Chem.*, 8, 95 (1943); (b) Hann, Ness and Hudson, THIS JOURNAL, 66, 73 (1944).

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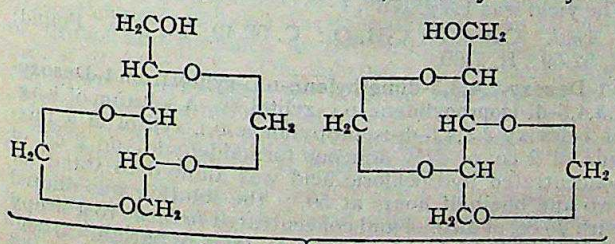
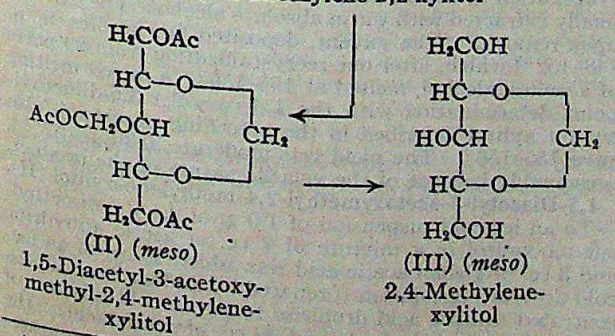
the only possible structure for the acetal is therefore that of 2,4-methylene-xylitol (III). Its optical inactivity is to be ascribed to its *meso* configuration.

Consider next the structure of the dimethylene-xylitol. Obviously the substance contains one free hydroxyl group and it readily formed crystalline mono acetyl, benzoyl, carbanilo and tosyl derivatives. The tosyl-dimethylene-xylitol reacted with a solution of sodium iodide in acetonylacetone to yield a crystalline iodo-dimethylene-xylitol which was reduced by hydrogen and Raney nickel to a desoxy-dimethylene-xylitol; the replacement of the tosyl group by the iodine atom is a strong indication, by the Oldham–Rutherford rule,[4] that it is attached at a terminal carbon atom. Conclusive proof of this inference was obtained when it was found that the desoxy-dimethylene-xylitol is identical with the desoxy-dimethylene-xylitol that is obtained by heating the known 1-desoxy-2,3,4,5-di-isopropylidene-D,L-xylitol[3b] with formaldehyde and concentrated hydrochloric acid. The substance can be only 1-desoxy-2,3,4,5-dimethylene-D, L-xylitol and the diacetal from which it is derived must be a 2,3,4,5-dimethylene-D,L-xylitol. The allocation of the acetal linkages among the four positions in its structure was made through the acetolysis reaction previously applied by us to trimethylene-D-mannitol.[5] Upon limited acetolysis in a one per cent. sulfuric acid mixture at about 0° the 2,3,4,5-dimethylene-D,L-xylitol is converted in 44% yield to a crystalline substance which had the composition of a diacetyl-acetoxymethyl-methylene-xylitol; upon saponification with sodium methylate the latter compound is converted in nearly quantitative yield to the previously mentioned 2,4-methylene-xylitol



(I) (racemic mixture)
2,4:3,5-Dimethylene-D,L-xylitol



(II) (*meso*)
1,5-Diacetyl-3-acetoxy-methyl-2,4-methylene-xylitol

(III) (*meso*)
2,4-Methylene-xylitol

(III), originally obtained from trimethylene-D-sorbitol. The 2,3,4,5-dimethylene-D,L-xylitol from which it was formed must be 2,4:3,5-dimethylene-D,L-xylitol (I) and its acetolysis product is in all probability 1,5-diacetyl-3-acetoxymethyl-2,4-methylene-xylitol (II), a *meso* structure.

We express our appreciation to Mr. George L. Keenan of the Food and Drug Administration, Federal Security Agency, for the determination of the optical crystallographic properties of the 2,4:3,5-dimethylene-L- and D,L-xylitols and their acetyl derivatives.

Experimental

2,4:3,5-Dimethylene-D,L-xylitol (I).—A solution of 5.0 g. of crystalline xylitol in a mixture of 5 cc. of concentrated hydrochloric acid and 5 cc. of 37% formaldehyde was allowed to stand at 50° for two hours; the magma which formed when the reaction mixture was cooled to room temperature was thinned with 25 cc. of alcohol and the precipitate (5.1 g.) was separated by filtration; the mother liquor was evaporated by an air current and the residual solid was crystallized from 10 cc. of alcohol to yield an additional 0.2 g. of product, making the total yield 91%. The colorless compound was recrystallized by solution in 3 parts of warm water and the addition of 15 parts of alcohol, and obtained as small thin lath-like crystals with a m. p. of 201–202°.[6] It is soluble in cold pyridine, warm methyl and ethyl alcohols and acetic acid, and insoluble in acetone, chloroform and benzene. At 24° a saturated aqueous solution contains 4.2 g. of the substance in 100 cc. of solution; a saturated aqueous solution of 2,4:3,5-dimethylene-L-xylitol at 24° contains 3.7 g. of the acetal in 100 cc. of solution. Thus the D,L-form is more soluble than the L-form but less than twice its solubility. The substance appears to belong to the class of compounds which have been defined by Kipping and Pope[7] as pseudo racemates. An optical crystallographic comparison of it and the previously described L-form [m. p. 217–219°; $[\alpha]^{20}D$ −25.3° in water] was made by Mr. George L. Keenan who reported as follows:

"In ordinary light (plane polarized) both substances were seen to consist of elongated rods and prisms. The L-form showed prism faces that were straight and parallel, while the D,L-compound showed many of the prisms to be somewhat fibrous and curved. In parallel polarized light (crossed nicols) the extinction was parallel and the sign of elongation negative for both compounds. The n_α, n_β, and n_γ refractive indices were identical in both compounds. However, in the case of the authentic L-compound the prisms are so oriented that the n_α and n_β values are commonly shown, while in the D,L-compound n_α and n_γ are commonly shown. Interference figures were not observed on either compound. As a result of the examination, these compounds are very similar if not identical optically. The most striking feature for differentiation is the difference in orientation. The indices are as follows:

	D,L-Compound	L-Compound
n_α	1.524	1.524
n_β	1.543	1.544
n_γ	1.560	1.558"

The melting point of the D,L-form was depressed upon admixture of a small amount of the L-form and the L-form did not dissolve in a saturated aqueous solution of the D,L-form. Although an exhaustive study was not undertaken, the experiments cited above agree in their indication that

(4) Oldham and Rutherford, THIS JOURNAL, **54**, 366 (1932); Oldham, *J. Chem. Soc.*, **127**, 2840 (1925).
(5) Ness, Hann and Hudson, THIS JOURNAL, **65**, 2215 (1943).
(6) All of the crystalline compounds described in the experimental part were recrystallized to constant melting point; all melting points were determined with the stem of the calibrated thermometer immersed in the rapidly stirred bath.
(7) Kipping and Pope, *J. Chem. Soc.*, **71**, 989 (1897).

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2,4:3,5-dimethylene-D,L-xylitol is a pseudo rather than a true racemate; its crystals are comparable with those from a solution of two isomorphous substances.

Anal. Calcd. for $C_7H_{12}O_6$: C, 47.72; H, 6.87. Found: C, 47.61; H, 6.93.

1-Acetyl-2,4:3,5-dimethylene-D,L-xylitol.—A mixture of 4.4 g. of 2,4:3,5-dimethylene-D,L-xylitol, 0.5 g. of fused sodium acetate and 22.5 cc. of acetic anhydride was heated gently and, following a vigorous exothermic reaction, refluxed for fifteen minutes; upon pouring the cooled reaction mixture into 25 cc. of water, 3.4 g. of the acetate crystallized, and an additional 2.0 g. was obtained by concentration of the acetic acid filtrate, making the yield quantitative. The compound was recrystallized from 20 parts of boiling water in the form of needles which melted at 156–157° and showed no rotation in chloroform solution, (*c*, 0.5). It can also be recrystallized from 10 parts of methyl or ethyl alcohol and is readily soluble in acetone, chloroform and benzene. The compound is a true racemate; a mixed melting point with a small amount of the previously described 1-acetyl-2,4:3,5-dimethylene-L-xylitol (m. p. 153–154°) gave a depressed value of 146–156°; an optical crystallographic examination by Mr. Keenan showed that in parallel polarized light (crossed nicols) the extinction was parallel and the elongation negative, the indices of refraction being $n_\alpha = 1.495$, $n_\beta = 1.514$ and $n_\gamma = 1.539$ (all ±0.002), these values being distinctly different from those of 1-acetyl-2,4:3,5-dimethylene-L-xylitol.[1] The substance is therefore to be classed as a true racemate.

Anal. Calcd. for $C_9H_{14}O_6$: C, 49.54; H, 6.47; CH_3CO, 19.7. Found: C, 49.66; H, 6.47; CH_3CO, 19.5.

1-Benzoyl-2,4:3,5-dimethylene-D,L-xylitol.—This compound was obtained in a yield of 88% (2.8 g.) by the benzoylation of 2,4:3,5-dimethylene-D,L-xylitol (2.0 g.) in pyridine solution with benzoyl chloride. It was recrystallized from 30 parts of alcohol and obtained in the form of fine needles which melted at 164–165°. The substance is soluble in acetone, methyl alcohol, chloroform and ethyl acetate and insoluble in water.

Anal. Calcd. for $C_{14}H_{16}O_6$: C, 60.00; H, 5.75; C_6H_5CO, 37.5. Found: C, 60.35; H, 5.79; C_6H_5CO, 37.2.

1-Carbanilo-2,4:3,5-dimethylene-D,L-xylitol.—This derivative was prepared by a procedure similar to that which Wolfrom and Pletcher[8] have employed for the preparation of the carbanilates of sugar glycosides. A mixture of 2.0 g. of 2,4:3,5-dimethylene-D,L-xylitol, 1.4 cc. of phenyl isocyanate and 20 cc. of pyridine was boiled for two hours under a reflux condenser protected from atmospheric moisture by a drying tube. The carbanilo derivative (1.2 g.) which precipitated from the solution on cooling was recrystallized from 20 parts of acetone as clusters of glistening prisms which melted at 196–197°. An additional 2.0 g. of compound showing the same melting point was obtained by allowing the pyridine to evaporate from the mother liquor and recrystallizing the residue from acetone. The total yield was 94%. The substance is readily soluble in warm methyl and ethyl alcohols, chloroform and dioxane, sparingly soluble in warm water and practically insoluble in cold water and benzene.

Anal. Calcd. for $C_{14}H_{17}O_6N$: C, 56.94; H, 5.80; N, 4.74. Found: C, 56.98; H, 5.64; N, 4.64.

1-Tosyl-2,4:3,5-dimethylene-D,L-xylitol.—A mixture of 1.0 g. of 2,4:3,5-dimethylene-D,L-xylitol, 1.2 g. (1.1 molecular equivalents) of *p*-toluenesulfonyl chloride and 10 cc. of pyridine was agitated at room temperature until the diacetal dissolved (four hours) and the resulting solution was allowed to stand for eighteen hours and then was poured upon crushed ice. The precipitated tosyl derivative (1.7 g., 90%) was recrystallized from 20 parts of alcohol and formed prisms which melted at 145–146°. The compound is readily soluble in cold chloroform and acetone, methyl alcohol, warm benzene and dioxane and insoluble in water.

Anal. Calcd. for $C_{14}H_{18}O_7S$: C, 50.90; H, 5.49; S, 9.70. Found: C, 50.92; H, 5.48; S, 9.58.

1-Iodo-2,4:3,5-dimethylene-D,L-xylitol.—The replacement of the tosyl group of 1-tosyl-2,4:3,5-dimethylene-D,L-xylitol by iodine was incomplete in an experiment in which 5.0 g. of the tosyl derivative, 5.0 g. of sodium iodide and 100 cc. of acetone were heated at 100° for four hours; only about 50% of the sodium *p*-toluenesulfonate which would be expected from the removal of the tosyl group precipitated in the acetone solution and the product, which melted from 119 to 130°, was a mixture of unchanged tosyl derivative and some of the desired 1-iodo-2,4:3,5-dimethylene-D,L-xylitol. A quantitative conversion was attained however by substitution of acetonylacetone (25 cc.) as a solvent[9] and carrying out the reaction at 120° for four hours or by refluxing the reactants in acetic anhydride (25 cc.) for one hour. The 1-iodo-2,4:3,5-dimethylene-D,L-xylitol deposited from its solution in 15 parts of alcohol in the form of needles which melted at 144–145°; a mixed melting point determination with 1-tosyl-2,4:3,5-dimethylene-D,L-xylitol, which melts at 145–146°, gave a value of 117–119°. The iodo derivative is readily soluble in cold acetone and chloroform and in warm methyl and ethyl alcohols and is insoluble in water.

Anal. Calcd. for $C_7H_{11}O_4I$: C, 29.39; H, 3.88; I, 44.36. Found: C, 29.39; H, 3.84; I, 44.28.

1-Desoxy-2,4:3,5-dimethylene-D,L-xylitol from 1-Iodo-2,4:3,5-dimethylene-D,L-xylitol.—To a solution of 3.0 g. of 1-iodo-2,4:3,5-dimethylene-D,L-xylitol in 150 cc. of methyl alcohol, 3 cc. of 20% methyl alcoholic potassium hydroxide solution and 2.0 g. of Raney nickel were added and the reaction mixture was agitated vigorously at 22° while hydrogen under a slight positive pressure was introduced. In thirty minutes 240 cc. (theory, 235 cc., S. T. P.) of hydrogen was taken up and only 5 cc. more was absorbed in a further thirty minutes. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo* to dryness. The solid was extracted with 20 cc. of boiling absolute alcohol and, upon cooling the extract, the desoxy diacetal crystallized in the form of fine needles; the compound, after recrystallization from 15 parts of alcohol, melted at 155–156°, and the value was not altered by further recrystallization; it is readily soluble in acetone, warm methyl alcohol and warm water, and relatively insoluble in cold water. The substance sublimes readily. The yield was 1.3 g. (76%).

Anal. Calcd. for $C_7H_{12}O_4$: C, 52.49; H, 7.55. Found: C, 52.59; H, 7.60.

1-Desoxy-2,4:3,5-dimethylene-D,L-xylitol from 1-Desoxy-2,3,4,5-di-isopropylidene-D,L-xylitol.[3b]—A solution of 1.5 g. of 1-desoxy-2,3,4,5-di-isopropylidene-D,L-xylitol in a mixture of 2 cc. of 37% aqueous formaldehyde and 2 cc. of concentrated hydrochloric acid was allowed to stand for two and one-half hours at 50°; the solution was diluted with 25 cc. of alcohol and concentrated *in vacuo* to a sirupy residue; following the addition of 2.0 g. of barium carbonate, the residue was dried by thes uccessive addition and evaporation of two 25 cc. portions of absolute alcohol and finally extracted with warm absolute alcohol The extract, upon removal of the solvent, deposited fine needles (m. p. 148–152°) which, after one recrystallization from 20 parts of absolute alcohol, melted at 155–156°; a mixed melting point determination with the 1-desoxy-2,4:3,5-dimethylene-D,L-xylitol described in the preceding paragraph also gave 155–156°. The yield was moderate, 0.30 g. (37%), presumably because of the volatile nature of the product.

1,5-Diacetyl-3-acetoxymethyl-2,4-methylene-xylitol (II).—To an ice-cold suspension of 1.0 g. of 2,4:3,5-dimethylene-D,L-xylitol in a mixture of 7 cc. of acetic anhydride and 3 cc. of glacial acetic acid was added 10 cc. of an ice-cold acetylating solution (prepared by adding 2 cc. of concentrated sulfuric acid dropwise to an ice-cold mixture of 70 cc. of acetic anhydride and 30 cc. of acetic acid); the diacetal dissolved and after standing for fifteen minutes at 5° the reaction mixture was poured upon crushed ice.

(8) Wolfrom and Pletcher, THIS JOURNAL, 62, 1151 (1940).

(9) Murray and Purves, *ibid.*, 62, 3195 (1940).

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The crystalline precipitate (0.3 g., m. p. 137°) was separated by filtration and the filtrate was neutralized with sodium bicarbonate and extracted with chloroform; the chloroform was evaporated and the sirupy residue remaining was crystallized from 10 cc. of hot water and yielded a further 0.5 g. of product melting at 137–138° making the yield of 1,5-diacetyl-3-acetoxymethyl-2,4-methylene-xylitol 44%; a residual sirup (0.5 g.) could not be induced to crystallize. The substance is readily soluble in cold methyl and ethyl alcohols, chloroform, acetone and benzene. It deposited from its solution in 30 parts of water as long needles which melted at 138–139°.

Anal. Calcd. for $C_{13}H_{20}O_9$: C, 48.75; H, 6.29; saponification, 0.1117 g. substance requires 10.46 cc. 0.1 *N* NaOH (3 saponifiable groups). Found: C, 48.85; H, 6.34; saponification, 0.1117 g. substance consumed 10.32 cc. 0.1 *N* NaOH.

2,4-Methylene-xylitol (III) from 1,5-Diacetyl-3-acetoxymethyl-2,4-methylene-xylitol (II).—A solution of 1.6 g. of 1,5-diacetyl-3-acetoxymethyl-2,4-methylene-xylitol in 15 cc. of chloroform was cooled to 0° and 1 cc. of 0.1 *N* sodium methylate solution was added. The next day the chloroform was evaporated by an air current and the sirup which remained was dissolved in 2 cc. of warm alcohol; the reaction product (0.7 g., 88%), which crystallized as the solution cooled, was recrystallized from 12 parts of alcohol as elongated prisms which melted at 108–109°. It is readily soluble in water, warm methyl and ethyl alcohols, and dioxane and relatively insoluble in benzene, acetone and chloroform.

Anal. Calcd. for $C_6H_{12}O_5$: C, 43.90; H, 7.37. Found: C, 43.98; H, 7.40.

Triacyl Derivatives of 2,4-Methylene-xylitol (III) (a) **1,3,5-Triacetyl-2,4-methylene-xylitol** was obtained in nearly quantitative yield (1.7 g.) by acetylation of the acetal (1.0 g.) in pyridine solution with acetic anhydride. It was recrystallized from 5 parts of alcohol as long needles which melted at 87–88°. It is readily soluble in acetic acid, acetone, chloroform and ethyl acetate and nearly insoluble in water.

Anal. Calcd. for $C_{12}H_{18}O_8$: C, 49.65; H, 6.25; CH_3CO, 44.5. Found: C, 49.69; H, 6.19; CH_3CO, 44.5.

(b) The **1,3,5-tribenzoyl-2,4-methylene-xylitol** (2.9 g., quantitative) which was obtained by the benzoylation of 1.0 g. of 2,4-methylene-xylitol in pyridine solution by benzoyl chloride (2.5 cc.) was recrystallized from 20 parts of alcohol and obtained in the form of needles which melted at 117–118°. The substance is soluble in cold chloroform, ethyl acetate and acetone, warm methyl and ethyl alcohols and insoluble in water.

Anal. Calcd. for $C_{27}H_{24}O_8$: C, 68.06; H, 5.08; C_6H_5CO, 66.2. Found: C, 68.16; H, 5.25; C_6H_5CO, 66.2.

(c) An ice-cold solution of 2.0 g. of 2,4-methylene-xylitol in 10 cc. of pyridine was mixed with a cold solution of 9.0 g. of *p*-toluenesulfonyl chloride in 15 cc. of pyridine and the mixture was allowed to stand at 20° for forty-eight hours. The **1,3,5,tritosyl-2,4-methylene-xylitol** (7.7 g.) which precipitated upon pouring the mixture upon crushed ice was recrystallized from 20 parts of 1:1 dioxane-alcohol as fine needles which melted at 198–199°. The compound is difficultly soluble in the usual organic solvents.

Anal. Calcd. for $C_{27}H_{30}O_{11}S_3$: C, 51.74; H, 4.83; S, 15.35. Found: C, 51.76; H, 4.89; S, 15.26.

1,5-Dibenzoyl-2,4-methylene-xylitol.—A solution of 1.0 g. of 2,4-methylene-xylitol in 10 cc. of pyridine was cooled in ice and to the stirred solution 1.4 cc. of benzoyl chloride (2 molecular equivalents) was added dropwise. After standing for two hours at 25° the mixture was poured upon crushed ice and the crystalline precipitate (1.3 g., 56%) was recrystallized from 20 parts of alcohol; the small needles so obtained showed a melting point of 139–140°; the substance is soluble in chloroform, pyridine and acetone and insoluble in water. The 1 and 5 positions for the benzoyl groups are assigned because of the well-known preferential benzoylation of primary hydroxyl groups under these experimental conditions; thus D-arabitol yields 1,5-dibenzoyl-D-arabitol,[10] the structure of which has been proved conclusively.

Anal. Calcd. for $C_{20}H_{20}O_7$: C, 64.51; H, 5.41; C_6H_5CO, 56.5. Found: C, 64.72; H, 5.34; C_6H_5CO, 55.9.

Stability of 2,4-Methylene-xylitol (III) against Oxidation by Sodium Periodate.—To a solution of 0.2032 g. of 2,4-methylene-xylitol in 10 cc. of water at 25°, 6.30 cc. of 0.432 *M* sodium periodate was added and the volume was adjusted to 25 cc. with water. Analysis of 5 cc. subsamples at the expiration of one and forty-eight hours showed that none of the sodium periodate had been consumed. The failure of this reagent to oxidize the 2,4-methylene-xylitol indicates that its structure does not include a glycol grouping. The only possible structure for a monoacetal of a pentitol which conforms with this limitation is that of a 2,4-acetal; methylene-xylitol is therefore 2,4-methylene-xylitol.

Summary

The isolation and proof of structure of 2,4:3,5-dimethylene-D,L-xylitol and 2,4-methylene-xylitol are described. The diacetal must be a 2,3,4,5-dimethylene-D,L-xylitol because its monotosyl derivative is converted to an iodo derivative which is reduced by hydrogen and Raney nickel to a desoxy-dimethylene-D,L-xylitol and this desoxy compound is identical with the 1-desoxy-2,3,4,5-dimethylene-D,L-xylitol that is obtained by treating the known 1-desoxy-2,3,4,5-di-isopropylidene-D,L-xylitol with formaldehyde and concentrated hydrochloric acid. The acetal linkages must be at positions 2,4 and 3,5 of the xylitol moiety because the saponification of the acetolysis product of the diacetal, namely, 1,5-diacetyl-3-acetoxymethyl-2,4-methylene-xylitol, yields a monomethylene-xylitol which is not oxidized by glycol-splitting reagents; this fact not only limits its structure to that of 2,4-methylene-xylitol but also proves that the structure of the dimethylene-D,L-xylitol from which it is derived must be that of 2,4:3,5-dimethylene-D,L-xylitol.

The experimental findings confirm and extend the previously published views regarding the limited acetolysis of the methylene acetals of the sugar alcohols.

BETHESDA, MARYLAND RECEIVED JANUARY 21, 1944

(10) Haskins, Haun and Hudson, THIS JOURNAL, **65**, 1664 (1943).

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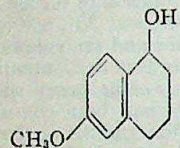
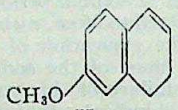
[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

The Dimerization of 6-Methoxy-3,4-dihydronaphthalene

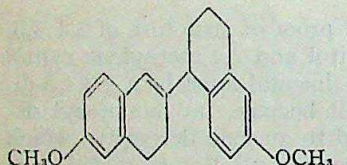
BY R. B. WOODWARD AND R. H. EASTMAN

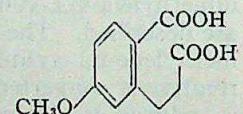
On dehydration of 6-methoxy-1,2,3,4-tetrahydro-1-naphthol (I) with aqueous hydrobromic acid, Long and Burger[1] obtained a crystalline *substance*, $C_{11}H_{12}O$, m. p. 73–74°, which was formulated as 6-methoxy-3,4-dihydronaphthalene (II). Our interest in II as a possible intermediate in the synthesis of oestrone, or allied substances, prompted us to reinvestigate this reaction.


I


II

In this communication it is shown that the above substance is in fact a dimer of II, *viz.*, 2-(6-methoxy-1,2,3,4-tetrahydro-1-naphthyl)-3,4-dihydro-6-methoxynaphthalene (III).


III

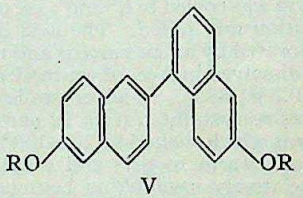

IV

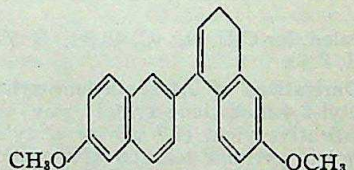
Since neither the dehydration product obtained by the earlier investigators, nor our material, even after a number of recrystallizations, gave concordant analyses for the formula $C_{11}H_{12}O$, we carried out a chromatographic fractionation of the recrystallized substance on alumina. Over 90% of material was recovered, which on one further recrystallization melted at 75.5–77°, and analysis of which left no doubt that the empirical formula of the substance was $(C_{11}H_{12}O)_n$.

Quantitative titration of the dehydration product with perbenzoic acid indicated one double bond for a molecular weight of 320, and from the oxidation mixture, a crystalline *oxide*, $C_{22}H_{24}O_3$, m. p. 127–128.5°, was obtained. These observations indicated clearly that the original product had the dimeric formula, $C_{22}H_{24}O_2$ (320), and this conclusion was substantiated by direct molecular weight determinations on the material (290, 333) and on the above oxide (322, 326).

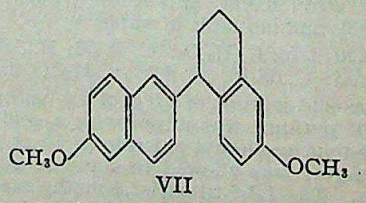
Oxidative degradation of the dimer with permanganate led to the isolation, in small quantity, of a dibasic acid, m. p. 201.5–203°, neutralization equivalent 112.6, undoubtedly β-(2-carboxy-4-methoxyphenyl)-propionic acid[2] (IV), and a *dehydro-compound*, $C_{22}H_{22}O_2$, m. p. 107.5–108.5° (VII, *vide infra*). The latter substance was subsequently obtained relatively smoothly and in better yield by the chromic acid oxidation of the dimer. Attempts to obtain products resulting from simple oxidative scission at the (presumable) double bond were unsuccessful.

Dehydrogenation of the dimer with sulfur, or better, catalytically over palladium-charcoal catalyst, gave a *hexadehydro-compound*, $C_{22}H_{18}O_2$, m. p. 91–92°, which was shown by synthesis to be 6,6′-dimethoxy-1,2′-binaphthyl (V, R = CH_3). Condensation of the Grignard reagent


V


VI

from 2-bromo-6-methoxynaphthalene[3] with 6-methoxy-α-tetralone gave directly the dihydrobinaphthyl (VI), m. p. 126°. Catalytic dehydrogenation of VI gave the 6,6′-dimethoxy-1,2′-dinaphthyl (V, R = CH_3), identical in all respects with the hexadehydro compound from the dimer. Further, hydrogenation of the Grignard product (VI) gave a dihydro derivative (VII), which proved to be identical with the de-


VII

hydro compound, m. p. 108°, obtained by direct permanganate or chromic acid oxidation of the dimer.

These observations establish the structure of the dimer as III. The identity of the synthetic binaphthyl with that obtained from the dimer affords conclusive proof of the nature of the carbon skeleton of the latter. The identity of the synthetic substance VII with the dehydro compound from the dimer confirms the skeletal structure,[4]

(1) Long and Burger, *J. Org. Chem.*, **6**, 854 (1941).

(2) The prior preparation of this acid has been reported, without details, by Johnson and Anderson, abstracts of papers presented at the Atlantic City Meeting of the A. C. S., September, 1941, p. 13.

(3) Franzen and Staubel, *J. prakt. Chem.*, **103**, 369 (1922).

(4) Since all of the reactions used in establishing this identity were carried out under mild conditions, this proof of the nature of the carbon skeleton is possibly preferable to that involving the high temperature dehydrogenations. However, the work as a whole demonstrates that no rearrangement takes place during the latter reaction.

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and further provides evidence in favor of the $\Delta^{1,2}$-position of the double bond, as opposed to the *a priori* alternatively possible positions, $\Delta^{2,1'}$, $\Delta^{2,3}$, or $\Delta^{1',2'}$. In this light, the failure to obtain products corresponding to simple oxidative fission at the double bond of the dimer is a consequence of the facility with which dihydronaphthalenes pass into the fully aromatic condition. Confirmation of the conjugation of the double bond with one of the aromatic rings is further provided by the absorption spectrum of the dimer (Fig. 1), which is strongly reminiscent of that of the (chromophorically) similarly constituted anethole, $CH_3OC_6H_4CH{=}CHCH_3$,[4a] and markedly different from that of a simple disubstituted anisole.

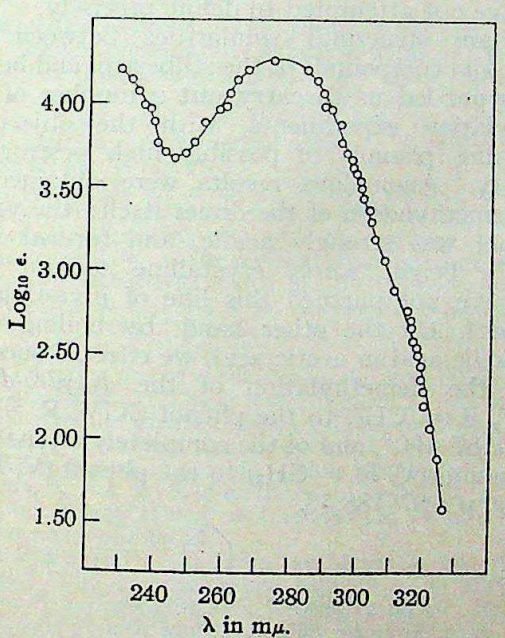
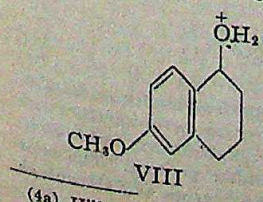
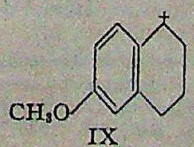


Fig. 1.—Absorption spectrum of 6,6′-dimethoxy-1,2,3,3′,-4,4′-hexahydro-1,2′-binaphthyl in ethanol; $\lambda_{max.}$ = 274 mμ, log ε = 4.25.

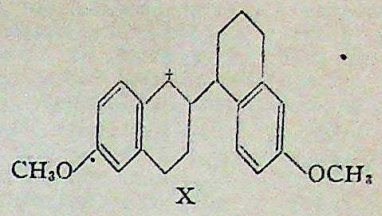
We turn now to a discussion of the mechanism by which the dimer is produced by the action of acid on 6-methoxy-α-tetralol. Loss of water from the conjugate acid (VIII) of the tetralol will give a carbonium ion (IX) (or its equivalent) which may (a) lose a proton with the formation of 6-methoxy-3,4-dihydronaphthalene (II) *and* (b) attack the latter product at the double bond (polarized in the sense $C^{1}{=}\overset{\curvearrowright}{C}^{2}$) to give the dimeric species (X). Loss of a proton from the latter intermediate then gives the dimer of structure



VIII

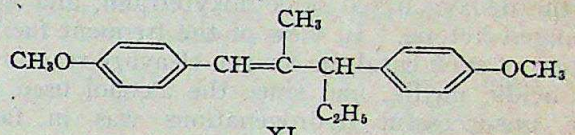


IX



X

III. A similar mechanism may be envisaged for the observed dimerization of anethole, in the presence of acidic reagents, to XI.[5]



XI

For the rest, we are concerned with a number of incidental observations made in the course of our experiments. The attack of perbenzoic acid on the dimer need not *a priori* have given an oxide: not infrequently, ketonic, or other isomeric, products are obtained with this reagent. In order to ascertain the structure of our *compound*, $C_{22}H_{24}O_3$, m. p. 127–128.5° (*vide supra*), we determined the ultraviolet absorption characteristics of the substance (Fig. 2). The spec-

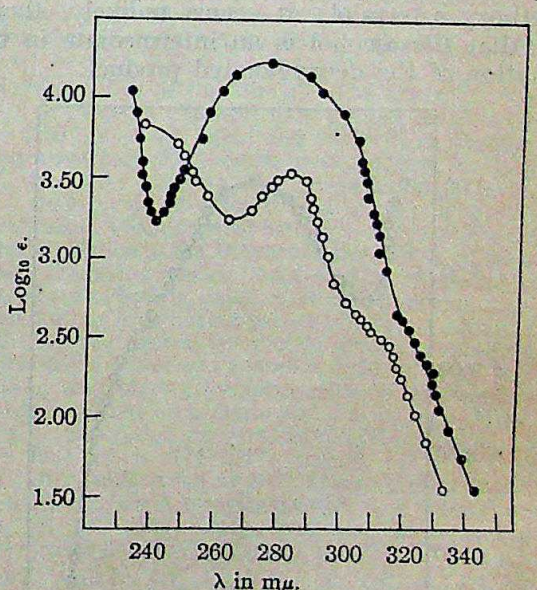


Fig. 2.—Absorption spectra in ethanol: ●, 6-methoxy-α-tetralone; $\lambda_{max.}$ = 276 mμ, log ε = 4.22; ○, 6,6′-dimethoxy-1,2,3,3′,4, 4′-hexahydro-1′, 2′-oxido-1, 2′-binaphthyl; $\lambda_{max.}$ = 283 mμ, log ε = 3.54.

trum shows a considerable resemblance in general form to isosafrole oxide,[6] and differs markedly, on the other hand, from that of 6-methoxy-α-tetralone. The conclusion would seem to be justified that our substance is a true oxide, of the structure XII.

The hydrogenation of 6-methoxy-α-tetralone to the corresponding alcohol (the immediate precursor of the dimer) is subject to variations,

(4a) Hillmer and Schorning, *Z. physik. Chem.*, **A167**, 407 (1933).

(5) Goodall and Haworth, *J. Chem. Soc.*, 2482 (1930).

(6) Hillmer and Schorning, *Z. physik. Chem.*, **A168**, 81 (1934).

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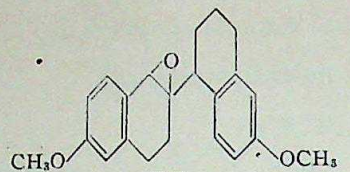


XII

the exact cause of which has not been established. Frequently there were isolated, after the absorption of one mole of hydrogen, equimolar amounts of the deoxygenated 6-methoxytetralin, and unchanged ketone. In view of the frequent facilitation of such catalytic oxygen-cleavage reactions by acidic media, and since the alcohol used in the unsuccessful hydrogenations was in fact slightly acidic, we attempted, usually with success, to avoid this undesirable result by using as solvent ethanol which had been freshly distilled from sodium hydroxide. On the other hand, the reductions by this method proceeded more slowly and, in one case, the reaction would not start at all until a very small quantity of hydrochloric acid was added: it then proceeded rapidly and without untoward result (*i. e.*, no oxygen cleavage). In none of our hydrogenations did we observe concomitant formation of 6-methoxytetralin and 6-methoxy-α-tetralol; it seems unlikely, therefore, that the alcohol is an intermediate in the formation of the deoxygenated product.

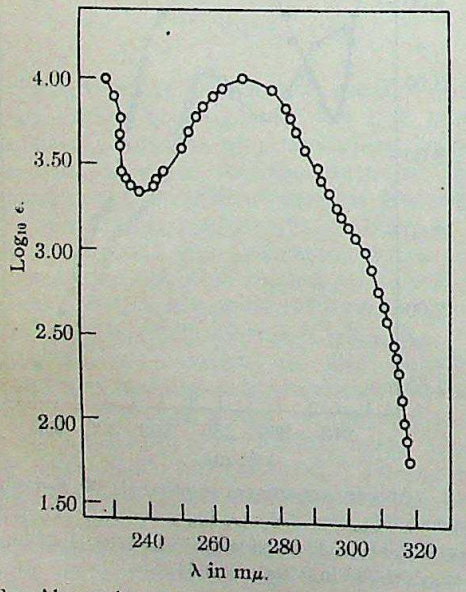
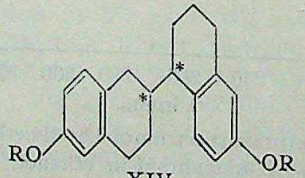


Fig. 3.—Absorption spectrum of 6-methoxy-3,4-dihydronaphthalene in ethanol.

Although 6-methoxy-α-tetralone is now a readily available intermediate[7] the somewhat unpredictable course of the hydrogenations described above led us to investigate a more reliable source of the dimer. Oxidation of 6-methoxytetralin with red lead in acetic acid at room temperature gave a good yield of 6-methoxy-α-tetralol acetate[8] which, like the corresponding alcohol, was smoothly transformed into the dimer (III) by the action of hydrobromic acid.

The alkaline hydrolysis of the above acetate did not proceed smoothly: the main product was a new liquid *substance*, which is formulated as 6-methoxy-3,4-dihydronaphthalene (II) on the basis of analyses, physical properties and, in particular, the absorption spectrum (Fig. 3). In accordance with this view, the compound is transformed by aqueous hydrobromic acid into the dimer (III). The substance also was obtained occasionally during the distillation of 6-methoxy-α-tetralol (prepared by hydrogenation of the corresponding ketone), in consequence of conditions which we have not attempted to define precisely.

Certain structural similarities between the dimer and compounds of the stilbestrol and hexestrol types led us to carry out a number of demethylation experiments, with the object of obtaining phenols of possible high oestrogenic activity. Anomalous results were obtained in the demethylation of the dimer itself; the *yellow* product was strongly acidic, and formed with soda a bright *scarlet* crystalline sodium salt. We have not pursued this line of investigation further.[9] On the other hand, by boiling with hydriodic acid in acetic acid, we effected successfully the demethylation of the *dihydro-dimer* (XIV, R = CH_3) to the phenol (XIV, R = H), m. p. 187–190°, and of the completely aromatized compound (V, R = CH_3) to the phenol (V, R = H), m. p. 187–188.5°.



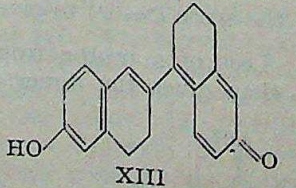
XIV

We should like to express our appreciation to Parke Davis and Co. for a grant to Harvard University for a Fellowship, which was held by the junior author while carrying out this investigation.

(7) One of us, with R. B. Loftfield, will describe in a subsequent communication, an excellent method for the preparation of the ketone from β-naphthol in 50% yield.

(8) Prior preliminary notice of the successful execution of this reaction has been given, without details, by Johnson and Anderson, *cf.* ref. 2.

(9) These observations suggest that oxidation has taken place at some stage in the reaction with formation of XIII. We may point out in support of this suggestion that the self-condensation of 6-methoxy-α-tetralone by *aqueous* sodium hydroxide (presumably with hydrolysis of the O-methyl groups [*cf.* Peak, Robinson and Walker, *J. Chem. Soc.*, 753 (1936)]) gives a similar product. The most reasonable formulation of the latter is a desmotrope of XIII with an additional hydroxyl at position



XIII

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Experimental

6-Methoxytetralin, b. p. 129–131° (11 mm.) and **6-methoxy-α-tetralone,** m. p. 77–78°, were prepared from *ar*-(2)-tetralol by methylation and oxidation, following procedures developed in this Laboratory by other workers.[7]

6-Methoxy-1-acetoxy-1,2,3,4-tetrahydronaphthalene.—To 34.2 cc. of 6-methoxytetralin dissolved in 200 cc. of glacial acetic acid and 100 cc. of acetic anhydride, 138 g. of red lead was added in portions with stirring during eight hours. The resultant clear yellow solution was poured into an equal volume of chopped ice, and stirred vigorously to facilitate the separation of a large yellow crystalline precipitate, which was removed at once, washed with a small amount of ice water, and dissolved in ether. After washing, drying and removal of solvent, the residual red oil was distilled *in vacuo*; after *ca.* 5 g. of lower boiling material, 22 g. of the tetralol acetate, b. p. 144–149° (3 mm.), was obtained.

Anal. Calcd. for $C_{13}H_{16}O_3$: C, 70.89; H, 7.33. Found: C, 71.54; H, 6.94.

6-Methoxy-α-tetralol.—This substance was prepared by catalytic hydrogenation of 6-methoxy-α-tetralone. We have carried out this reaction a great many times; in our experience, the results are apt to vary, apparently adventitiously. Often the reduction proceeds directly to 6-methoxytetralin (*cf.* theoretical section). A typical cleavage experiment is reported.

The ketone (20 g.) in 400 cc. of 95% ethanol absorbed one mole of hydrogen in twenty-four hours on shaking over 0.3 g. of platinum oxide catalyst in the presence of 1 cc. of 1 *M* ferrous sulfate. After removal of catalyst and solvent, fractionation *in vacuo* gave 10 g. of 6-methoxytetralin, b. p. 135° (17 mm.), and 9.5 g. of unchanged 6-methoxy-α-tetralone, b. p. 180° (17 mm.), m. p. 76–78°, mixed with an authentic sample, m. p. 76–78°.

The following procedure illustrates the most consistently successful method: The ketone (10 g.) in 200 cc. of 95% ethanol (freshly distilled from sodium hydroxide) absorbed 1.2 moles of hydrogen in seventeen hours on shaking over 0.2 g. of platinum oxide. After removal of catalyst and solvent, 9.1 g. of 6-methoxy-α-tetralol, b. p. 175° (16 mm.), was obtained on fractionation *in vacuo* as a colorless, very viscous oil.

The Dimer (III): (a) From the Alcohol.—6-Methoxytetralol-1 (3.25 g.) was shaken with 32 cc. of 46% (by titration[10]) hydrobromic acid for twelve hours. The resultant solid pinkish-white ball, after recrystallization from ethanol, weighed 1.9 g. and had m. p. 74–75°.

Anal. Calcd. for $(C_{11}H_{12}O)_n$: C, 82.46; H, 7.55. Found: C, 83.33; H, 7.75.[11]

In view of the unsatisfactory analytical figures, the material was chromatographed on Brockmann alumina; the substance was put on with benzene, and eluted first with low-boiling petroleum ether, and then with benzene–petroleum ether (20/80). Fourteen (approximately weight equivalent) fractions were taken. All but three fractions, on evaporation and trituration with methanol, gave white crystalline material, m. p. 75–77°. The eleven fractions together constituted more than 90% of the original material, and were recrystallized from methanol, m. p. 75.5–77°.

Anal. Calcd. for $(C_{11}H_{12}O)_n$: C, 82.46; H, 7.55. Found: C, 82.59; H, 7.62. The other three fractions had melting points 69–74, 71–76, and 65–110°, and were not further investigated. As will be evident from (b, below), the tedious chromatographic separation may be obviated by distillation *in vacuo* of the crude dimer.

(b) From 6-Methoxy-α-tetralol Acetate.—The acetate (*vide supra*) (12.2 g.) was shaken for forty-eight hours with 150 cc. of 46% hydrobromic acid. The resultant viscous red material was taken up in ether, washed with soda, then water, dried, and distilled *in vacuo* after removal of solvent. The very viscous yellow oil (6.0 g., b. p. 233–238° (3 mm.)) obtained, on crystallization from methanol–ethyl acetate, separated in beautiful long needles, m. p. 75.5–76.5° (3.6 g.); recrystallized from ethanol, m. p. 76–77°.

Anal. Calcd. for $(C_{11}H_{12}O)_n$: C, 82.46; H, 7.55. Found: C, 82.65; H, 7.58. The absorption spectrum was taken in absolute ethanol (*vide* Fig. 1). Determination of the molecular weight (Rast). Calcd. for $C_{22}H_{24}O_2$: 320.4. Found: 290 (Tiedcke); 333 (R. H. E.).

Perbenzoic Acid Oxidation of the Dimer.—The purified dimer (2.53 g., 0.0079 mole) dissolved in 200 cc. of chloroform was treated with 1.19 g. of perbenzoic acid in 50 cc. of chloroform. The reaction, which was carried out below 5°, was followed iodimetrically:

Time, hr.	0.0645 *N* $Na_2S_2O_3$/cc. (aliquot), cc.
0	1.07
2	0.27
19	.11
25	.10
26	.10

These figures indicate one double bond for a molecular weight of 320. The reaction mixture, which still possessed oxidizing power, was washed with dilute bisulfite solution, soda, and water; removal of solvent and trituration with methanol–petroleum ether gave 0.8 g. of material, m. p. 124–126°; recrystallized from ethanol, faintly yellow needles, m. p. 127–128.5°.

Anal. Calcd. for $C_{22}H_{24}O_3$: C, 78.54; H, 7.19. Found: C, 78.45; H, 7.69. The absorption spectrum was taken in absolute ethanol (*vide* Fig. 2). Determination of the molecular weight (Rast). Calcd. for $C_{22}H_{24}O_3$: 336.4. Found: 322, 326 (Tiedcke).

Hydrogenation of the Dimer.—The dimer (1.30 g.) in 10 cc. of glacial acetic acid took up 116 cc. of hydrogen (t = 25.5°, p = 680 mm.) and stopped, on shaking 254 minutes over reduced platinum oxide. Calcd. for $C_{22}H_{24}O_2$: mol. wt., 320.4. Found (by hydrogenation): mol. wt. 307. On removal of catalyst and solvent, a viscous oil was obtained which resisted attempts at crystallization.

Demethylation of the Dihydro-dimer.—The oil from the above experiment was dissolved in 5 cc. of glacial acetic acid, heated to boiling, and 5 cc. of 57% hydriodic acid was added drop by drop during twenty minutes. After boiling until a test portion was completely soluble in caustic soda, the reaction mixture was poured into 50 cc. of 1% sodium bisulfite; the resulting flocculent yellow precipitate (1.1 g.) was recrystallized from dilute acetic acid, m. p. 170–176° (0.5 g.). Successive recrystallizations from glacial acetic acid: first, m. p. 174–184°; second, m. p. 177–184°; third [after sublimation at 190° (2 mm.), glass obtained] 177–186°. A fourth recrystallization from *n*-butyl ether, m. p. 181–187°, and, finally, from aqueous alcohol, gave white microcrystalline needles, m. p. 187–190° (0.2 g.).

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.59; H, 7.53. Found: C, 81.01; H, 8.08.

Sharp-melting samples of this material were extremely difficult to obtain; the crude material is undoubtedly a mixture of stereoisomers of the formula XIV (R = H), which has two asymmetric carbon atoms (starred). The similar situation in the case of the hydrogenated dimer XIV (R = CH_3) was doubtless responsible for the failure of this material to crystallize.

Oxidation of the Dimer: (a) By Potassium Permanganate.—The dimer (2.3 g.) in 55 cc. of acetone with 2.3 g. of sodium bicarbonate was oxidized with 2.64 g. of potassium permanganate during nine hours at 0°. After standing overnight the precipitated manganese dioxide was removed. The residual red oil after evaporation of the acetone was taken up in acetic acid and precipitated with water. The crystalline material which separated (0.78 g., m. p. 79–81°) was recrystallized (m. p. 83.5–85°) and gave analytical figures indicating partial oxidation (C, 81.55; H, 7.01); the material was then oxidized in 50 cc. of acetic

(10) The use of 46% acid (Long and Burger[1] used 48% material) actually results in a much smoother reaction; a solid product is obtained directly.

(11) Long and Burger[1] found: C, 83.13; H, 7.86.

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acid with 0.5 g. of permanganate at room temperature during three hours. The residue after filtration and evaporation *in vacuo* was taken up in ether, washed with soda, water, dried, and decolorized. From the extract, 0.6 g. of a viscous red oil was obtained which on solution in methanol, decolorization, precipitation with water, and two recrystallizations from methanol, gave VII, 0.02 g., clusters of white needles, m. p. 107.5–108.5°. The material was identical in all respects with that obtained by chromic acid oxidation of the dimer (*vide infra*). Mixtures of VII with the dimer had melting points intermediate between those of the pure substances (*cf.*, *e. g.*, the partially oxidized material described above).

The manganese dioxide from the first oxidation (above) was leached with 350 cc. of boiling water. After concentration to half-volume, acidification gave 0.5 g. of a dark gum, which was taken up in soda, decolorized, extracted with ether to remove neutral impurities, and reacidified. The resultant granular yellow solid was crystallized from acetic acid to give pure IV: first, m. p. 201–203°; second, m. p. 201.5–203° (0.10 g. of colorless needles). Neut. equiv. Calcd. for $C_{11}H_{12}O_5$: 112.2. Found: 112.6.

(b) **By Chromic Acid.**—To the dimer (0.90 g.) in 75 cc. of glacial acetic acid, a solution of 0.56 g. of chromium trioxide in 15 cc. of glacial acetic acid and 10 cc. of water was added dropwise with stirring during one hour. After removal of most of the acetic acid *in vacuo*, water was added. The reaction mixture was extracted with ether, which was then washed with soda, water, and dried. The neutral residue after removal of solvent, crystallized from ethanol (0.15 g.), m. p. 107–108.5°. This material (VII), twice recrystallized from ethanol, formed long white needles, m. p. 108–109°.

Anal. Calcd. for $C_{22}H_{22}O_2$: C, 82.95; H, 7.00. Found: C, 83.56; H, 7.14.

Mixed with the material of like melting point from the permanganate oxidation (*vide supra*), m. p. 107.5–109°. The synthesis of this substance is described below.

Dehydrogenation of the Dimer: (a) With Sulfur.—The dimer (1.20 g., 0.0038 mole) mixed intimately with 0.60 g. of sulfur was heated on a metal bath; the hydrogen sulfide evolved was collected in a nitrometer over dilute sulfuric acid previously saturated with the gas. Evolution of gas began at 200°, and heating to 300° during two hours drove off 221 cc. (0.0092 mole) of hydrogen sulfide. The black mass was extracted with hot dilute acetic acid, the extract was evaporated *in vacuo*, the residue was extracted with methanol, from which a gummy solid separated on cooling. On recrystallization from methanol–ethyl acetate, 0.3 g. of V (R = CH_3) was obtained as white needles, m. p. 88–90°. This material was identical with that prepared more smoothly and in better yield by catalytic dehydrogenation (see (b), below).

In a similar experiment, extraction of the initial fusion product with ether left a light yellow residue, which on crystallization from toluene separated in straw-colored needles, m. p. 210–212° (10 mg.). Qualitative tests indicated the presence of sulfur in the material, and it was not further investigated.[12]

(b) **By Catalytic Dehydrogenation.**—The dimer (4.2 g., 0.013 mole) was mixed with 2.6 g. of 10% palladium-charcoal catalyst, and heated in a stream of carbon dioxide at 300° during four hours; the evolved gases (866 cc., 91% of the theoretical quantity for three moles of hydrogen per mole of compound) were collected over 20% sodium hydroxide solution in the usual way. The product was taken up in ether. The residual oil after evaporation of the filtered ethereal solution was distilled *in vacuo*, b. p. 255–260° (3 mm.). Crystallization of the viscous yellow distillate from the minimum quantity of acetic acid gave V (R = CH_3) as beautiful white needles, m. p. 89–90° (1.95 g.). Recrystallized from glacial acetic acid, m. p. 91–92°.

Anal. Calcd. for $C_{22}H_{18}O_2$: C, 84.03; H, 5.77. Found: C, 84.29; H, 5.93.

(12) *Cf.* Hudson and Robinson, *J. Chem. Soc.*, 718 (1941), for a similar result in the sulfur dehydrogenation of a tetralin derivative.

Mixed with the material of like melting point from the sulfur dehydrogenation ((a), above), the m. p. was 88–90°. The synthesis of this compound is described below.

6,6′-Dihydroxy-1,2′-binaphthyl (V, R = H).—To 6,6′-dimethoxy-1,2′-binaphthyl (0.8 g.) in 5 cc. of boiling glacial acetic acid, 5 cc. of 57% hydriodic acid was added dropwise during twenty minutes. The reaction mixture was boiled until a test portion was completely soluble in 5% aqueous sodium hydroxide. On pouring into 50 cc. of 1% sodium bisulfite solution, 0.6 g. of gummy material separated, which was crystallized from the minimum quantity of acetic acid as a purplish microcrystalline powder, m. p. 184–185° (0.4 g.). On recrystallization from acetic acid in the presence of a trace of zinc dust, the substance (V, R = H) separated in small light-yellow needles, m. p. 187–188.5°.

Anal. Calcd. for $C_{20}H_{14}O_2$: C, 83.90; H, 4.93. Found: C, 83.53; H, 5.43.

6-Bromo-β-naphthol was prepared by the elegant method of Franzen and Staubel[3]; from it, however, **6-methoxy-2-bromonaphthalene** was prepared more smoothly and in better yield by catalytic etherification, with methanol and sulfuric acid, than by the dimethyl sulfate–alkali method of those authors. The phenol (46 g.) in 50 cc. of methanol and 10 cc. of concentrated sulfuric acid was heated under reflux overnight. The solid mass of crystalline material was removed, washed in turn with methanol, water, caustic soda, and water, and crystallized from ethanol, white needles (43 g.), m. p. 102–103°. After distillation *in vacuo* (b. p. 160–164° (3 mm.)), m. p. 105–106°.

Condensation of 6-Methoxy-2-naphthylmagnesium Bromide with 6-Methoxy-α-tetralone.—In order to carry out successfully the preparation of the Grignard reagent, it was essential to use freshly distilled bromo compound.

6-Methoxy-2-bromonaphthalene (7.11 g.) in 250 cc. of dry ether was added during eight hours to 0.85 g. of magnesium turnings suspended in a small volume of ether under a current of dry nitrogen at the reflux temperature [ethyl bromide (0.8 cc.) and a crystal of iodine were added to start the reaction]. The solution was concentrated to 100 cc., 75 cc. of dry benzene was added, and the reaction-mixture was boiled for forty-eight hours with stirring. After addition of 6-methoxy-α-tetralone (4.3 g.) in 50 cc. of dry benzene, the solution was heated further for twenty-four hours. Then, with vigorous stirring, 100 cc. of 20% ammonium chloride solution was added; the organic layer was separated, washed, dried (sodium sulfate) and concentrated, finally *in vacuo*. Trituration of the residue with ether and methanol gave 3 g. of a yellowish-white solid, which crystallized from benzene–methanol in white needles, m. p. 127–128°. Twice recrystallized from benzene–methanol, the 6,6′-dimethoxy-3,4-dihydro-1,2′-binaphthyl (VI) separated in needles, m. p. 126°.

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.50; H, 6.38. Found: C, 83.26; H, 6.04.

6,6′-Dimethoxy-1,2′-binaphthyl (V, R = CH_3) (by synthesis).—Dehydrogenation over 10% palladium charcoal catalyst (1 g.) of 1.5 g. of the synthetic compound (VI) at 300° gave 90 cc. of hydrogen (80%) at 25° and 760 mm., and, after solution of the organic product in ether, removal of catalyst, and evaporation of solvent, 1.4 g. of crystalline material, m. p. 87–92°. On recrystallization from glacial acetic acid, 6,6′-dimethoxy-1,2′-binaphthyl (V, R = CH_3) separated in white needles, m. p. 91–92°, identical in appearance with the substance obtained by the dehydrogenation of the dimer (*vide supra*), and mixed with that material, m. p. 91–92°.

Synthesis of 6,6′-Dimethoxy-1,2,3,4-tetrahydro-1,2′-binaphthyl (VII).—On hydrogenation of 107 mg. of the Grignard product (VI) (above), in glacial acetic acid over 50 mg. of reduced platinum oxide, 9.8 cc. (110% of the theoretical) of hydrogen was taken up during forty minutes (*p*, 760 mm.; *t*, 25°). After removal of catalyst, the product was precipitated as lustrous white plates (80 mg.), which were crystallized from alcohol, m. p. 106–107°. After two recrystallizations from ligroin, m. p. 107.5–

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108.5°, mixed with the chromic acid (*or* permanganate) oxidation product of the dimer (*vide supra*), m. p. 107–108°.

6-Methoxy-3,4-dihydronaphthalene.—In the course of the above work, this material was obtained occasionally during distillation of 6-methoxy-α-tetralol, from hydrogenation of 6-methoxy-α-tetralone. The observation that the material in the pot was deep green when the decomposition occurred suggests that the irregularity was caused by the presence of a small amount of chromium salts in the ketone.

6-Methoxy-α-tetralone (9.0 g.) was hydrogenated in the usual way (*vide supra*). During distillation, decomposition occurred, and water appeared in the condenser: Fraction 1; 5.8 g., b. p. 110–118° (3 mm.); Fraction 2: 2.6 g. crystalline solid, m. p. 77–78°, b. p. 130–135° (3 mm.), mixed with 6-methoxy-α-tetralone, m. p. 77–78°. The low-boiling material was redistilled, 3.0 g., b. p. 107–111° (2.5 mm.); d^{30} 1.068; $n^{21}D$ 1.5825; M_R, 50.5. Calcd. for $C_{11}H_{12}O$, 4|⁻, 48.3, $\Delta M_R = 2.2$.

Anal. Calcd. for $C_{11}H_{12}O$: C, 82.46; H, 7.55. Found: C, 81.82; H, 7.53.

The physical constants may be compared with those of 6-methoxy-1,2,3,4-tetrahydronaphthalene [b. p. 105–106° (4 mm.), d^{19} 1.039, $n^{26.5}D$ 1.5441]. The absorption spectrum of the dihydro compound was measured in ethanol (Fig. 3), $\lambda_{max.} = 269$ mμ, $\log \epsilon = 4.00$.

After shaking 2.8 g. of the material with 46% hydrobromic acid for twelve hours, a crystalline solid was obtained, which on crystallization from alcohol separated in lustrous white needles (1.72 g.), m. p. 70–72°. Recrystallized from alcohol, the m. p. was 75°; mixed with the dimer, m. p. 75°.

The dihydro compound also was obtained by the hydrolysis of 6-methoxy-1-acetoxytetralin with alcoholic sodium hydroxide.

Summary

The acid-catalyzed dehydration of 6-methoxy-1,2,3,4-tetrahydro-1-naphthol gives 6,6′-dimethoxy-1,2,3,3′,4,4′-hexahydro-1,2′-binaphthyl.

CAMBRIDGE, MASSACHUSETTS RECEIVED JANUARY 31, 1944

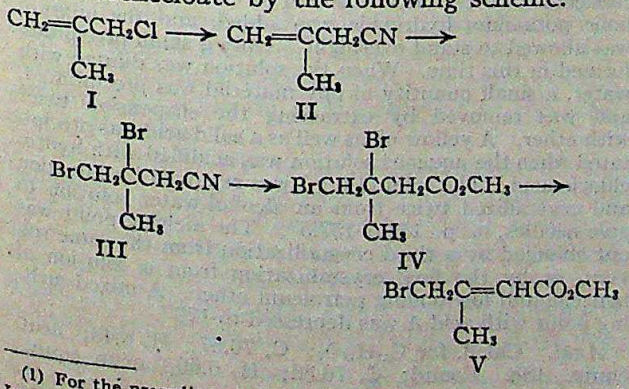
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Reformatsky Condensations Involving Vinylogs of Haloacetic Esters. II.[1] Methyl γ-Bromosenecioate

BY REYNOLD C. FUSON AND PHILIP L. SOUTHWICK[2]

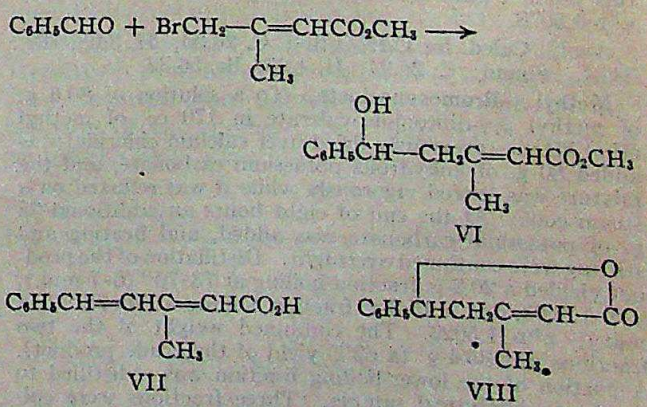
By the use of γ-halocrotonates in the Reformatsky reaction a synthetic route was found to polyene acids.[1] This method has now been extended to a β-methyl-γ-halocrotonate, methyl γ-bromosenecioate (V). The use of this new ester makes possible the extension of a carbon chain by an isoprene unit and thus opens the way for the synthesis of truly carotenoid chains.

After this work had been completed it was discovered that very similar results had been obtained by Ziegler, Schumann and Winkelmann.[3] One of the chief differences between our work and that of the German writers lies in the method of synthesis of the bromoester (V). The direct bromination of the senecioic ester[4] appears to be more convenient than our method which involved the conversion of methallyl chloride into methyl γ-bromosenecioate by the following scheme.



It was found that attempts to purify the ester obtained by this method were attended by very serious losses. For this reason the ester was used in a somewhat impure condition.

To determine whether the methyl γ-bromosenecioate could be condensed with carbonyl compounds by the Reformatsky method, a test run was made with benzaldehyde. The results were similar to those of Ziegler, Schumann and Winkelmann. The isolation and purification of the products presented difficulties. During the distillation and hydrolysis of the expected hydroxy ester (VI), decomposition occurred giving rise to a mixture of compounds. Chief of these were two isomeric unsaturated acids, evidently *cis–trans* forms of β-styrylcrotonic acid (VII). It is not clear which of these isomers corresponds to the product (m. p. 157°) described by Ziegler, Schumann and Winkelmann.



A third product isomeric with the two acids appeared to be the corresponding lactone (VIII).

(1) For the preceding paper see Fuson, Arnold and Cooke, THIS JOURNAL, 60, 2272 (1938).
(2) Abbott Fellow, 1942–1943.
(3) Ziegler, Schumann and Winkelmann, *Ann.*, 551, 120 (1942).
(4) Ziegler, Späth, Schaaf, Schumann and Winkelmann, *ibid.*, 551, 80 (1942).

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Experimental

Methallyl Cyanide.—The method of Tamele, Ott, Marple and Hearne[5] was used. From 422 g. of commercial cuprous cyanide and 418 g. of methallyl chloride there was obtained 285 g. (76%) of a water-white liquid boiling at 134.5–136.5°; $n^{20}D$ 1.4180.

Anal. Calcd. for C_5H_7N: C, 74.03; H, 8.70. Found: C, 74.28; H, 8.97.

In another run using 456 g. of cuprous cyanide and an initial 454 g. of methallyl chloride, more methallyl chloride was added until it no longer continued to react, as evidenced by vigorous refluxing of the mixture. An additional 160 cc. was required. By this means 349 g. of methallyl cyanide was obtained (an 86% yield based on the cuprous cyanide).

β,γ-Dibromoisovaleronitrile.—A solution of 200 g. of bromine in 200 cc. of dry chloroform was added dropwise to a stirred solution of 100 g. of methallyl cyanide in 400 cc. of dry chloroform. The mixture was cooled in a water-bath during the addition. When the solution ceased to absorb bromine, shortly before all of it had been added, the addition was stopped.

Removal of the solvent at temperatures not above 60° left 297 g. of crude dibromo nitrile. A portion of the heavy, yellow oil was distilled twice at reduced pressure. Distillation was accompanied by the evolution of hydrogen bromide, even when conducted at relatively low pressures. The product was a colorless oil, b. p. 89° (2–3 mm.), $n^{20}D$ 1.5308.

Anal. Calcd. for $C_5H_7NBr_2$: C, 24.92; H, 2.93; N, 5.81; Br, 66.33. Found: C, 25.62; H, 3.32; N, 6.33; Br, 65.79.

γ-Bromosenecionitrile.—Eighty-nine grams of the crude dibromonitrile was dissolved in 200 cc. of methyl ethyl ketone, and 92 g. of anhydrous potassium carbonate was added. The mixture was refluxed on a steam cone and stirred overnight. The product was a nearly colorless, lachrymatory liquid, boiling at 84° (8 mm.); $n^{20}D$ 1.5175. The yield was nearly 50%.

Anal. Calcd. for C_5H_5NBr: C, 37.55; H, 3.78; N, 8.75; Br, 49.94. Found: C, 38.09, 37.90; H, 3.98, 3.96; N, 8.76; Br, 49.37.

Methyl β,γ-Dibromoisovalerate.—To 200 g. of crude β,γ-dibromoisovaleronitrile was added a solution of 250 cc. of concentrated sulfuric acid in 400 cc. of methanol, and the mixture was stirred vigorously at the reflux temperature. More methanol was added from time to time to replace that which escaped from the condenser. Heating and stirring were discontinued after nine hours, and the mixture was allowed to stand overnight.

The crude product (124 g.), together with 20 g. of a similar crude product from a trial run, was distilled at reduced pressure through a carborundum-packed column. The major fraction, a colorless liquid boiling at 80–83° (2–3 mm.), weighed 104 g. Redistillation of a portion of this product gave a sample boiling at 84–85° (3 mm.); $n^{20}D$ 1.5078.

Anal. Calcd. for $C_6H_{10}O_2Br_2$: C, 26.30; H, 3.68; Br, 58.34. Found: C, 26.94; H, 4.25; Br, 56.32.

Methyl γ-Bromosenecioate.—To a solution of 80.6 g. of methyl β,γ-dibromoisovalerate in 170 cc. of methyl ethyl ketone (previously dried over calcium chloride) was added 80 g. of anhydrous potassium carbonate, and the mixture was stirred vigorously while it was refluxed on a steam cone. At the end of eight hours an additional 25 g. of potassium carbonate was added, and heating and stirring were continued overnight. Distillation of the product yielded a 20.2-g. fraction boiling at 73–76° (6–7 mm.); $n^{20}D$ 1.5003, and a 15.2-g. fraction boiling at 76–78° (6–7 mm.); $n^{20}D$ 1.5023. The combined weight of the two fractions was 35.4 g. (a 62% yield of the crude product). A portion of the lower-boiling fraction was redistilled to obtain an analytical sample. Three fractions were collected, the first boiling at 63° (3 mm.); $n^{20}D$ 1.5002, the second at 63–66° (3 mm.), and the third at 66° (3 mm.); $n^{20}D$ 1.5010. A Kjeldahl determination showed the presence of 0.1% of nitrogen in the first fraction, from which the following analytical results were obtained:

Anal. Calcd. for $C_6H_9O_2Br$: C, 37.33; H, 4.70; Br, 41.40. Found: C, 38.26; H, 5.13; Br, 39.28.

The remainder of the crude product was redistilled at a higher pressure. A large part of it boiled at 98–100° (24 mm.), although the last distillate from the higher-boiling crude fraction came over at 107°. The compound was highly lachrymatory.

Condensation of Methyl γ-Bromosenecioate with Benzaldehyde.—The procedure was similar to that described by Ziegler, Schumann and Winkelmann. A mixture of 24.6 g. of methyl γ-bromosenecioate, 16 g. of purified benzaldehyde, 25 cc. of dry benzene and 6 cc. of dry ether was placed in the dropping funnel, and 10.5 g. of 20-mesh granulated zinc (freshly cleaned with hydrochloric acid and dried with absolute alcohol and dry ether) was placed in the flask.

Approximately one-tenth of the mixture was run into the flask, and a crystal of iodine was added. When the flask was warmed over a low flame, the reaction began almost immediately. Stirring was then begun, and the mixture was added rapidly enough to maintain gentle refluxing of the solvents. The addition required about twenty-five minutes. Stirring was continued, and the mixture was maintained at the reflux temperature over a low flame for an additional two and one-half hours. Distillation of the product at a pressure of 2–3 mm. yielded a 3-g. fraction boiling at 146–148°, a 2.6-g. fraction at 148–152°, and a 9.2-g. fraction at 152–176°.

β-Styrylcrotonic Acid (Form A).—When 1 g. of the fraction boiling at 146–148° (2–3 mm.) was dissolved in 10 cc. of saturated alcoholic potassium hydroxide solution, a voluminous precipitate formed in a few minutes. The mixture was allowed to stand overnight, then diluted with water, and acidified. The precipitated acid was crystallized successively from benzene, alcohol and water, and benzene. White needles, melting at 158.5–159.5°, were obtained.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43; neut. equiv., 188. Found: C, 76.76; H, 6.56; neut. equiv., 190.

This acid is probably identical with the high-melting form reported by Kuhn and Hoffer.[6]

β-Styrylcrotonic Acid (Form B).—The high-boiling fraction from the condensation (b. p. 152–176° (2–3 mm.)) was redistilled in the presence of a few crystals of iodine[7] in the hope of dehydrating the hydroxy ester which it was believed to contain. No water distilled from the mixture, however. A fore-run boiling at 146–155° (2–3 mm.) and a 3.9-g. fraction boiling at 172–178° (2–3 mm.) were collected. To the latter fraction 50 cc. of saturated alcoholic potassium hydroxide was added, and the mixture was allowed to stand overnight. Only a small precipitate formed in this time. When the solution was diluted with water, a small quantity of oily material was precipitated, and was removed by extracting the suspension twice with ether. A yellow oil as well as a solid acid was precipitated when the aqueous solution was acidified with hydrochloric acid. The solid (1.5 g.) was removed by filtration and crystallized twice from an alcohol-water solution to give needles, m. p. 156.5–157.5°. The melting point was not changed by a third crystallization from the same solvent, or by the final crystallization from a solution of benzene and low-boiling petroleum ether. A mixed melting point with acid A was depressed to 120°.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43; neut. equiv., 188. Found: C, 76.36; H, 6.66; neut. equiv., 190.

Lactone of β-Styrylcrotonic Acid (IX).—After acid B had been removed by filtration, as described above, the oil

(5) Tamele, Ott, Marple and Hearne, *Ind. Eng. Chem.*, **33**, 115 (1941).

(6) Kuhn and Hoffer, *Ber.*, **65**, 651 (1932).

(7) Hibbert, This Journal, **37**, 1748 (1915).

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which was precipitated at the same time was extracted from the filtrate with ether. The ethereal extract evaporated to leave a residual oil and several large crystals. The crystals dissolved when the mixture was stirred with 10% potassium carbonate solution, but the oil did not, and was removed from the suspension by ether extraction. Acidification of the bicarbonate solution precipitated an additional 0.3 g. of acid, and evaporation of the ether extract left 0.8 g. of an oil which solidified completely after standing for two days. This material melted at 55–57°, and crystallized in the form of needles or plates from mixtures of ether and low-boiling petroleum ether. After two crystallizations from these solvents it melted at 61–62°.

Anal. Calcd. for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43. Found: C, 76.46; H, 6.66.

The compound dissolved slowly in cold aqueous potassium hydroxide solution and could be recovered by acidification of this solution. It dissolved more rapidly in saturated alcoholic potassium hydroxide solution and was not precipitated by dilution of the solution with water. When the diluted solution was acidified with hydrochloric acid a solid product, m. p. 155–157°, was precipitated. This compound was found by the mixed melting point method to be identical with acid B. It seems probable that the compound melting at 61–62° is the lactone of δ-hydroxy-β-methyl-δ-phenyl-α-pentenoic acid.

β-Styrylcrotonic Acid (Form A) from Benzalacetone and Ethyl Bromoacetate.—The procedure employed was essentially that of Kohler and Heritage.[8] These investigators, however, distilled the hydroxy ester which they obtained and subsequently dehydrated it by heating with hydrochloric acid, whereas in the present instance it was more convenient to dehydrate the crude ester directly by distillation in the presence of a few crystals of iodine. To the product obtained from the Reformatsky condensation of 61 g. of benzalacetone with 70 g. of ethyl bromoacetate, 0.1 g. of iodine was added and distillation was carried out under reduced pressure. After the water had been removed, three fractions were collected; a 14.5-g. fraction at 141–145° (2 mm.), a 20-g. fraction at 145–147° (2 mm.) and a 3-g. fraction at 147–149° (2 mm.).

To 1 g. of the middle fraction was added 25 cc. of saturated alcoholic potassium hydroxide solution, and the mixture, in which a precipitate quickly formed, was allowed to stand for two days. The precipitate dissolved when the solution was diluted with water, and a crude acid, m. p. 120–140°, was precipitated when the solution was acidified with hydrochloric acid. White needles melting at 158–159° were obtained after three crystallizations from benzene. No depression of the melting point was observed when this product was mixed with acid A from condensation of benzaldehyde with methyl γ-bromosenecioate.

The melting point reported by Kohler and Heritage[8] was 153°. von Auwers and Müller,[9] using the same method, obtained a product melting at 156–157°. Kuhn and Hoffer reported a melting point of 160°. It seems probable that all the samples made by this method are identical, and different from form B.

(8) Kohler and Heritage, *Am. Chem. J.*, **43**, 475 (1909).

(9) von Auwers and Müller, *J. prakt. Chem.* [2] **105**, 379 (1932).

URBANA, ILLINOIS RECEIVED JANUARY 20, 1944

Summary

A method has been developed for the preparation of methyl γ-bromosenecioate from methallyl chloride.

Methyl γ-bromosenecioate has been condensed with benzaldehyde to yield two forms of β-styrylcrotonic acid and a third compound thought to be the lactone corresponding to the expected hydroxy acid.

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

1,2-Addition of Methylmagnesium Iodide to Mesityl Ketones

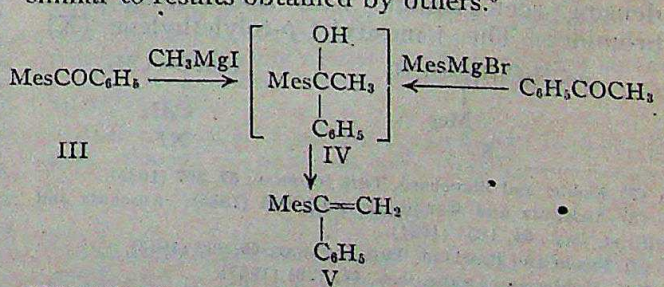
BY REYNOLD C. FUSON, M. D. ARMSTRONG, WM. E. WALLACE[1] AND J. WAYNE KNEISLEY[2]

The carbonyl group of simple mesityl ketones has been known to react additively only with hydrogen. In particular, normal or 1,2 addition of a Grignard reagent has never been observed.[3] Recently mesityl *t*-butyl diketone (I) was found to undergo 1,2 addition of methylmagnesium iodide to each of the carbonyl groups.[4] Also the conversion of certain mesitoic esters to ketones by the action of Grignard reagents[5] may be explained by assuming 1,2 addition of the reagent to the ester carbonyl group.

These results led to a reëxamination of the behavior of simple mesityl ketones toward the Grignard reagent. The most favorable structure appeared to be that in which the mesitoyl radical was joined to the smallest possible group that possessed no *alpha* hydrogen atom. Among aliphatic radicals *t*-butyl was the logical choice. However, pivalylmesitylene (II) could not be induced to react with methylmagnesium iodide.[4] In the aromatic series benzoylmesitylene (III) appeared to offer the best chance of realizing 1,2 addition.

$MesCOCOC(CH_3)_3$ (I) $\qquad$ $MesCOC(CH_3)_3$ (II)

When benzoylmesitylene was treated with methylmagnesium iodide it was converted in 64% yield to 1-mesityl-1-phenylethylene (V), the dehydration product of the carbinol (IV) that would have resulted from 1,2 addition. The direct production of the olefin rather than the carbinol is similar to results obtained by others.[6]



(1) Present address: General Aniline and Film Corporation, Easton, Pennsylvania.

(2) Present address: Hercules Powder Company, Wilmington, Delaware.

(3) Kohler and Baltzly, THIS JOURNAL, **54**, 4015 (1932).

(4) Fuson and Robertson, *J. Org. Chem.*, **7**, 466 (1942).

(5) Fuson, Bottorff and Speck, THIS JOURNAL, **64**, 1450 (1942).

(6) Tissier and Grignard, *Compt. rend.*, **132**, 1184 (1901).

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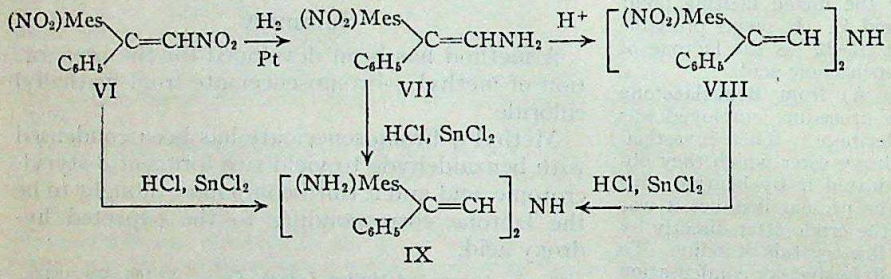
The structure of the olefin was established by an independent synthesis. 1-Mesityl-1-phenylethylene was formed in 15% yield by the condensation of mesitylmagnesium bromide with acetophenone. The experimental conditions were similar to those which were employed with the benzoylmesitylene and the product was the ethylene rather than the carbinol.[7]

Since the olefin was a liquid, it was desirable to compare the two samples by reference to a solid derivative. Such a derivative was prepared by nitration according to the procedure used by Anschütz and Romig to nitrate 1,1-diphenylethylene.[8]

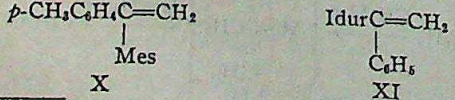
The nitro derivative, 2-(3-nitromesityl)-2-phenyl-1-nitroethylene (VI), was very much like known nitroölefins. The reduction products are shown in the following outline.



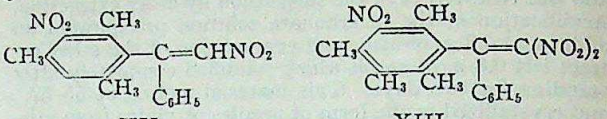
The nitroamine (VII) has been written as a vinylamine rather than as an imine because of the analogy with 2,2-dimesitylvinyl alcohol.[9] It was neutral and could not be hydrolyzed to the corresponding aldehyde and thus appeared to differ in type from the corresponding derivative of 1,1-diphenylethylene.[10]

It did resemble 2,2-diphenylvinylamine,[11] however, in the ease with which it lost ammonia in the presence of acids to yield the corresponding divinylamine (VIII). Reduction with stannous chloride in ethanolic hydrochloric acid converted VI, VII and VIII to the aminodivinylamine, IX. The divinylamines are similar to 2,2,2′,2′-tetraphenyldivinylamine, described by Lipp[12] and by Krabbe and Schmidt.[11]

p-Toluylmesitylene and benzoylisodurene reacted with methylmagnesium iodide in a manner similar to that observed with benzoylmesitylene. The products were 1-mesityl-1-(*p*-tolyl) ethylene (X) and 1-isoduryl-1-phenylethylene (XI), respectively. The latter also was prepared by condensing acetophenone with isodurylmagnesium bromide. The 1-mesityl-1-*p*-tolylethylene (X),



obtained only in impure form, yielded a dinitro derivative (XII) analogous to VI. 1-Isoduryl-1-phenylethylene, by a slightly different procedure, gave a trinitro derivative (XIII).



The new olefins immediately decolorized a solution of permanganate and were attacked by chromic acid. They decolorized a solution of bromine in carbon tetrachloride with the evolution of a small amount of hydrogen bromide.

Experimental

Benzoylisodurene.—This ketone was made by condensing 134 g. of isodurene with 140 g. of benzoyl chloride by the Friedel–Crafts method. The ketone was purified by fractionation *in vacuo;* b. p. 159–164° (4 mm.); m. p. 60–61°; yield 78%.

Anal.[13] Calcd. for $C_{17}H_{18}O$: C, 85.67; H, 7.61. Found: C, 85.98; H, 7.57.

Benzoylmesitylene and Methylmagnesium Iodide.—A solution of 30 g. of benzoylmesitylene, prepared according to the directions of Montagne,[14] in 50 cc. of dry ether was added slowly to a solution of methylmagnesium iodide, prepared from 30 g. of methyl iodide, 5.4 g. of magnesium and 75 cc. of dry ether. After the addition was completed, a little benzene was added and ether was allowed to evaporate until the temperature of the vapors was 60°. The reaction mixture was then stirred under reflux for sixteen hours. The contents of the flask were decomposed and the organic layer was separated. After the solution had been washed with water and dried, the solvent was removed by evaporation. The resulting oil was distilled *in vacuo*. The fraction which came over at 129–134° (3 mm.) was collected; yield 19 g. (64%); $n^{20}D$ 1.5812. Redistillation yielded the pure olefin; b. p. 120° (3 mm.); $n^{20}D$ 1.5835; d_{20}^{20} 1.0003.

Anal. Calcd. for $C_{17}H_{18}$: C, 91.84; H, 8.16; *MR*, 74.2. Found: C, 91.57; H, 8.19; *MR*, 74.4.

1-Mesityl-1-phenylethylene was obtained also by the condensation of acetophenone with mesitylmagnesium bromide. To a mesitylmagnesium bromide solution, prepared from 41 g. of bromomesitylene and 6.5 g. of magnesium in 100 cc. of dry ether, a solution of 20 g. of acetophenone in 25 cc. of dry ether was added at such a rate that the ether refluxed vigorously. When the addition was completed the reaction mixture was refluxed for one hour, cooled in an ice-bath and decomposed with cold, dilute hydrochloric acid. The ether layer was treated in the usual manner and the viscous, yellow oil which was isolated was distilled *in vacuo*. The forefraction contained 12 g. of mesitylene and 12 g. of acetophenone. The main fraction was redistilled *in vacuo* until the index of refraction remained constant; this required four distillations; yield 3 g.; b. p. 117–120° (4 mm.); $n^{20}D$ 1.5831; d_{20}^{20} 1.0004. The olefin was a light yellow oil which decolorized neutral permanganate immediately and reacted with bromine with the evolution of hydrogen bromide.

Reactions of 1-Mesityl-1-phenylethylene.—A solution of the olefin rapidly decolorized a solution of potassium

(7) Kohler and Blanchard, THIS JOURNAL, **57**, 367 (1935).

(8) Anschütz and Romig, *Ber.*, **18**, 662 (1885); Anschütz and Hilbert, *ibid.*, **54**, 1854 (1921).

(9) Fuson and Rowland, THIS JOURNAL, **65**, 992 (1943).

(10) Kohler and Drake, *ibid.*, **45**, 1281 (1923).

(11) Krabbe and Schmidt, *Ber.*, **72B**, 381 (1939).

(12) Lipp, *Ann.*, **449**, 15 (1926).

(13) The microanalyses reported in this paper were carried out by Miss Margaret McCarthy, Miss Theta Spoor and Miss Dorothy Schneider.

(14) Montagne, *Rec. trav. chim.*, **27**, 327 (1908).

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permanganate in the cold. It absorbed bromine from a bromine solution in carbon tetrachloride; the evolution of hydrogen bromide was detected.

A small amount of platinum oxide was added to a solution of 0.73 g. of the olefin in 40 cc. of 95% ethanol, and the solution was shaken for several hours with hydrogen at one atmosphere. One mole of hydrogen was absorbed.

The 1-mesityl-1-phenylethane boiled at 154–155° (4 mm.); $n^{23}D$ 1.5621.[15]

Anal. Calcd. for $C_{17}H_{20}$: C, 91.01; H, 8.99. Found: C, 90.64; H, 9.11.

The isomeric hydrocarbon 1-mesityl-2-phenylethane is a solid melting at 39–39°.[16]

2-(3-Nitromesityl)-2-phenyl-1-nitroethylene (VI).—A mixture of 6.5 g. of fuming nitric acid, 4 cc. of glacial acetic acid and 4 cc. of acetic anhydride was added dropwise, with stirring, over a period of one hour to an ice-cold solution of 8 g. of 1-mesityl-1-phenylethylene in 5.5 cc. of acetic anhydride. Yellow crystals appeared during the addition of the nitrating mixture. The crude dinitro derivative was collected on a filter; yield 7 g. It crystallized from ethanol in yellow plates melting at 144–145°.

Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97; mol. wt., 312. Found: C, 65.23; H, 5.36; N, 8.89; mol. wt. (cryoscopic in benzophenone), 306.

2-(3-Nitromesityl)-2-phenylvinylamine (VII).—A mixture of 5 g. of 2-(3-nitromesityl)-2-phenyl-1-nitroethylene (VI), 100 cc. of ethyl acetate and 0.1 g. of platinum oxide catalyst was shaken in an atmosphere of hydrogen. Hydrogen was absorbed rapidly. After thirty minutes the mixture was filtered to remove the catalyst and the solvent was evaporated by a stream of air. The orange residue was recrystallized from ethanol; m. p. 100–101°; yield 4 g.

Anal. Calcd. for $C_{17}H_{18}N_2O_2$: C, 72.32; H, 6.43; N, 9.92; mol. wt., 280. Found: C, 72.42; H, 6.30; N, 10.03; mol. wt. (cryoscopic in benzophenone), 290.

The **acetyl derivative** was formed by heating a mixture of the amine (VII) (1 g.) with acetic anhydride (5 cc.) under reflux for fifteen minutes. It separated from ethanol in pale yellow crystals; m. p. 199–200°.

Anal. Calcd. for $C_{19}H_{20}N_2O_3$: C, 70.35; H, 6.23; N, 8.64. Found: C, 70.45; H, 6.24; N, 8.67.

The **benzoyl derivative** was produced by shaking 0.5 g. of the amine (VII) with 1 cc. of benzoyl chloride and 5 cc. of 10% sodium hydroxide for ten minutes. The mixture was poured into water and the product was purified by recrystallization from ethanol. It formed pale yellow crystals melting at 143–144°.

Anal. Calcd. for $C_{24}H_{22}N_2O_3$: C, 74.59; H, 5.74; N, 7.25. Found: C, 74.60; H, 5.96; N, 7.19.

2,2′-Di-(3-aminomesityl)-2,2′-diphenylvinylamine (IX).—A mixture of 5 g. of 2-phenyl-2-(3-nitromesityl)-1-nitroethylene (VI), 250 cc. of absolute ethanol, 25 g. of hydrated stannous chloride and 25 cc. of concentrated hydrochloric acid was heated gradually at first and finally under reflux, for six hours. The product was the divinylamine, IX. It was recrystallized from 95% ethanol. It rapidly turned blue when allowed to stand in the air. In the pure state it had a light cream color; m. p. 184–186°.

Anal. Calcd. for $C_{34}H_{37}N_3$: C, 83.73; H, 7.65; N, 8.62; mol. wt., 488. Found: C, 83.86; H, 7.65, 7.50; N, 8.78; mol. wt. (cryoscopic in benzophenone), 489.

The divinylamine (IX) was obtained also by the reduction of the nitro amine (VII). A mixture of 2 g. of the amine, 100 cc. of absolute ethanol, 8 g. of hydrated stannous chloride and 10 cc. of concentrated hydrochloric acid was heated for eight hours under reflux. The amine was isolated in the usual manner; m. p. 184–186°.

The divinylamine was produced also by reduction of 2,2′-di-(3-nitromesityl)-2,2′-diphenyldivinylamine (VIII). The procedure was similar to that just described for reducing the mononitro amine (VII); m. p. 184–186°.

(15) This compound was prepared by Dr. Norman Rabjohn.

(16) Fuson, Denton and Best, *J. Org. Chem.*, **8**, 64 (1943).

2,2′-Di-(3-nitromesityl)-2,2′-diphenyldivinylamine (XIII).—When 5 g. of 2-(3-nitromesityl)-2-phenylvinylamine (VII) was dissolved in 95% ethanol and 10 cc. of 6 *N* hydrochloric acid was added, the divinylamine (VIII) separated from the solution as a yellow solid. It was recrystallized from glacial acetic acid; m. p. 235–236°.

Anal. Calcd. for $C_{34}H_{33}N_3O_4$: C, 74.56; H, 6.07; N, 7.67; mol. wt., 548. Found: C, 74.75; H, 6.16; N, 7.77; mol. wt. (cryoscopic in benzophenone), 582.

Treatment of this amine with a hot mixture of concentrated hydrochloric acid and glacial acetic acid produced no change.

1-Isoduryl-1-phenylethylene.—The condensation of benzoylisodurene with methylmagnesium iodide, carried out in the manner described for that of the mesityl analog, produced 1-isoduryl-1-phenylethylene as a yellow oil boiling at 152–154° (3 mm.); $n^{20}D$ 1.5872; d_4^{20} 1.000; yield 42%.

Anal. Calcd. for $C_{18}H_{20}$: C, 91.47; H, 8.53; *MR*, 77.7. Found: C, 91.31; H, 8.35; *MR*, 79.2.

The same compound was obtained, in 10% yield, by the condensation of acetophenone with isodurylmagnesium bromide; b. p. 156–157° (4 mm.); $n^{20}D$ 1.5864. This olefin decolorized an acetone solution of potassium permanganate. It was readily attacked by chromic acid in acetic acid.

A by-product of the reaction between methylmagnesium iodide and benzoylisodurene was a red-orange solid. After repeated recrystallization from absolute ethanol, it melted at 191–192.5°. The yield in grams was about the same as that of the olefin.

Anal. Calcd. for $C_{34}H_{38}O_2$: C, 85.31; H, 8.00; mol. wt., 478. Found: C, 85.80; H, 8.17; mol. wt. (ebullioscopic in chloroform), 457.

This compound did not reduce neutral potassium permanganate solution; it reacted slowly with bromine in carbon tetrachloride, with the evolution of hydrogen bromide. It was treated with acetyl chloride, but no derivative could be isolated.

Three grams of the olefin was treated with hydrogen at 50° and 2000 lb. pressure in the presence of Raney nickel. The product, 1-isoduryl-1-phenylethane, boiled at 160° (5 mm.); $n^{20}D$ 1.5695; d_4^{20} 0.990; m. p. 54.5–55°.

Anal. Calcd. for $C_{18}H_{22}$: C, 90.69; H, 9.31; *MR*, 78.4. Found: C, 90.78; H, 9.54; *MR*, 78.9.

2-(3-Nitroisoduryl)-2-phenyl-1,1-dinitroethylene (X).—1-Isoduryl-1-phenylethylene was nitrated in a manner similar to that described for mesitylphenylethylene except that the nitration mixture was allowed to stand for two days at room temperature. The trinitro derivative separated from ethanol in pale yellow crystals; m. p. 193–194°.

Anal. Calcd. for $C_{18}H_{17}N_3O_6$: C, 58.22; H, 4.62; N, 11.29. Found: C, 58.00; H, 4.84; N, 11.15.

1-Mesityl-1-(*p*-tolyl)-ethylene.—To prepare this olefin methylmagnesium iodide was condensed with *p*-toluylmesitylene by a procedure similar to that used to make the corresponding mesitylphenylethylene. The product was difficult to purify, being contaminated in all probability with the ketone. Nitration, however, produced a satisfactory sample of the dinitro derivative (IX).

2-(3-Nitromesityl)-2-*p*-tolyl-1-nitroethylene (IX).—This compound was prepared from 1-mesityl-1-*p*-tolylethylene by a procedure similar to that described for the phenyl derivative. The gummy residue solidified only after several weeks. It separated from ethanol in yellow crystals; m. p. 174–175°.

Anal. Calcd. for $C_{18}H_{18}N_2O_4$: C, 66.24; H, 5.56; N, 8.59. Found: C, 65.88; H, 5.47; N, 8.75.

Summary

It has been shown that methylmagnesium iodide condenses in the 1,2 manner with benzoylmesitylene, benzoylisodurene and *p*-toluylmesitylene.

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The product in each case is not the expected carbinol, but the olefin that would be formed from it by dehydration. The yields of 1-mesityl-1-phenylethylene and of 1-isoduryl-1-phenylethylene were 64 and 42%, respectively.

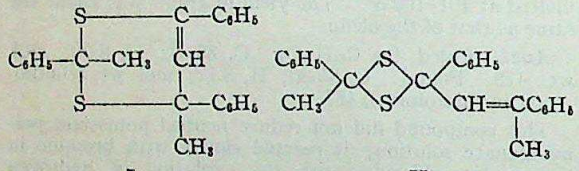
URBANA, ILLINOIS RECEIVED FEBRUARY 9, 1944

[CONTRIBUTION FROM THE M. D. ANDERSON HOSPITAL FOR CANCER RESEARCH, AND THE DEPARTMENT OF PREVENTIVE MEDICINE AND PUBLIC HEALTH OF THE UNIVERSITY OF TEXAS MEDICAL BRANCH]

The Synthesis of 2,4-Diarylthiophenes[1]

BY E. CAMPAIGNE

Baumann and Fromm,[2] while investigating thioacetophenone, reported the isolation of a compound, $C_{24}H_{22}S_2$, in good yield from the alcoholic mother liquors of the thioacetophenone preparation. Pyrolysis of this disulfide gave 2,4-diphenylthiophene but no yield was reported. On the basis of analysis and the formation of 2,4-diphenylthiophene, two possible structures were assigned to this compound, which they called "Anhydroacetophenone disulfide"

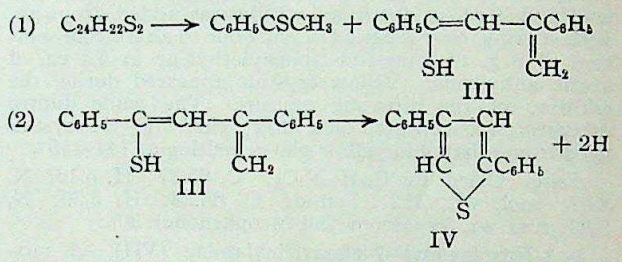


I II

Structure I was assumed to be the most probable, since dithioacetophenone had never been isolated.

The synthesis of 2,4-diarylthiophenes has been reviewed by Bogert and Herrera.[3] These compounds are usually prepared by the reaction of phenylethylene or its derivatives with sulfur. This type of reaction gives a possibility of three different isomers, and consequently the yields have been extremely low. Bogert and Herrera[3] reported that by fusing acetophenone anil with sulfur, 2,4-diphenylthiophene was obtained in 28% yield. No 2,5-diphenylthiophene was found. These authors suggest that the formation of thioacetophenone as an intermediate accounts for the higher yield and lack of formation of 2,5-diphenylthiophene. However, Baumann and Fromm[2] reported the isolation of both 2,4- and 2,5-diphenylthiophene from the pyrolysis of thioacetophenone.

It seemed most probable that if either structure, (I) or (II), of "Anhydroacetophenone disulfide" given by Baumann and Fromm[2] were correct, highest yields of pure compounds could be obtained through this intermediate, since only 2,4-diarylthiophene, (IV), could be formed, according to the equations



III IV

The hypothetical compound III forms 2,4-diphenylthiophene by the loss of two atoms of hydrogen. In the pyrolysis of "Anhydroacetophenone disulfide" apparently acetophenone acts as the hydrogen acceptor, since in addition to the diarylthiophene, styrene and hydrogen sulfide were isolated.[2]

Several experiments were conducted to determine the yield of 2,4-diphenylthiophene from "Anhydroacetophenone disulfide." Pyrolysis of the material at 180° gave a tarry residue from which it was only possible to obtain sufficient pure 2,4-diphenylthiophene for identification. Refluxing the compound for several hours in boiling xylene caused a color change from colorless to deep purple. This would be expected, since the compound is unstable above its melting point, decomposing to give the highly colored thioketone monomers. No diarylthiophene could be isolated from this reaction, but the oily residue contained unsaturated carbon linkages. Apparently the reaction represented by the second equation does not take place readily. When this mixture was treated with copper chromite catalyst, IV was obtained in 83% yield. This reaction might be expected, since this catalyst has been used in the dehydrogenation of alcohols.[4]

A similar experiment with the "Anhydrodisulfide," V, prepared from *p*-methoxypropiophenone gave a 66% yield of 2,4-di-*p*-anisyl-3,5-dimethylthiophene, VI. This reaction was shown to proceed in two steps, as indicated by equations 1 and 2, as follows: the "Anhydrodisulfide" V, was refluxed in xylene, causing decomposition to an unsaturated oil. No thiophene derivative was formed by this treatment. However, when this residual oil was refluxed in alcohol with copper chromite, the dianisylthiophene, VI, was formed in good yield. "Anhydro-*p*-methoxypropiophenone disulfide," V, was not changed by re-

(1) Presented before the Organic Division at the 106th meeting of the American Chemical Society in Pittsburgh, Pa., September, 1943.

(2) Baumann and Fromm, *Ber.*, **28**, 895 (1895).

(3) Bogert and Herrera, THIS JOURNAL, **45**, 238 (1923).

(4) Jenkins, British Patent 301,896; *C. A.*, **23**, 4306 (1929).

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fluxing in alcohol alone, or with copper chromite. Therefore, it seems probable that the first step in the reaction is not influenced by copper chromite, but only occurs at high temperatures, near the melting point of the "anhydro-disulfide." The temperature necessary to initiate the second step is dependent on the efficiency of the hydrogen acceptor, because at the temperature of refluxing alcohol copper chromite is active, while it was necessary to heat the compound above 180° for thioacetophenone to be active.

Since compound VI theoretically has no active hydrogens, the usual derivatives were not formed. However, the compound was sufficiently stable, so that the ether linkages could be hydrolyzed to give a di-*p*-hydroxy compound, which was acetylated to the diacetate. In addition to analysis of its derivatives, the identity of the new compound was further clarified by comparison of its ultraviolet absorption curve with that of IV, 2,4-diphenylthiophene. The absorption curves were taken in methanol solutions, using a Hilger Model E-498 spectrograph and a Spekker Photometer. The solutions were approximately 5×10^{-5} molar, and the cell thickness was 1 cm. The molar extinction coefficient, E, is plotted against the wave length in Fig. 1. It is apparent that the new compound VI, Curve II, and 2,4-diphenylthiophene, IV, Curve I, are very similar in structure, since both show maximum absorption at 250, 265 and 280 millimicrons.

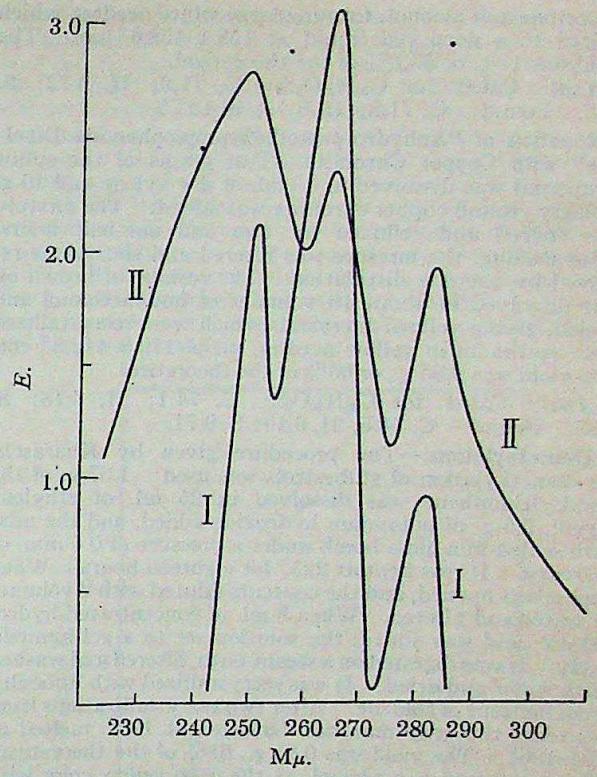

Fig. 1.—Absorption curves taken in methanol of: I, 2,4-diphenylthiophene, and II, 2,4-di-*p*-anisyl-3,5-dimethylthiophene.

Experimental

Preparation of "Anhydroacetophenone Disulfide."—Forty grams of acetophenone was dissolved in 300 ml. of absolute alcohol, and cooled to 0° in an ice–salt bath. Dry hydrogen chloride was passed in for a few minutes, until the rate of gas influx could be regulated, and then hydrogen sulfide also was passed in at a slow rate. Approximately 140 g. of dry hydrogen chloride (the amount calculated to saturate the alcohol) was passed into the solution over a period of six hours. During this time the reaction flask was kept in the ice–salt bath. When all the hydrogen chloride was used, the bath was allowed to come to room temperature while hydrogen sulfide was passed continuously into the flask for eight hours longer. About three hours after starting white crystals began to form in the flask, and a purple resin precipitated. After fourteen hours, the gas-inlet tubes were removed, and the flask was stored in the refrigerator overnight. The white crystals were stirred up and filtered from the mother liquor, leaving the purple resin of thioacetophenone in the flask. The crystals of "Anhydroacetophenone disulfide" were washed once with alcohol and dried. The crude product melted from 106–109°. The yield was 23.5 g. or 57% of theoretical. After two recrystallizations from acetone, the product was obtained in white hexagonal bars, m. p. 107–108° cor.

Anal.[5] Calcd. for $C_{24}H_{22}S_2$: C, 77.00; H, 5.88; S, 17.11. Found: C, 77.04; H, 5.64; S, 17.09.

Reaction of "Anhydroacetophenone Disulfide" with Copper Chromite.—The copper chromite catalyst was prepared according to the directions of Lazier and Arnold.[6] It was finely ground in a mortar before use. Three grams of the sulfur compound was dissolved in 35 ml. of dry xylene, and 10 g. of the copper chromite powder was added. The mixture was brought to reflux and stirred. No hydrogen sulfide was evolved during the course of three hours. At the end of this time the mixture was cooled and filtered. The residual catalyst was washed thoroughly with xylene, and the combined washings and filtrate distilled under water-pump vacuum to remove xylene. The brown residue solidified on cooling. It was dissolved in about 80 ml. of boiling methanol, and treated with norite. Upon cooling, white flaky crystals deposited. These were recrystallized from methanol, and dried. The melting point was 120.6–121.5° cor. The yield was 1.58 g., 83% of theoretical.

Anal. Calcd. for $C_{16}H_{12}S$: C, 81.31; H, 5.08; S, 13.56. Found: C, 81.24; H, 4.89; S, 13.53.

This compound has a reactive hydrogen at position 5, and readily forms a picrate in bright red needles, m. p. 133.1–133.6° cor. Fromm and Fantl[7] give the melting point of the picrate of 2,4-diphenylthiophene as 133–134°. It also gives the 5-chloromercuri- derivative with alcoholic mercuric chloride, white needles, m. p. 222–223° corresponding to the 5-chloromercuri-2,4-diphenylthiophene obtained by Bogert and Herrera.[3]

Preparation of "Anhydro-*p*-methoxypropiophenone Disulfide."—Twenty grams of *p*-methoxypropiophenone, b. p. 124–128° (4 mm.), (from anisole and propionic anhydride with aluminum chloride[8]) was dissolved in 120 ml. of absolute alcohol, and hydrogen chloride and hydrogen sulfide passed in at 0° as in the previous preparation. Approximately 50 g. of dry hydrogen chloride was used. The reaction was allowed to continue for twelve hours. The solution became deep red in color, due to *p*-methoxythiopropiophenone. As the reaction proceeded, white needle-like crystals precipitated. After storing in the refrigerator overnight, the precipitate was filtered off. The red color had faded to a faint pink by this time. The precipitate was recrystallized from a mixture of equal parts

(5) All analyses are by Mr. H. Morris of this Laboratory.

(6) Lazier and Arnold in Blatt, "Organic Syntheses," Collective Volume II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 142.

(7) Fromm and Fantl, *Ann.*, **457**, 267 (1927).

(8) Noller and Adams, THIS JOURNAL, **46**, 1889 (1924).

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of acetone and alcohol, forming large white needles, which melted to a deep red liquid at 158.1–158.6° cor. The yield was 11 g. or 53.5% of the theoretical.

Anal. Calcd. for $C_{30}H_{34}O_3S_2$: C, 71.2; H, 6.72; S, 12.6. Found: C, 71.8; H, 6.41; S, 12.75.

Reaction of "Anhydro-*p*-methoxypropiophenone Disulfide" with Copper Chromite.—Two grams of the sulfur compound was dissolved in 40 ml. of dry xylene and 10 g. of finely ground copper chromite was added. The mixture was stirred and refluxed for two and one-half hours. After cooling, the mixture was filtered and the xylene removed by vacuum distillation. The residue of brown oil was dissolved in about 10 volumes of hot methanol and cooled, giving yellowish crystals which were recrystallized from methanol in yellow needles, m. p. 112.3–112.8° cor. The yield was 0.85 g., or 66% of the theoretical.

Anal. Calcd. for $C_{29}H_{30}O_2S$: C, 74.1; H, 6.18; S, 9.87. Found: C, 74.5; H, 6.19; S, 9.71.

Demethylation.—The procedure given by Kharasch[9] for demethylation of stilbestrols was used: 1.07 g. of the dianisylthiophene was dissolved in 25 ml. of ethylene glycol, 2.5 g. of potassium hydroxide added, and the mixture sealed in a glass bomb under a pressure of 0.5 mm. of mercury. It was kept at 225° for eighteen hours. When cool it was opened, and the contents diluted with 2 volumes of water and filtered. When 8 ml. of concentrated hydrochloric acid was added, the solution set to a gel immediately. It was digested on a steam-bath, filtered and washed with water and dried. It was recrystallized with difficulty from benzene or toluene. After two recrystallizations from benzene, the gray material darkened at 185°, melted at 194–196°. The yield was 0.61 g., 61% of the theoretical. The compound is a phenol, as the deep yellow color with ferric chloride and the solubility in base indicate.

Anal. Calcd. for $C_{18}H_{16}O_2S$: C, 73.0; H, 5.41; S, 10.81. Found: C, 72.5; H, 5.37; S, 10.83.

Acetylation.—The 2,4-di-*p*-hydroxyphenyl-3,5-dimethylthiophene was readily acetylated by heating 0.1 g. with 0.1 g. of fused sodium acetate in 2.5 ml. of acetic anhydride on a steam-bath for one hour. The mixture was then poured over ice and stirred until the oil had solidified. The amorphous solid was centrifuged out and recrystallized three times from ethyl alcohol, giving fine white needles of the diacetate, which softened at 121°, but melted at 125.9–126.9° cor.

Anal. Calcd. for $C_{22}H_{20}O_4S$: C, 69.5; H, 5.26; S, 8.42. Found: C, 69.7; H, 5.29; S, 8.25.

Formation of the Thiophene in Two Steps.—Approximately 2 g. of "Anhydro-*p*-methoxypropiophenone disulfide" was refluxed in 30 ml. of xylene for three hours. The solution became deep purple in color. The xylene was distilled off under vacuum, and the residual brown oil was taken up in ethanol and stored in the refrigerator. No crystals were obtained in twenty-four hours, although both 2,4-di-*p*-anisyl-3,5-dimethylthiophene and "anhydro-*p*-methoxypropiophenone disulfide" are readily crystallized from alcohol. A few drops of the alcohol solution decolorized an acetone solution of potassium permanganate, indicating unsaturation. The alcohol solution was refluxed for two hours with copper chromite. Upon cooling the filtered alcohol solution, yellow needles were obtained, m. p. 112–113.5°. Mixed with 2,4-di-*p*-anisyl-3,5-dimethylthiophene, the melting point was 112–113°.

(9) Kharasch and Kleiman, THIS JOURNAL, **65**, 11 (1943).

Summary

A new method for the synthesis of 2,4-diarylthiophenes, in yields of 65 to 85% based on the reaction of "anhydroketone disulfides" with copper chromite, is described.

The mechanism of this reaction is discussed.

Four new compounds, "Anhydro-*p*-methoxypropiophenone disulfide," 2,4-di-*p*-hydroxyphenyl-3,5-dimethylthiophene, and its dimethyl ether and diacetate, are characterized.

BLOOMINGTON, INDIANA RECEIVED JANUARY 31, 1944

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Acetylenic Ethers. IV.[1] Hydration

BY THOMAS L. JACOBS AND SCOTT SEARLES, JR.

It has been shown[2] that acetylenic ethers add water more rapidly than vinyl ethers but less rapidly than ketene acetals. The hydration is acid catalyzed and the rate has been followed quantitatively for several vinyl ethers.[3,4,5] It was of interest to carry out similar experiments with several acetylenic ethers for comparison.

Experimental

A dilatometric method was used to follow the hydration because it has been employed successfully to study the vinyl ethers[3,4,5] and because methods of analysis for acetylenic hydrogen or for the unsaturation of the triple bond are relatively inexact and have not been applied with success to acetylenic ethers. Butyl acetate was isolated[2] in 67% yield by heating butoxyacetylene with distilled water. In dilute solutions containing traces of acid this hydration is the only significant reaction; both the polymerization of the acetylenic ether and the hydrolysis of the ester are slow enough to be neglected. In aqueous alcohol the reaction is accompanied by marked volume contraction. The concentrations of the solutions studied were 0.025 to 0.03 molar.

The acetylenic ethers used in this work were carefully refractionated samples.[2,6] The ethoxyacetylene may have contained a little water and traces of water may have been introduced into all the ethers when samples were being sealed in small bulbs since for this operation the bulbs were embedded in dry-ice and open to the air.

The dilatometer was similar to that described by Leutner[7] and used to study the hydration of vinyl ethers.[3,4,5] The measuring bulb had a volume of 110 ml. and the capillary was 25 cm. long, had a diameter of 0.36 mm. and was uniform within 1% over the calibrated portion.

The acetylenic ethers are not very soluble in water and

(1) For the third paper of this series see Jacobs and Whitcher, THIS JOURNAL, **64**, 2635 (1942).

(2) Jacobs, Cramer and Hanson, *ibid.*, **64**, 223 (1942).

(3) A. Skrabal and R. Skrabal, *Z. physik. Chem.*, **181A**, 449 (1938).

(4) R. Skrabal, *ibid.*, **185A**, 81 (1939).

(5) Zahorka and Wiemann, *Monatsh.*, **71**, 229 (1938).

(6) Jacobs, Cramer and Weiss, THIS JOURNAL, **62**, 1849 (1940). The ethoxyacetylene was prepared by Mr. John E. Hanson and Mr. Elbert Davis. The phenoxyacetylene was prepared by Mr. William Penn Tuttle, Jr.

(7) Leutner, *Monatsh.*, **65**, 222 (1935).

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measurements were made in 12.5 and 42.7% by weight alcohol and water.[8] The rate of hydration of ethoxyacetylene and butoxyacetylene was followed most accurately and conveniently at *p*H 6 to 7. The solutions were weakly buffered and the acetylenic ethers were dissolved by crushing the bulbs containing the samples under a known amount of the solvent containing the basic portion of the buffer. This solution was transferred to the mixing chamber of the dilatometer in the thermostat and stirred until the temperature was constant. A dilute, thermostated solution of the acidic portion of the buffer was then transferred to the mixing chamber and the solution stirred and forced several times into the measuring chamber and back. The measuring chamber was finally filled to the desired capillary height using mercury to seal the stopcock as described by Leutner[7] and readings were taken at regular intervals.

The hydration of phenoxyacetylene was followed conveniently at *p*H 2; hydrochloric acid was used and the solution was not buffered.

It was necessary to allow considerable time for thermostatting after the sample bulbs were broken because the heats of solution of acetylenic ethers in aqueous alcohol are rather large. When a bulb containing 0.151 g. of ethoxyacetylene was broken in 140 ml. of 12.5% alcohol (*p*H 7.4) at 24.8° in a Dewar flask the temperature drop was 0.120°. Using a value of 1.026 cal. per g. degree as the specific heat of the solvent[9] and neglecting the heat capacity of the Dewar flask, the heat of solution of one mole of ethoxyacetylene in 64.9 liters of 12.5% alcohol is −7.9 kcal.

Measurements were carried out at 25.0° in a thermostat controlled by a large mercury regulator. The maximum temperature variation during a run was 0.003° and in some experiments it was as little as 0.001°. It was not possible to correct the capillary reading accurately for temperature variations since the changes were not synchronous. A preferable procedure is to use the readings of a second dilatometer containing only the solvent to correct the measurements.[10] Due to the war, it was not possible to obtain more of the capillary tubing of the correct size to construct another dilatometer. In 12.5% alcohol when the temperature changes were random and fairly rapid a variation of 0.001° altered the capillary height 0.05 to 0.1 mm. and the maximum effect on the capillary reading lagged behind the temperature change by 0.1 to 0.8 minute. Any sustained shift in the temperature altered the reading 3 or 4 times as much. In 42.7% alcohol the capillary reading varied 4 or 5 times as much as in 12.5% alcohol and the rate constants are correspondingly less reliable. However, the volume changes which occur with acetylenic ethers during hydration are larger than with vinyl ethers. The dilatometer capillary in work with the latter[3,4,5] had a diameter of only 0.05 mm.

The *p*H's of the solution were measured with a Model G Beckmann *p*H meter which makes use of a glass electrode. Dole[11] reported that in dilute alcohol there is practically no error in the voltage of the glass electrode and this was found to be true for 12.5% alcohol solutions. In solutions containing more alcohol there is an error depending upon the amount of alcohol present[11] and in addition the electrode is somewhat erratic.[12] The readings were found to be unreliable if the instrument was used in alcohol solution continuously for fifteen minutes or longer, but such treatment did no damage to the electrode, for correct values were obtained on standard aqueous buffers immediately after such erratic behavior in alcohol. Figure 1 gives the relationship between *p*H readings of hydrochloric acid solutions in 42.7% ethanol and the log $1/H_3O^+$ of identical concentrations of the same acid in water. The graphical mean of the deviations is 0.16 *p*H unit with a possible variation of 0.05 *p*H unit. Such a variation corresponds to an uncertainty in the hydrogen ion concentration of ±12%. This is present only in the rate determinations on ethoxy- and butoxyacetylene in 42.7% alcohol, since with phenoxyacetylene, the hydrochloric acid concentrations were known accurately.

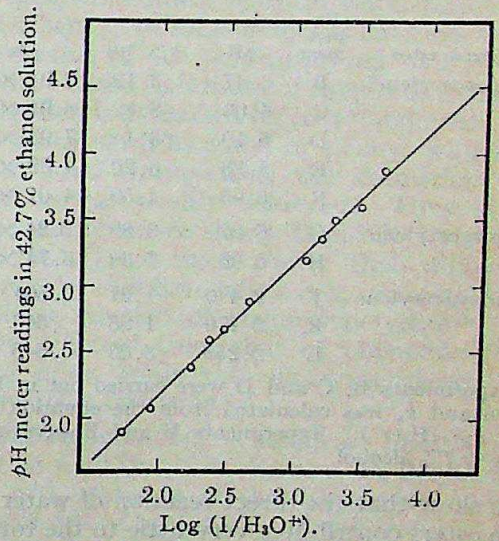

Fig. 1.—The relationship between *p*H readings in 42.7% ethanol solutions and log $(1/H_3O^+)$ in water solutions of identical concentration.

Either phosphate or acetate buffers were used with the alkoxyacetylenes and the exact concentrations of the salts were not known. In the phosphate buffers the concentration of disodium acid phosphate was approximately 1×10^{-4} *M* and of monosodium acid phosphate 1 to 2.5×10^{-3} *M*. This corresponds to an ionic strength of 1.3 to 2.8×10^{-3} *M*. The concentration of sodium acetate in the acetate buffer was approximately 4.5×10^{-3} *M* and of acetic acid 1.5 to 3×10^{-3} *M*.

Calculations, Results and Discussion

The hydration was found to be first order with respect to acetylenic ether and to hydronium ion. Since the latter acts as a catalyst only, the rate law at any given *p*H was $-dc/dt = kc$. The equation may, therefore, be written in its integrated form as

$$\log \frac{(h_\infty - h)}{(h_\infty - h_0)} = -\frac{kt}{2.3}$$

where h_0, h_∞ and h are the capillary readings at the beginning and end of the reaction and at time t. The specific rate constant, k, was evaluated graphically by plotting log $(h_\infty - h)$ against t in minutes and determining the slope of the curve. Accurate experimental values of h_∞ were not obtained due to the difficulty of maintaining a constant temperature for a sufficiently long period of time, but by a trial and error method an empirical h_∞ was chosen which gave most nearly a straight

(8) Dilute alcohol was chosen as the solvent because it was used by Skrabal[3] in his studies of the vinyl ethers. The 12.5% by weight ethanol was prepared conveniently by mixing 800 ml. of distilled water and 150 ml. of the azeotropic mixture of water and ethanol which is 95.57% by weight ethanol. The ethanol was a carefully refractionated sample. The 42.7% by weight ethanol was prepared by mixing equal volumes of water and 95.57% ethanol. Only ethoxyacetylene was sufficiently soluble to be studied in the more dilute alcohol.

(9) "International Critical Tables," McGraw-Hill Book Co., New York, N. Y., 1929, Vol. 5, p. 116.

(10) Palomaa, Salmi and Suoja, *Ber.*, **72**, 313 (1939).

(11) Dole, THIS JOURNAL, **54**, 3095 (1932).

(12) Dole, "The Glass Electrode," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 145.

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line. The method of Guggenheim[13] which eliminates h_∞ was also applied to the data. The points did not fall as accurately on a straight line as in the first method since random errors in the individual readings are magnified. However, the rate constants as determined by the two methods always agreed within 2%. Table I summarizes the results and Fig. 2 gives the experimental curves from which the values of k were obtained for runs C, E, H, and K. The other runs give equally good lines.

TABLE I

Acetylenic ether	Experiment	pH	$k \times 10^2$	k_a
Ethoxyacetylene[a]	B	6.47	3.12	8.91×10^3
	C	6.03	8.42	8.91×10^3
	D	5.10	63.1	7.93×10^3
	E	5.85	6.20	4.39×10^3
	F	5.95	4.50	4.01×10^3
Butoxyacetylene	G	6.27	3.89	7.24×10^3
	H	5.96	7.39	6.74×10^3
Phenoxyacetylene	J	2.470	1.91	0.564
	K	2.470	1.85	.546
	L	2.255	3.03	.545

[a] Experiments B, C and D were carried out in 12.5% alcohol and k_a was calculated from the equation $k_a = (k - k_w)/(H_3O^+)$. Experiments E and F were carried out in 42.7% alcohol.

To show that the direct reaction of water with these esters contributes very little to the total reaction rate one experiment was carried out on ethoxyacetylene in 12.5% alcohol at pH 8.97. The reaction was less than a third complete in sixty hours and the determination was much less accurate than experiments in acid solution. From the slope of the curve, k was found to be 1.1×10^{-4}. This represents the sum of the rate constant of acid catalyzed hydration, $k_a(H_3O^+)$ and the rate constant of hydration by water, k_w. Since $k_a = 9 \times 10^3$ and $(H_3O^+) = 1.1 \times 10^{-9}$, $k_w = 1.0 \times 10^{-4}$. The hydration by water should be independent of the acid concentration and k_w was therefore subtracted from k in the calculation of k_a for experiments in 12.5% ethanol (Experiments B, C, and D). The value of k_w in 42.7% alcohol was not determined because it was less than in 12.5% alcohol and the variations of capillary reading with temperature were so large.

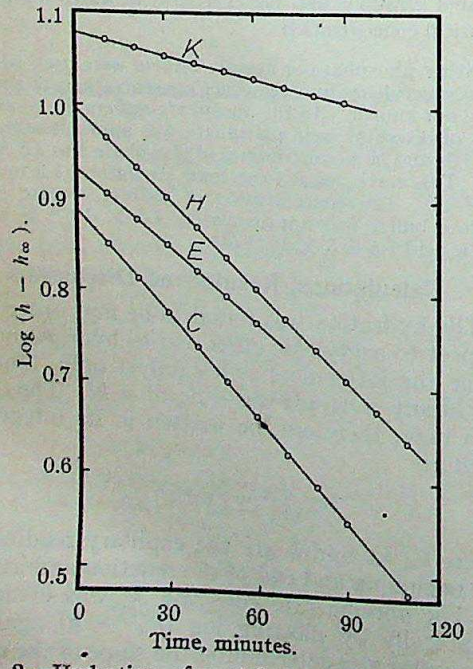

Fig. 2.—Hydration of acetylenic ethers at 25°: C, ethoxyacetylene in 12.5% ethanol; E, ethoxyacetylene in 42.7% ethanol; H, butoxyacetylene in 42.7% ethanol; K, phenoxyacetylene in 42.7% ethanol.

The hydrolysis of saturated ethers is believed to proceed through an oxonium intermediate of the type $[RO(H)R]^+$ and cleavage of one of the alkyl-oxygen bonds.[14,15] A. Skrabal[16] and R. Skrabal[4] have formulated the reaction mathematically to permit calculation of the rates of hydrolysis of unsymmetrical ethers from the rates of symmetrical ones. This treatment does not hold for vinyl ethers and R. Skrabal[4] believed that this was due to a different mechanism of hydrolysis, probably the addition of water to the double bond of the vinyl group as Paul[17] suggested earlier. No direct evidence for this addition could be obtained because the hemiacetal produced is hydrolyzed more rapidly than the vinyl compound.[16] The hydrolysis of ethynyl ethers appears to be similar to that of vinyl ethers, but in this case the compound obtained by the addition of water to the triple bond is the enol form of an ester. This rearranges to the ester which hydrolyzes very much less rapidly than the acetylenic ether.[18] A mechanism which is consistent with the observed kinetics may be formulated as follows

(1) $ROC{\equiv}CH + H_3O^+ \longrightarrow (ROC{=}CH_2)^+ + H_2O$

(2) $(ROC{=}CH_2)^+ + H_2O \longrightarrow (ROC(OH_2){=}CH_2)^+$

(3) $(ROC(OH_2){=}CH_2)^+ + H_2O \longrightarrow ROC(OH){=}CH_2 + H_3O^+$

(13) Guggenheim, *Phil. Mag.*, [7] **2**, 538 (1926).

(14) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 299.

(15) Bonhoeffer and Reitz, *Z. physik. Chem.*, **179A**, 135 (1937).

(16) A. Skrabal, *Ber.*, **72**, 446 (1939).

(17) Paul, *Bull. soc. chim.*, [5] **1**, 971 (1934).

(18) The rate constant, k_a, for the acid catalyzed hydrolysis of ethyl acetate in water at 25° is 6.5×10^{-3} min.$^{-1}$ moles^{-1} liters [Dawson and Lowson, *J. Chem. Soc.*, 2146 (1928)] and the constant for the reaction with base in water at 25° is 6.76 min.$^{-1}$ moles^{-1} liter [Terry and Stieglitz, THIS JOURNAL, **49**, 2216 (1927)]. It has been shown by Caudri [*Rec. trav. chim.*, **48**, 422 (1929)] that in aqueous alcohol the rate constant for the reaction with base decreases as the amount of alcohol increases (in 10% and 20% alcohol by volume k has values of 6.23 and 5.70, respectively, compared with a value of 6.54 which he obtained in water). At a pH of 6 the pseudo first order rate constant for the over-all hydrolysis in water is 7.4×10^{-8} min.$^{-1}$. This is negligible compared with the pseudo first order rate constant of 8.7×10^{-3} for ethoxyacetylene at pH 6 in 12.5% alcohol at 25°.

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(4) $ROC(OH)=CH_2 \longrightarrow ROC(=O)-CH_3$

The first step involves the transfer of a proton to the β-carbon atom and is probably the same as the first step in the acid catalyzed hydration of an ordinary ethylenic bond,[19] a reaction which shows the same kinetics and for which hydronium ion appears to be the only acid with an appreciable effect on the rate. This specific acid catalysis seems to hold for the acetylenic ethers as well since the values of k_a obtained from different runs on the same compound by dividing k by the hydronium ion concentration are the same even when the concentration of other acids such as dihydrogen phosphate ion or acetic acid are varied several fold. The question of the rate determining step remains open. An alternative mechanism which may be important in 42.7% alcohol involves the formation of a ketene acetal. This would be converted

(2) $(ROC=CH_2)^+ + C_2H_5OH \longrightarrow$

$$\left(\begin{array}{l} RO \\ C_2H_5O-C=CH_2 \\ \quad | \\ \quad H \end{array}\right)^+$$

(3)

$$\left(\begin{array}{l} RO \\ C_2H_5O \end{array}\!\!>\!C=CH_2 \right)^+ + H_2O \longrightarrow$$

$$\begin{array}{l} RO \\ C_2H_5O \end{array}\!\!>\!C=CH_2 + H_3O^+$$

rapidly to the ester, possibly to some extent through the ortho ester.

Table II lists the average values of k_a for vinyl and ethynyl ethers, for diethyl ether and for two olefins.

TABLE II

RATE CONSTANTS FOR ACID CATALYZED HYDRATIONS OR HYDROLYSES AT 25°

Compound	k_a (min.$^{-1}$, moles^{-1} l.)	Solvent
Diethyl ether[3]	1.46×10^{-11}	Water
Ethyl vinyl ether[5]	1.73×10^{2}	Water
Isopropyl vinyl ether[4]	5.20×10^{2}	Water
Divinyl ether[3]	5.0×10^{-1}	Water
	2.9×10^{-1}	25% alc. (by vol.)
Ethoxyacetylene	8.6×10^{3}	12.5% alc. (by wt.)
	4.2×10^{3}	42.7% alc. (by wt.)
Butoxyacetylene	7.0×10^{3}	42.7% alc. (by wt.)
Phenoxyacetylene	5.5×10^{-1}	42.7% alc. (by wt.)
Isobutylene[19]	2.3×10^{-2}[a]	Water
Trimethylethylene[19]	1.3×10^{-2}[a]	Water

[a] These are the values for k_a at an ionic strength of 0.05 N. For isobutylene the extrapolated value at zero ionic strength is 2.2×10^{-2} (min.$^{-1}$, moles^{-1}, l.).

All of the differences in rate constants are in the directions expected if step (1) is rate determining. Vinyl ethers hydrate more rapidly than alkenes because of the extra stabilization due to resonance in the intermediate onium ion and hence in the transition state as well. The effect is larger when

(1) $ROCH=CH_2 + H_3O^+ \longrightarrow$

$$\left\{\begin{array}{l} R-O-\overset{+}{C}H-CH_3 \\ R-\overset{+}{O}=CH-CH_3 \end{array}\right\} + H_2O$$

the double bond is replaced by a triple bond since the ability of the latter to take part in such resonance is greater.[20] This does not permit a direct prediction of the relative rates of hydration of ethynyl and vinyl ethers, but only of the former relative to alkynes; however it is not surprising that acetylenic ethers hydrate more readily than vinyl ethers. No measurements have been made of the rates of the acid-catalyzed hydration of alkynes. When the ability of oxygen to enter such conjugation is decreased by its attachment to another group such as vinyl or phenyl which permits crossed conjugation, the transition state would be less readily achieved. Thus divinyl ether hydrates more slowly than ethyl vinyl and phenoxyacetylene more slowly than alkoxyacetylenes. In this connection it is interesting that the dipole moment of phenoxyacetylene[21] is not greatly different from that of phenetole or diphenyl ether while the alkoxyacetylenes have higher dipole moments.[21]

Acknowledgments.—Thanks are due to Dr. S. Winstein and Dr. J. B. Ramsay of the Department of Chemistry of the University of California at Los Angeles for many helpful suggestions throughout the course of this work. Part of the preliminary work on the problem was done by Mr. L. R. Pollack. We also wish to thank Mr. Harry L. Masser of the Southern California Gas Company for a scholarship granted to the junior author.

Summary

The rates of the acid catalyzed hydration of ethoxy-, butoxy- and phenoxy-acetylene have been measured at 25° in dilute alcoholic solutions by a dilatometric method. The reaction is first order with respect to ether and hydronium ion concentration and consists in the addition of water to the triple bond yielding an ester. The hydration is very similar to that of vinyl ethers, but proceeds more rapidly. A mechanism consistent with the kinetics is proposed.

LOS ANGELES, CALIFORNIA RECEIVED JANUARY 11, 1944

(19) Lucas and Eberz, THIS JOURNAL, **56**, 460 (1934); Lucas and Liu, *ibid.*, **56**, 2138 (1934); Hammett, ref. 14, p. 292.

(20) This is most clearly shown by the greater shortening of the carbon–halogen bond distances in halogenoacetylenes such as bromoacetylene as compared with halogenoethylenes. Pauling, "The Nature of the Chemical Bond," Cornell University Press, 1940, p. 216; Brockway, Beach and Pauling, THIS JOURNAL, **57**, 2693 (1935); de Laszlo, *Nature*, **135**, 474 (1935); Brockway and Coop, *Trans. Faraday Soc.*, **34**, 1429 (1938). The lower dipole moments of halogenated acetylenes relative to halogenated olefins is further evidence. Pflaum and Wenzke, THIS JOURNAL, **56**, 1106 (1934); Wilson and Wenzke, *ibid.*, **56**, 2025 (1934).

(21) Jacobs, Roberts and MacMillan, THIS JOURNAL, **66**, 656 (1944). The dipole moments of the acetylenic ethers were calculated by the Onsager equation [THIS JOURNAL, **58**, 1486 (1936)] from measurements of the dielectric constants of the pure liquids and are not directly comparable with the accurate values for the aryl ethers.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Unsaturated Synthetic Glycerides. VI.[1] Polymorphism of Symmetrical Monoöleyl-disaturated Triglycerides[2]

BY B. F. DAUBERT AND T. H. CLARKE

Since studies on the polymorphic phases of glycerides, both natural and synthetic, have been excellently reviewed recently by Ferguson and Lutton,[3] no detailed reference to past investigations will be made in this report.

While much of the earlier and basic work concerning the abnormal melting behavior of fats was confined to simple triglycerides and complex glyceride mixtures of natural fats, it remained for Malkin and associates[4,5,6] to establish a foundation upon which the polymorphism of glycerides could be studied and understood. The latter investigators, on the basis of their experimental work mainly with synthetic compounds, indicate that mixed triglycerides can exist in at least four different modifications (which they designate by Greek letters as β, β', α and γ, each with a characteristic melting point.

Transition point data for the polymorphic forms of synthetic glycerides containing unsaturated acids, only recently synthesized, have not been published. The purpose of the present paper, therefore, is to report the experimental data for a series of symmetrical monoöleyl-disaturated triglycerides.[7]

In this and future publications dealing with polymorphism in glycerides we shall refer to the different polymorphic forms for the unsaturated synthetic glycerides by the use of Roman numerals, *e. g.*, Form I, Form II, etc. Form I will always refer to the highest melting or most stable form.

Experimental

Methods and Apparatus.—The measuring system consisted of an eight-junction copper–constantan thermel, a Leeds and Northrup type K1 potentiometer and a type R galvanometer with a glass scale reading device. The thermel was about 1.5 mm. in diameter and the active section about 7 mm. in length. The ends of the thermel were enclosed in thin-wall glass tubes. The thermel was calibrated against a platinum resistance thermometer from 100 to −79° using the Callender equation above 0° and the van Deusen equation below 0°, in order to determine the temperature of the thermometer at a given point. The Na_2SO_4–$Na_2SO_4 \cdot 10H_2O$ point and the freezing point of mercury (−38.89°) were checked to within ±0.02°. The maximum sensitivity of the system was 0.02° per cm. of scale deflection when the scale was placed at a distance of one meter from the galvanometer mirror. The change in microvolts was 300, on the average, over the temperature range involved.

A sample of the synthetic glyceride (0.7 to 1.0 g.) was weighed into a small glass vial and then the end of the thermel was inserted to a depth of about 25 mm. The vial was then inserted into a small vacuum flask so that a 1-cm. clearance around the vial was available. The small vacuum flask could be lowered into any one of a series of liter vacuum flasks serving as warming or cooling baths. Within reasonable limits any desired rate of warming or cooling could be obtained.

During the determination of a cooling or warming curve, the setting of the potentiometer was changed by even increments and the time recorded when the galvanometer image crossed the zero point on the scale. The magnitude of the increments on the potentiometer dial depended upon the rate of cooling or warming. On a time basis the most rapid practical rate was a reading every six seconds. During a very slow rate of change of temperature, the time interval between readings was as long as two minutes.

For the purpose of checking technique and determining the accuracy of the apparatus, transition points were redetermined for 1-monostearin and 1-monomyristin. Comparison of the results with those previously reported by Malkin and Shurbagy[5] are tabulated in Table I.

TABLE I

TRANSITION POINTS FOR POLYMORPHIC FORMS OF 1-MONOSTEARIN AND 1-MONOMYRISTIN

Form	1-Monostearin, °C.	1-Monomyristin, °C.
I	81.8	71.0
Malkin's β	81.5	70.5
II	78.0	67.5
Malkin's β'	79.0	67.5
III	75.4	55.3
Malkin's α	74.0	56.0
IV	48.5	21.3
Malkin's γ	47.5	24.0

Discussion of Cooling and Warming Curves.—The type of warming curve obtained on heating a sample of a synthetic glyceride depends entirely on its previous history, *i. e.*, the manner by which it was cooled and subsequently stored. This observation, pointed out by other investigators, has been verified in the present study.

Since it was not possible under our experimental conditions to observe the transformations of the different forms of the synthetic glycerides, transition point is used in preference to melting point to indicate the temperature at which the change occurred.

Types of cooling and warming curves for 2-oleyl-1,3-dimyristin, resulting from many thermometric measurements and typical for the series of symmetrical monoöleyl-disaturated triglycerides, are shown in Figs. 1 and 2. In these figures the temperature scale is entirely accurate, but certain liberties have been taken with the time axis so that a complete set of curves could be drawn on a single chart. Approximate time intervals are indicated (see below) for certain sections of the curves.

The cooling of a melted sample resulted in its solidification in one of three forms depending on the rate of cooling. Very rapid cooling (three to five minutes) brought about solidification in Form IV (curve CC′, Fig. 1). Subsequent warming of the cooled glyceride (curve C′C″) produced a pronounced change of slope 0.2 to 0.6° below the transition point of Form IV (this behavior was checked many

(1) Earlier communications appeared in THIS JOURNAL, **65**, 2142, 2144 (1943); **66**, 53, 289, 290 (1944).

(2) A grant from the Buhl Foundation in support of this investigation and the suggestions of Dr. H. E. Longenecker in the preparation of this manuscript are gratefully acknowledged.

(3) Ferguson and Lutton, *Chem. Rev.*, **28**, 355 (1941).

(4) Clarkson and Malkin, *J. Chem. Soc.*, 666 (1934).

(5) Malkin and Shurbagy, *ibid.*, 1628 (1936).

(6) Malkin and Meara, *ibid.*, 103, 1141 (1939).

(7) Jackson, Daubert, King and Longenecker, THIS JOURNAL, **66**, 289 (1944).

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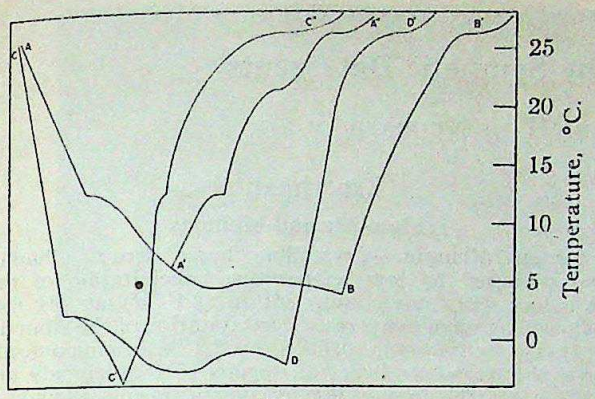

Fig. 1.—Types of cooling and warming curves for 2-oleyl-1,3-dimyristin.

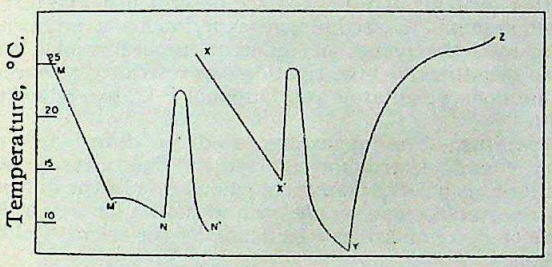

Fig. 2.—Types of cooling and warming curves for 2-oleyl-1,3-dimyristin.

times and seemed very specific) followed by a very sudden rise to the transition point of Form III and a slower rise to the transition point of Form I. The presence of Form II was not indicated on this warming curve. If the rapidly cooled sample (curve CC′) was held slightly below the transition point of Form IV for some time (thirty to forty-five minutes) indicated in curve CD, a rise in the curve occurred, indicating a slight heat evolution. This heat evolution was apparently caused by the conversion of Form IV to some higher temperature form or forms, for subsequent warming (curve DD′) gave only a slight indication of the presence of Form III, a definite change in slope, and then a good transition point for Form I. Again the presence of Form II was not indicated.

A somewhat slower rate of cooling (eight to twelve minutes) of the original melted sample resulted in solidification of the sample in Form III (curve AA′). Immediate warming gave changes of slope corresponding to the transition points from Form III, Form II and Form I (curve A′A″). As in the case of curve CD, if the sample solidified in Form III was held for some time (thirty to forty-five minutes) as indicated in curve A′B, conversion occurred to the higher temperature forms as shown by curve BB′, wherein a small but definite break occurred at the transition point of Form II followed by a marked change of slope at the transition point of Form I. If the cooled samples at points B or D were held at those temperatures for a longer period of time (sixty to seventy-five minutes), subsequent warming indicated practically complete conversion to Form I.

Very slow cooling (twenty to twenty-five minutes) of the melted sample of 2-oleyl-1,3-dimyristin resulted in solidification of Form I (curve XX′Y, Fig. 2). The liquid supercooled to point X′; the temperature then rose very rapidly to a point between the transition points of Form I and Form II as the heat of solidification was evolved and then decreased rapidly. Warming of the sample (curve YZ) showed a transition point of Form I only. Curve MM′NN′ would seem to indicate the possibility of crystallization of more than one form at a time from a melted sample. Upon cooling, solidification occurred in Form III at M′ on the curve. The sample continued to cool for several degrees to point N and then suddenly increased to a temperature between the transition points of Form I and Form II with no indication of the presence of Form III.

Important factors determining the shape of the curves, time of cooling and warming, etc., are the nature and size of the sample, and the temperature gradient between the sample and surroundings. We believe we have studied a sufficient number of rates of cooling and warming to show that the transition point temperatures, in the main, are not rate dependent. The determination of the transition point of Form IV on a warming curve did show slight rate dependence. The transition point approached that found for Form IV on cooling curves (which were not rate dependent) as the warming rate was increased.

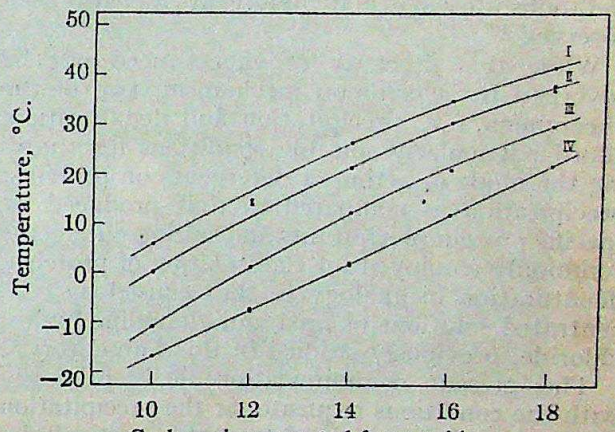

Fig. 3.—Transition point curves for the polymorphic forms of symmetrical 2-oleyl-1,3-diacylglycerols.

The transition points for the polymorphic forms of each member of the series of symmetrical monoöleyl-disaturated triglycerides are given in Table II. A single value is given wherever a transition point could be duplicated to within ±0.1°. The relationships between the various polymorphic forms are shown in Fig. 3. While the consistency of the data is apparent, one anomaly, however, is to be noted. For 2-oleyl-1,3-dilaurin, no transition point clearly defining either Form I or Form II was obtained. Three values, all lying between the curves for Form I and Form II were experimentally obtained, none of which clearly characterizes either form. The capillary melting point for Form I (16.0 to 16.5°) would fall close to the curve for the melting points of other members of the series.

TABLE II

TRANSITION POINTS FOR POLYMORPHIC FORMS OF SYMMETRICAL MONOÖLEYL-DIACYL TRIGLYCERIDES[a]

Acyl radical	Transition points, °C. Form I	Form II	Form III	Form IV
Stearyl	41.6	37.0, 37.6	29.8	22.3
Palmityl	35.2	30.4	20.8	12.0
Myristyl	26.3	21.5	12.3	2.1
Lauryl	16.5[b]	11.0[b]	1.4	−7.1, −7.5
Capryl	6.2	0.6	−10.2	−16.4

[a] Capillary melting points reported previously.[7] [b] Determined from curve, Fig. 3.

Summary

Transition point data for the polymorphic forms of a series of symmetrical monoöleyl-disaturated triglycerides obtained from cooling and warming curves are reported.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, DUKE UNIVERSITY SCHOOL OF MEDICINE]

The Precipitation of Proteins by Synthetic Detergents[1a]

BY FRANK W. PUTNAM AND HANS NEURATH

Synthetic detergents are capable of reacting with proteins to produce precipitation[1,2,3,4] and denaturation,[1,2,5,6] the inactivation of some viruses[7,8] and enzymes,[9] the fragmentation of certain natural pigment-protein complexes,[2,10] and the catalytic hydrolysis of protein amide and peptide bonds.[11] The inhibition of bacterial metabolism by synthetic detergents has also been observed.[12]

While this diversity of effects need not be governed by a common mechanism, two of the phenomena, *i. e.*, precipitation and denaturation, afford particularly suitable conditions for studying the mode of action of detergents on proteins: precipitation as compared to that produced by specific protein precipitants and salting-out agents commonly employed for the isolation of proteins; denaturation in analogy to that caused by concentrated solutions of urea and guanidine hydrochloride, previously studied in this Laboratory.[13]

The present communication deals primarily with the conditions requisite for the precipitation of proteins by anionic detergents, particularly, the precipitation of crystalline horse serum albumin by sodium dodecyl sulfate, and with the properties of the protein-detergent complex.[14] The effects of anionic detergents on the denaturation and regeneration of proteins will be the subject of subsequent papers.

(1a) Presented before the Division of Biological Chemistry at the 106th Meeting of the American Chemical Society which was held on September 6–10, 1943, in Pittsburgh, Pennsylvania. A preliminary communication has already been published, see ref. 1.

(1) F. W. Putnam and H. Neurath, *J. Biol. Chem.*, **150**, 263 (1943).

(2) R. Kuhn, H. J. Bielig and O. Dann, *Ber.*, **73B**, 1080 (1940).

(3) T. L. McMeekin, *Federation Proc.*, **1**, Pt. 2, 125 (1942).

(4) K. H. Schmidt, *Z. physiol. Chem.*, **277**, 117 (1943).

(5) M. L. Anson, *J. Gen. Physiol.*, **23**, 239 (1939).

(6) H. P. Lundgren, THIS JOURNAL, **63**, 2854 (1941).

(7) M. Sreenivasaya and N. W. Pirie, *Biochem. J.*, **32**, 1707 (1938).

(8) F. C. Bawden and N. W. Pirie, *ibid.*, **34**, 1278 (1940).

(9) D. Shoch and S. J. Fogelson, *Proc. Soc. Exp. Biol. Med.*, **50**, 304 (1942).

(10) E. L. Smith and E. G. Pickels, *J. Gen. Physiol.*, **24**, 753 (1941).

(11) J. Steinhardt and C. H. Fugitt, *J. Res. Natl. Bur. Stds.*, **29**, 315 (1942).

(12) Z. Baker, R. W. Harrison and B. F. Miller, *J. Exp. Med.*, **73**, 249 (1941).

(13) H. Neurath, G. R. Cooper and J. O. Erickson, *J. Biol. Chem.*, **142**, 249 (1942).

(14) Since the work reported in this paper was completed, electrophoretic[15] and X-ray studies[16] have been reported dealing with the action of alkylbenzene sulfonates on egg albumin. Those results together with unpublished observations of our own indicate the profound effect of anionic detergents on proteins under conditions unfavorable for precipitation.

(15) H. P. Lundgren, D. W. Elam and R. A. O'Connell, *J. Biol. Chem.*, **149**, 183 (1943).

(16) K. J. Palmer and J. A. Galvin, THIS JOURNAL, **65**, 2187 (1943).

Experimental

Materials and Methods

Serum Albumin.—Crystalline horse serum albumin was prepared by low temperature precipitation of the globulins with ammonium sulfate (2.1 *M*) at *p*H 6.4, followed by room temperature precipitation of the albumin at its isoelectric point (*p*H 4.8) by 2.3 *M* ammonium sulfate, the procedure being analogous to that already described for the preparation of bovine serum albumin.[17] The four-times crystallized albumin had a carbohydrate content of 0.10% and corresponded approximately to Kekwick's Fraction B. The preparation was electrophoretically homogeneous at *p*H 7.6.

Other proteins investigated are described in the text.

Detergents.—In preliminary experiments a number of commercial detergents of different type formulas were used. Quantitative investigation was restricted to purified sodium dodecyl sulfate[18] and Duponol P C, free of sodium sulfate.[19]

Apparatus.—The apparatus used in diffusion,[20] viscosity,[21] and electrophoresis studies[22] has already been described, as has the manner of calculation of the diffusion constant, molecular asymmetry and molecular weight.[20,21] Nitrogen determinations were made by the micro-Kjeldahl method.

Preliminary Observations

The action of a number of commercial detergents[19,23,24] on several purified proteins was investigated qualitatively in the following manner: to Wassermann tubes containing 2-cc. aliquots of 2% protein in phosphate buffer *p*H 7.7, or in acetate buffer *p*H 4.2, were added serially from another tube 2 cc. of tenfold dilutions (0.0002–2.0%) of an aqueous solution of the detergent. Thorough mixing was accomplished by repeated pouring back and forth.

It was observed that with anionic detergents precipitation was restricted to the acidic *p*H and that with all types of detergents maximum precipitation occurred at 0.1–1.0%, increasing detergent concentrations resulting in dispersion of the precipitate.

p*H* Region of Precipitation.—In order to investigate further the effect of *p*H on precipitation, a series of buffers hydrochloric acid–sodium chloride, sodium acetate or phosphate) differing by 0.1 or 0.2 *p*H unit, was prepared.[25]

(17) F. W. Putnam, J. O. Erickson, E. Volkin and H. Neurath, *J. Gen. Physiol.*, **26**, 513 (1943).

(18) We are indebted to Dr. S. Lenher of the Fine Chemicals Division of E. I. du Pont de Nemours and Co. for a generous supply of purified sodium alkyl sulfates. Dr. Lenher's communication gives the analysis of sodium dodecyl sulfate as follows: Calcd. for $C_{12}H_{25}SO_4Na$: S, 11.1; Na, 7.98. Found: S, 10.57; Na, 7.63. Moisture content 1.37%, NaCl 0.31%. The alcohol from which the product was prepared was 99.7% pure.

(19) A mixture of the sodium salts of homologous alkyl sulfates of chain length C_8-C_{18}, obtained free of sodium sulfate, through the courtesy of E. I. du Pont de Nemours and Co.

(20) H. Neurath, *Chem. Rev.*, **30**, 357 (1942).

(21) H. Neurath, G. R. Cooper and J. O. Erickson, *J. Biol. Chem.*, **138**, 411 (1941).

(22) D. G. Sharp, G. R. Cooper and H. Neurath, *ibid.*, **142**, 203 (1942).

(23) Nacconol N. R. S. F., a sodium alkylbenzenesulfonate mixture, National Aniline Division, Allied Chemical and Dye Corporation.

(24) Aerosol OT, di-octyl sodium sulfosuccinate, American Cyanamid and Chemical Corporation.

(25) The relative insolubility of the potassium salts of certain detergents, *e. g.*, the homologous alkyl sulfates, precludes the use of this cation in the buffers employed. The high temperature coeffi-

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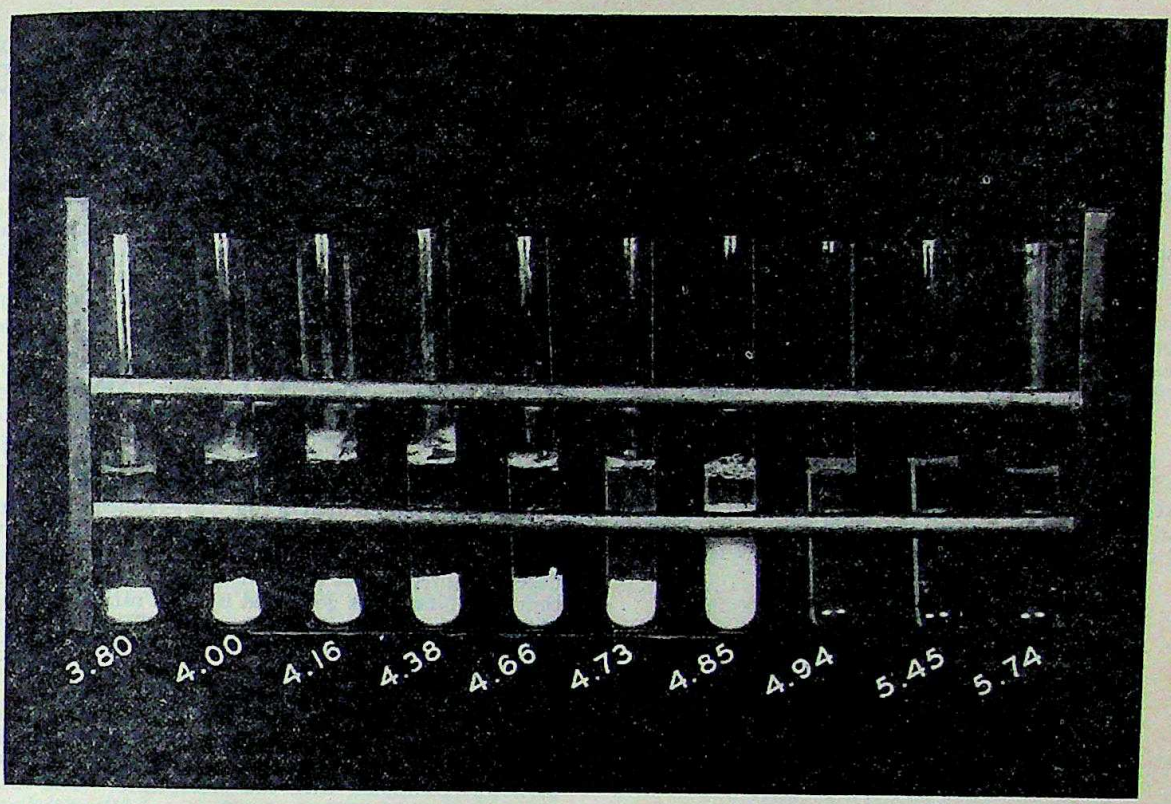

Fig. 1.—pH region of precipitation. The test-tubes contain 40 mg. of crystalline horse serum albumin and 10 mg. of purified sodium dodecyl sulfate in 4 cc. of 0.1 N sodium acetate buffer of the pH indicated. Photographed without centrifuging two hours after mixing. Since up to pH 4.85 the protein was completely precipitated, in all of the tubes, the heights of the precipitates are indicative only of the rate of sedimentation.

The protein was dissolved in the buffers and sufficient sodium dodecyl sulfate (SDS) was then added to ensure complete precipitation. The final pH was determined on the supernatant with the glass electrode since slight changes in pH occurred incidental to mixing.

Serum Albumin.—The test tubes depicted in Fig. 1 contain 40 mg. of crystalline horse serum albumin to which had been added 10 mg. of SDS, the solutions being 0.1 N with respect to sodium acetate, in a total volume of 4 cc. The isoelectric point of horse serum albumin in this buffer is reported to be pH 4.75[26] while precipitation ceases at pH 4.85.

Except in the region of the isoelectric point, settling is very rapid. Within less than one hour a compact pellet is formed from which the supernatant solution may be decanted readily without prior centrifugation. The photograph taken after standing for two hours after mixing is evidence of this fact. Since all the protein was precipitated in the pH range 3.80–4.85, the heights of the precipitates are indicative only of the rate of sedimentation.

Other Proteins.—Other proteins investigated in a similar manner were: pepsin, β-lactoglobulin, horse serum pseudoglobulin GI, and crystalline beef serum albumin, obtained as already described,[16,21] egg albumin, made available through the courtesy of Dr. A. R. Taylor of the Duke Medical School; and crystalline human carboxyhemoglobin prepared according to the method of Cannan and Redish.[27] All preparations were found to be homogeneous in diffusion or electrophoresis, except for hemoglobin which was not investigated.

As revealed by the data given in Table I, all these proteins are precipitated only in the cationic form, the maximum pH at which precipitation ensues closely approximating the isoelectric point except for hemoglobin. Agreement between the isoelectric point and the maximum pH of precipitation is most satisfactory for proteins which are isoelectric within the acetate buffer range. In the case of pseudoglobulin GI, a small amount of precipitate which formed above the isoelectric point redissolved spontaneously on standing overnight. Likewise, in the case of pepsin, a small amount of precipitate was observed at

TABLE I

COMPARISON OF ISOELECTRIC POINT, AND MAXIMUM pH FOR PRECIPITATION OF PROTEINS BY SDS

Protein	I. P.	Ref.	Maximum pH for precipitation
Pepsin	2.7	(28)	about 2.7
Egg albumin	4.6	(29)	4.6
Horse serum albumin	4.75	(26)	4.85
Beef serum albumin	4.8	(30)	4.8
β-Lactoglobulin	5.2	(31)	5.2
Horse pseudoglobulin GI	6.0	(22)	5.9
Human carboxyhemoglobin	7.1	(32)	6.4

cient of solubility also restricts the conditions of the experiment: for example, Duponol FC which may readily be kept at room temperature as a 10% stock solution crystallizes out at 4° above concentrations of 0.2%.

(26) H. A. Abramson, L. S. Moyer and M. H. Gorin, "Electrophoresis of Proteins," New York, 1942, p. 182.

(27) R. K. Cannan and J. Redish, in "Blood substitutes and blood transfusion" (S. Mudd and W. Thalhimer editors), Springfield, Illinois, 1942, p. 147.

(28) J. H. Northrop, "Crystalline Enzymes," New York, 1939, p. 49.

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(30) E. J. Cohn, *Chem. Rev.*, **28**, 395 (1941).

(31) K. O. Pedersen, *Biochem. J.*, **30**, 961 (1936).

(32) T. Svedberg and K. O. Pedersen, "The Ultracentrifuge," Oxford, 1940, p. 407.

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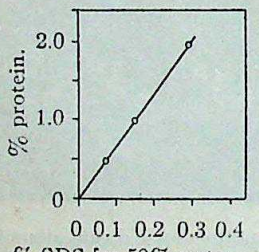
reactions exceeding the isoelectric point; however, acidification of the supernatant solutions yielded additional precipitation only in tubes initially at *p*H 2.75 or higher.

The conclusion derived from these experiments is that *anionic detergents precipitate proteins only when the latter are in the cationic form*[33] and that the maximum *p*H at which precipitation occurs closely approximates the isoelectric point.

Analytical Investigations

Quantitative investigations of the influence of the following factors on the precipitation of crystalline horse serum albumin by purified SDS was undertaken: (1) the protein-detergent weight concentration ratio, (2) *p*H, and (3) temperature and salt concentration. SDS was chosen because (a) it is available in the pure anhydrous form, (b) it is nitrogen free, and (c) its presence may readily be detected and its removal effected by the addition of barium salts.

1. Protein-Detergent Weight Concentration Ratio.—The effect of varying detergent concentration on the precipitation of a given amount of serum albumin was studied at three different protein concentrations (4.80, 9.80 and 19.72 mg. per cc.), in the presence of 0.1 *N* sodium acetate, *p*H 4.5, at room temperature. One-half hour after mixing the tubes were centrifuged and aliquots of the filtered supernatant solutions were analyzed for nitrogen, the amount of protein precipitated being obtained by difference.



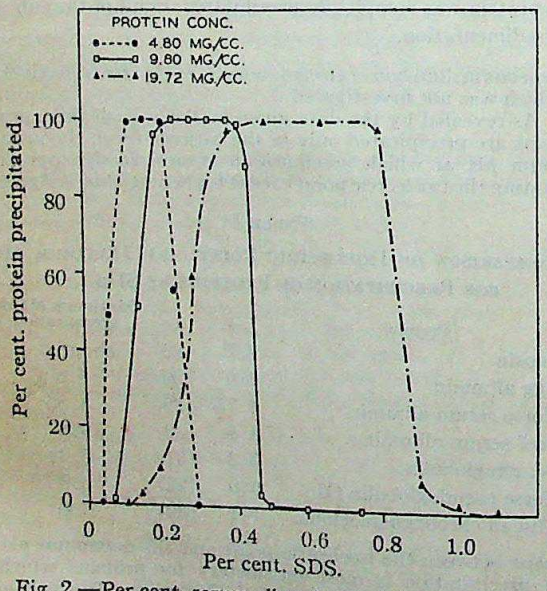


Fig. 2.—Per cent. serum albumin precipitated at *p*H 4.5 in 0.1 *N* sodium acetate plotted against concentration of sodium dodecyl sulfate. The initial protein concentration of the solution is denoted as follows: - - - - 4.80 mg. per cc., —— 9.80 mg. per cc., and ·—· 19.72 mg. per cc. The small graph represents the linear relation between the protein concentration and the per cent. SDS required for 50% precipitation.

In Fig. 2 the per cent. of total protein precipitated is plotted against the final concentration of SDS.

Taking the middle curve representing a protein concentration of 9.80 mg. per cc. as an example, three distinct regions may be discerned: (a) that of *protein excess* where the protein is incompletely precipitated; (b) the *equivalence zone* where complete precipitation is achieved; and (c) the region of *detergent excess*, in which the precipitate initially formed may be partly or completely dispersed by shaking. At a given protein concentration, the transition between these regions with increasing concentration of SDS is abrupt. Therefore, to ensure 100% precipitation an optimal protein-detergent concentration ratio must be observed. Since the equivalence zone is fixed within the limits of the protein-detergent weight ratio (5:1 to 2.5:1), its width varies directly with protein concentration.

If the data represented in Fig. 2 are reduced to a common basis by plotting the protein-detergent weight ratio as abscissa against the per cent. protein precipitated as ordinate, the three curves very closely superimpose, indicating that precipitation is governed by this ratio. This is also illustrated by the small inset graph of Fig. 2 in which the per cent. SDS required to precipitate 50% of the albumin is plotted against the protein concentration, the figures being interpolated from the larger graph in Fig. 2.

Qualitative tests for SDS made by the addition of barium chloride to the supernatant solutions indicated that below the region of detergent excess nearly all of the SDS was combined with the precipitate. The maximal concentration of SDS that will completely precipitate a given amount of horse serum albumin at room temperature corresponds approximately to the total acid-binding capacity of the protein. The average value obtained by interpolation from the curves in Fig. 2 is 145 moles of SDS per g. of protein $\times 10^5$. This correlation suggests that anionic detergents may act to precipitate proteins by combining stoichiometrically with the positively charged groups of the protein. However, since precipitation is already complete at a detergent concentration corresponding to about one-half of the total acid-binding capacity, this relation may be fortuitous and, therefore, did not warrant a detailed analysis of the composition of the precipitates in the region of protein excess.

2. *p*H Region of Precipitation.—The effect of *p*H on the precipitation of horse serum albumin by SDS was determined in the acetate buffer range (0.1 *N* sodium acetate) at a final protein concentration of 9.70 mg. per cc., at 31°. Two different concentrations of SDS were chosen; the one, 2.5 mg. per cc., was calculated as just sufficient to precipitate all the protein present, while the other, 1.5 mg. per cc., was estimated to yield about 50% precipitation (Fig. 3).

The lower curve, corresponding to partial precipitation, was established by Kjeldahl analysis. The upper curve was obtained by the observation that no precipitate was formed at *p*H 4.94 or higher, while at *p*H 4.73 and lower, no precipitate resulted on the addition of trichloroacetic acid to the clear supernatant solutions.[34]

When a solution of SDS or Duponol (adjusted to *p*H 4.85) is added to a salt-free, isoelectric solution of serum albumin (*p*H 4.85), no precipitation ensues, and the *p*H rises to a maximum value of about 6.4. On the addition of acid to the clear solution it becomes cloudy at the isoelectric point, and the protein is completely precipitated on further acidification. The *p*H increase undergone upon the titration of 1 g. of horse serum albumin in 100 cc. of water with 100 cc. of 0.25% Duponol is illustrated in Fig.

(33) A personal communication from Dr. T. L. McMeekin reveals that this point is in substantial agreement with his unpublished observations.

(34) We have verified the statement of Anson[5] that under specified conditions the presence of Duponol interferes with the precipitation of hemoglobin by trichloroacetic acid (see also (11)). Under similar conditions we have observed no interference with the trichloroacetic acid precipitation of serum albumin or serum globulin.

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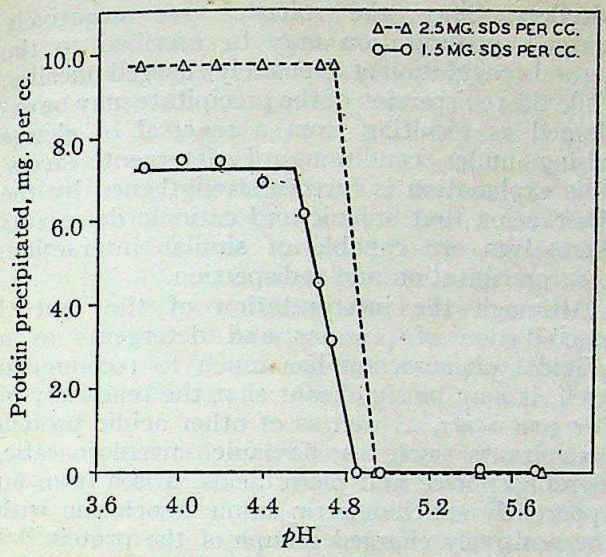

Fig. 3.—*p*H region of precipitation of crystalline horse serum albumin (9.70 mg. per cc.) by sodium dodecyl sulfate in 0.1 *N* sodium acetate. The upper curve (complete precipitation) refers to a detergent concentration of 2.5 mg. per cc., the lower curve (partial precipitation) to 1.5 mg. cc.

4. It is evident that in order to precipitate proteins with anionic detergents it is necessary to work in buffered solutions.

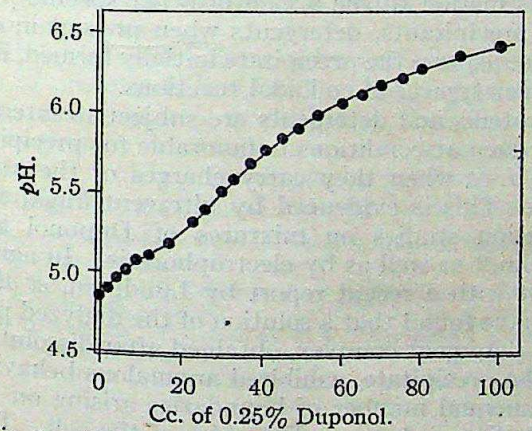

Fig. 4.—Change in *p*H of a salt-free 1% serum albumin solution (isoelectric point, *p*H 4.85) upon the addition of increments of Duponol (adjusted to *p*H 4.85).

3. Influence of Temperature and Salt Concentration.—The effect of temperature was first studied at a protein-detergent concentration ratio corresponding to the half-precipitation level. The reacting solutions were equilibrated at various temperatures, mixed, allowed to stand one-half hour, then centrifuged at the same temperature, and analyzed as already described. The protein concentration was 9.76 mg. per cc., the SDS concentration 1.5 mg. per cc., the solvent being 0.1 *N* sodium acetate, *p*H 4.5.

The large temperature effect observed under these conditions is shown in Fig. 5.

Although an albumin solution precipitated at 4° yields additional precipitate upon equilibration at 36°, to an extent corresponding to this point, the path going from 36 to 4° is only partially reversible.

Investigation of the influence of temperature on precipitation at various protein-detergent ratios revealed that this effect was confined to the protein or detergent

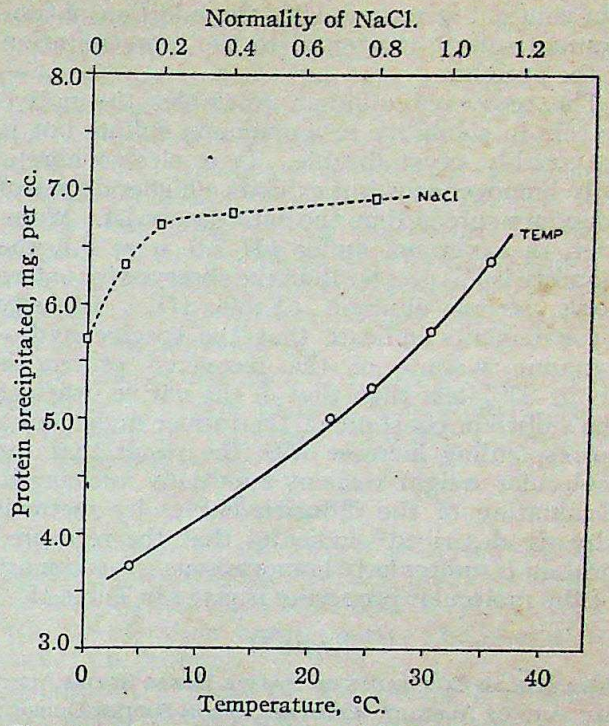

Fig. 5.—Influence of temperature and salt concentration on the partial precipitation of horse serum albumin (9.76 mg. per cc.) by sodium dodecyl sulfate (1.5 mg. per cc.). The bottom abscissa refers to temperature, the solvent being 0.1 *N* sodium acetate, *p*H 4.5. The top abscissa refers to sodium chloride concentration, the solvent likewise containing 0.1 *N* sodium acetate, *p*H 4.5 ($t = 31°$).

excess regions, the width of the equivalence zone being but little affected by changing temperature.

As shown in Fig. 5, increasing the salt concentration likewise enhances the precipitation of serum albumin at the half-precipitation level, the first increments of salt being most effective.

Properties of the Protein-Detergent Complex and of the Recovered Protein.—The complex precipitated in the equivalence zone is sparingly soluble in water, neutral salt solutions, or in weakly acidic buffers, but dissolves in alkaline solutions or on dialysis against water. Upon prolonged dialysis of an alkaline solution, some of the SDS passes through the membrane. However, complete separation of protein and detergent cannot be accomplished by this method, for the presence of undialyzable SDS may be demonstrated by the addition of barium chloride, or by the precipitation of the protein upon slight acidification of the solution. Moreover, considerably lower concentrations of ammonium sulfate are required for the precipitation of the protein under these conditions, than for the precipitation of native serum albumin.

Complete dissociation of the complex and removal of SDS may be accomplished by the addition of a small excess of barium chloride (1 mM. per 0.9 mM. of SDS). The highly insoluble barium dodecyl sulfate so formed is negative to qualitative protein tests after two washings. Excess barium remaining in the supernatant pro-

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tein solution is removed by the addition of ammonium sulfate incidental to the reprecipitation of the protein.

The recovered albumin resembles the native protein in solubility in ammonium sulfate but is not readily crystallizable. It is electrophoretically homogeneous but exhibits a higher degree of boundary spread than the native material. Moreover, in a veronal buffer *p*H 7.6, $\mu = 0.1$, the mobility is 7% greater than the observed for native horse serum albumin (Table II). Viscosity measurements indicate that the specific hydrodynamic volume of the recovered protein is about 25% less than that of the native, whereas the diffusion constant of the former undergoes a corresponding increase with the result that the molecular weight remains essentially unchanged. Evaluation of the diffusion curves by methods already described[20] indicates that the recovered protein is molecularly homogeneous. A summary of the molecular properties is given in Table II.

TABLE II

MOLECULAR CONSTANTS OF NATIVE HORSE SERUM ALBUMIN AND OF ALBUMIN RECOVERED FROM SODIUM DODECYL SULFATE PRECIPITATE

U = the electrophoretic mobility in sq. cm. per second per volt $\times 10^{-5}$ in 0.03 N sodium veronal − 0.07 N sodium chloride buffer, *p*H 7.60, at 1.0° after four hours migration. For the explanation of other symbols see ref. (21).

Protein	η_{sp}	$(b/a)_A$	$(f/f_0)_\eta$	$d_{25°}$, cm.^{2} sec.$^{-1}$ $\times 10^{-7}$	M	U, cm.^{2} sec.$^{-1}$ volt^{-1} $\times 10^{-5}$
Native	4.1	3.2	1.23	6.99	75,700	6.25
Recov.	3.1	2.0	1.15	7.44	77,000	6.70

Discussion

The precipitating action of detergents on proteins has already been observed in previous work. Following an observation by Bull and Neurath on the precipitating and dispersing effects of sodium dodecyl sulfate on egg albumin,[35] similar findings were reported by Miller and Andersson for insulin.[36] McMeekin[3] has investigated quantitatively the relative effectiveness of a number of homologous anionic detergents in precipitating crystalline egg albumin and β-lactoglobulin, while Schmidt[4] has reported analogous experiments involving cationic detergents.

Precipitation of proteins by synthetic detergents appears to be caused by electrostatic forces. This is suggested by the finding reported herein that with anionic detergents, precipitation is restricted to protein cations, while with cationic detergents it is limited to protein anions.[2,37] Ultracentrifugal and diffusion measurements indicate that the sodium alkyl sulfates exist in solution in micellar form, with a molecular weight of about 12,500.[36] Accordingly, it may be calculated that in the region of complete precipitation each protein molecule combines with 1 to 2 detergent micelles. Since the micelles are negatively charged, precipitation may be ascribed to the mutual coagulation of oppositely charged micelles, while the redispersion of the precipitate may be explained as resulting from a reversal of charge arising under conditions of detergent excess. This explanation is further strengthened by the observation that anionic and cationic detergents themselves are capable of similar interaction, *i. e.*, precipitation and redispersion.

Although the interpretation of the mutual precipitation of proteins and detergents as a colloidal phenomenon has much to recommend itself, it may be significant that the reactivity of *detergent acids*, as well as of other acidic protein precipitants such as flavianic, trichloroacetic, metaphosphoric and picric acids, arises from an apparently stoichiometric anion association with the positively charged groups of the protein.[38,39] The precipitating efficiency of these reagents, as well as their catalytic effectiveness in the hydrolysis of protein amide and peptide bonds, parallels their anion affinities, the affinities of dodecyl sulfate and dodecyl sulfonate being among the highest so far measured.[11] However, not all proteins are precipitated by detergents at a given acidity but each at a *p*H determined by the respective isoelectric point.[40] Moreover, in contradistinction to the action of other specific protein precipitants, detergents when present in excess redisperse the precipitate initially formed, in a manner typical of colloidal reactions.

Proteins and detergents are subject to interaction even at conditions unfavorable for precipitation, *i. e.*, when they carry charges of the same sign. This is evidenced by ultracentrifugal and diffusion studies on mixtures of Duponol and insulin,[36] as well as by electrophoresis. In agreement with a recent report by Lundgren, *et al.*,[15] we have found that a solution of the dialyzed protein-detergent complex, obtained after dissolution of the precipitate, exhibited anomalous behavior, an unequal number of boundaries arising on the ascending and descending sides of the cell. This phenomenon is similar in kind to that observed in the interaction between thymonucleic acid and serum albumin in *p*H regions alkaline to the isoelectric point of the protein.[42] In this case, too, precipitation ensues when the *p*H is adjusted to the acid side of the isoelectric point.

(35) H. B. Bull and H. Neurath, *J. Biol. Chem.*, **118**, 163 (1937).
(36) G. L. Miller and K. J. I. Andersson, *ibid.*, **144**, 475 (1942).
(37) W. J. Jaffé, *J. Biol. Chem.*, **148**, 185 (1943).
(38) J. Steinhardt, C. H. Fugitt and M. Harris, *J. Res. Natl. Bur. Stds.*, **26**, 293 (1941).
(39) J. Steinhardt, C. H. Fugitt and M. Harris, *ibid.*, **28**, 201 (1942).
(40) Polymerized sodium metaphosphate offers an interesting analogy to the action of SDS. Briggs[41] has observed that on mixing sodium metaphosphate (*p*H 5.0) with isoelectric salt-free horse serum albumin, the solution remains clear and the *p*H rises abruptly in a manner somewhat similar to that observed herein for the addition of SDS (Fig. 4). On acidification, the metaphosphate protein solution becomes cloudy just above the isoelectric point and precipitates as the pH is decreased.
(41) D. R. Briggs, *J. Biol. Chem.*, **134**, 261 (1940).
(42) E. Stenhagen and T. Teorell, *Trans. Faraday Soc.*, **35**, 743 (1939).

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While the very structural features which render detergents protein precipitants may likewise be involved in their denaturing action, the two phenomena may be discerned under certain conditions. Thus, while for anionic detergents precipitation is confined to the acid side of the isoelectric point, denaturation, as revealed by viscosity measurements,[43] occurs to about the same extent in both acid and alkaline regions, with detergents of both the anionic and cationic types. Moreover, while relatively low concentrations of detergents exert a high denaturing action on proteins,[1,5] this effect increases with detergent concentration in the region of detergent excess.[43]

The properties of serum albumin recovered from the precipitated complex approximate more closely those of the protein regenerated from concentrated urea or guanidine hydrochloride solutions[13,44] than they do those of the native material. Since precipitation by SDS leads to changes in properties which may not be wholly reversed even upon subsequent dissociation of the protein-detergent complex, the recovered protein must be denatured according to the general definition proposed for denaturation.[45] However, it is the degree of denaturation that varies with detergent concentration, regardless of whether the combination between protein and detergent leads to precipitation.

While the application of detergents to the isolation of proteins is restricted by the degree of denaturation incurred, nevertheless, their use may be warranted in specific instances, even in the preparation of biologically *active* materials. For example, the serological activity of antibodies[46] or the hormonal activity of insulin[47] have been shown to be rather insensitive to even high degrees of denaturation. Also, under suitable conditions detergents may be employed in the preparation of protein-free filtrates or of regenerated proteins. Since precipitation of a given protein ceases at the isoelectric point, detergents may conceivably be adapted to the separation of protein mixtures under conditions at which the components carry opposite charges, *e. g.*, serum proteins. This aspect of the problem is now being investigated in this Laboratory.

The authors are indebted to the Rockefeller Foundation, to the Lederle Laboratories, Inc., and to the Duke University Research Council for support of this work.

(43) J. O. Erickson, F. W. Putnam and H. Neurath, unpublished observations; see also ref. 1.

(44) D. G. Sharp, G. R. Cooper, J. O. Erickson and H. Neurath, *J. Biol. Chem.*, **144**, 139 (1942).

(45) H. Neurath, J. P. Greenstein, F. W. Putnam and J. O. Erickson, *Chem. Rev.*, in press.

(46) J. O. Erickson and H. Neurath, *Science*, **98**, 284 (1943).

(47) A. Rothen, B. F. Chow, R. O. Greep and H. B. van Dyke, *Cold Spring Harbor Symposia Quant. Biol.*, **9**, 272 (1941).

Summary

Investigation of the effects of synthetic detergents on proteins has revealed that anionic detergents precipitate proteins only in the cationic form, precipitation ceasing above the isoelectric point of the protein.

Quantitative study of the system crystalline horse serum albumin-sodium dodecyl sulfate has shown that precipitation is governed by the following factors: protein-detergent weight concentration ratio, *p*H, temperature and ionic strength. At low detergent concentrations the protein may be completely precipitated while in regions of detergent excess redispersion of the precipitate occurs.

Dissociation of the protein-detergent complex by means of barium salts yields a protein which, as indicated by diffusion, viscosity and electrophoresis, is in a regenerated rather than in the native state.

The mechanism of precipitation and the potential application of detergents to the preparation and separation of proteins have been considered.

DURHAM, N. C. RECEIVED DECEMBER 31, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF DELAWARE, AND THE AMMONIA DEPARTMENT OF E. I. DU PONT DE NEMOURS AND COMPANY, INC., WILMINGTON, DELAWARE]

Polarographic Examination of Carbonyl Compounds

BY JOHN M. LUPTON AND CECIL C. LYNCH

Although the polarographic reduction of many carbonyl compounds has been reported,[1] it is not possible to obtain reduction waves with saturated, unsubstituted ketones. This fact led us to the study of methods by which carbonyl compounds may be examined polarographically.

In searching for an environment in which carbonyl reaction products would give polarographic waves, several reagents were tested. In acid hydrazine solution,[2] ketones give double waves as shown in Fig. 1. Aldehydes give similar waves. The half-wave potentials vary somewhat with concentration, but for ketones the first wave occurs near −1.1 v. (*vs.* S. C. E.); for aldehydes, near −0.9 v. For both aldehydes and ketones the half-wave potential of the second wave is in the

(1) I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers, Inc., New York, N. Y., 1941.

(2) The polarographic reduction of the hydrazonium and phenylhydrazonium ions has not been investigated. Since they do not appreciably alter the hydrogen discharge in hydrochloric and sulfuric acid solutions (0.1 *N*) their half-wave potentials must be more negative than −1.5 v.

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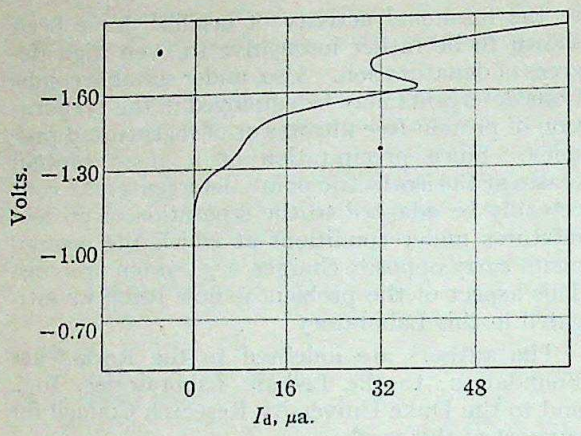

Fig. 1.—The reduction of methyl *n*-amyl ketone (0.006 *M*) in hydrazine solution.

range −1.3 to −1.4 v. The carbonyl compound reacts with the hydrazine solution, forming the hydrazone ($RR'CNNH_2$), the azine ($RR'CNNCRR'$), or a mixture of the two. The constants governing the relative quantities of the hydrazone and the azine produced under these conditions have not been determined here. The data indicate that a state of equilibrium exists in the system.

Acetone and *i*-butyraldehyde give reduction waves in acid phenylhydrazine[2] solution closely similar to those obtained in hydrazine solution, but the difficulty of obtaining and storing pure phenylhydrazine hydrochloride made the hydrazine reagent more satisfactory.

No carbonyl reduction waves were found with solutions of *i*-butyraldehyde and of methyl *i*-butyl ketone in ammonium chloride–hydrochloric acid solutions. Isobutyraldehyde gave no reduction wave in alkaline sodium sulfite solution. In slightly acid and neutral sodium sulfite solution only the bisulfite waves were observed.

Experimental

Work contained in this paper is limited to the investigation of the relationship between diffusion current and concentration in acid hydrazine solution for the following carbonyl compounds: isobutyraldehyde, acetone, methyl *i*-butyl ketone, methyl *n*-amyl ketone.

Apparatus.—The Leeds and Northrup Electrochemograph was used in obtaining all polarograms. Supplementary potential measurements were made with the Leeds and Northrup Universal *p*H Indicator.

The capillary tip was a piece of Pyrex capillary tubing about 0.05 mm. inner diameter, 6 mm. outer diameter, 8 cm. long. The mercury reservoir and regulating device was similar to that described by Furman, Bricker and Whitesell[3] except that connection to the capillary was made by a standard taper 10/30 ground joint. A typical value for the product $m^{2/3}t^{1/6}$ was 1.745 mg.$^{2/3}$ sec.$^{1/6}$, corresponding to a mean chloride diffusion current i'_d = 5.59 *Ma*, at 0.00100 *M*.

A mercury pool, never less than 3 sq. cm. in area, was used as the anode. The potential of this electrode in the standard hydrazine solution was 0.22 v. *vs.* the saturated calomel electrode. To convert potentials to the saturated calomel electrode base, 0.22 v. must be subtracted from observed values.

A large portion of the polarograms were run using the cell and transfer system shown in Fig. 2. A definite volume of supporting electrolyte solution, usually 25 ml., was added to a weighing buret. A stream of water-saturated nitrogen was passed through the liquid for twenty minutes to remove oxygen. After oxygen removal, the buret was opened briefly for the weighed addition of carbonyl compound, and shaken.

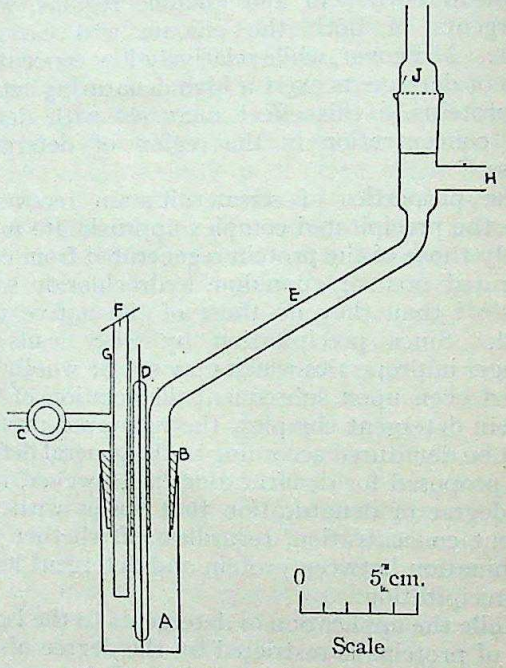

Fig. 2.—Cell and transfer system.

The cell (Fig. 2-A), the bottom covered with a layer of mercury, was fitted tightly over the #5 rubber stopper (B) through which were sealed auxiliary connections: a vent (C) equipped with a stopcock, a glass-covered connection to the mercury pool (D), and a filling tube (E). The dropping mercury electrode (F) entered the cell through the vent to which it must be sealed (G) by a rubber sleeve or by a sealing compound. Nitrogen under a pressure of 15 cm. of water was connected to the filling tube at the hose connection (H) and by the adapter (J).

After assembling the system the vent was opened and the system flushed with nitrogen for about five minutes. The vent was then closed, the ground glass joint opened, and the weighing buret, containing the sample, rapidly inserted between the adapter (J) and the filling tube. The cell and sample were protected from oxygen during this operation by the stream of nitrogen issuing from the filling tube and the adapter. When the buret stopcock was opened the sample solution could flow into the cell.

This system permitted mixing and transfer of solutions without serious absorption of oxygen and without serious loss of volatile carbonyl compounds.

Other runs were made using a large cell (capacity, 25 to 50 ml.) covered with a #10 rubber stopper. The dropping mercury electrode, the connection to the mercury pool, an aeration tube, a vent, and two standard taper 10/30 ground joints, outer members, were sealed into the stopper. A buret, 5 × 0.02 ml. capacity, fitted into one ground joint. The other served as the bearing for a paddle stirrer which could be turned manually through about 60° of angular rotation. In using this cell a definite volume of supporting electrolyte was added and the cell tightly closed except for the vent. Oxygen was removed by bubbling with water-saturated nitrogen. Aeration was then stopped leaving nitrogen at a pressure of about 2 inches of water connected to the vent. A blank was run, then carbonyl solution (in

(3) N. H. Furman, C. E. Bricker and E. B. Whitesell, *Ind. Eng. Chem., Anal. Ed.*, **14**, 333 (1942).

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oxygen-free standard supporting electrolyte) was added from the buret, mixed by the stirring paddle with the liquid in the cell, and run. By this means a series of results could be obtained without changing the cell.

The actual cells used corresponded to the above descriptions except that some were provided with water jackets for temperature control. Cells without jackets were controlled by immersion in thermostat water. All polarograms were run at 25.0 ± 0.2°.

Purity and Purification of Materials.—The inorganic reagents were of reagent grade and were used without further purification. Polarographic tests indicated that no significant quantity of impurity was present. The hydrazine sulfate (Baker Analyzed) was assumed to be pure. Sulfuric and hydrochloric acids were analyzed before use. Mercury was of a grade suitable for polarographic work.

Merck Reagent acetone, b. p. 55.5–57.5°, was used without further purification. Other carbonyl compounds were of C. P. or technical grade and were carefully purified in a 3 foot by 0.5 inch rectifying column packed with Fenske rings. Fractions were considered to be pure when they condensed within 0.1° of the accepted boiling point at reflux ratios exceeding 20/1.

Results

Diffusion current values for the four carbonyl compounds were determined over the concentration range 0.0001 to 0.01 M and are summarized in Table I and in Figs. 3 and 4. In this table the data are represented through second degree equations of the type $R = AC + BC^2$. All results were obtained with a standard supporting electrolyte solution having the composition: hydrazine sulfate 0.100 M, sulfuric acid 0.0500 M, hydrochloric acid 0.00100 M. Higher concentrations of hydrazine sulfate were impractical, due to solubility considerations. In this solution the ratio, total electrolyte/carbonyl, falls below the conventional minimum, 50, when the carbonyl concentration exceeds 0.006 M. This would normally lead to coulomb effects. Since, however, diffusion current values are consistent over the concentration range 0.0001 to 0.010 M (i_d/C is a linear function of C) coulomb forces do not appear to be appreciable. Control experiments showed that thirty minutes must be allowed for reaction of the carbonyl compounds with this solution.

The method is useful at concentrations below 0.0001 M, but the configuration of the waves is such that a highly empirical method for determination of the diffusion current must be used. Because of the large maximum in the second carbonyl wave quantitative measurements of its diffusion current were not attempted. The diffusion current of the first carbonyl wave was determined by locating the inflection point between the two carbonyl waves and by measuring the difference in current between the inflection point and the point at which the extrapolated residual current reaches the potential of the inflection point. The same method was used in evaluating the chloride diffusion current.

Diffusion currents were calibrated by the pilot-ion technique.[1] The carbonyl diffusion current, i_d, was divided by the diffusion current of chloride ion, i'_d, at 0.00100 M, giving the ratio, R. All results were expressed in terms of R but may be converted to absolute values by the tip data above and the corresponding average value for i'_d at 0.00100 M, $i'_d = 5.59$ μa.

$$i'_d/m^{2/3}t^{1/6} = 5.59/1.745 = 3.20$$
$$i_d = i'_d R = 3.20 m^{2/3}t^{1/6} R$$

Use of the values for R below with other dropping electrodes and with other polarographs may be made by conversions to absolute values or by the pilot-ion technique.

Two attempts were made to predict total diffusion current for carbonyl mixtures (aldehydes and ketones do not give separate waves) from the

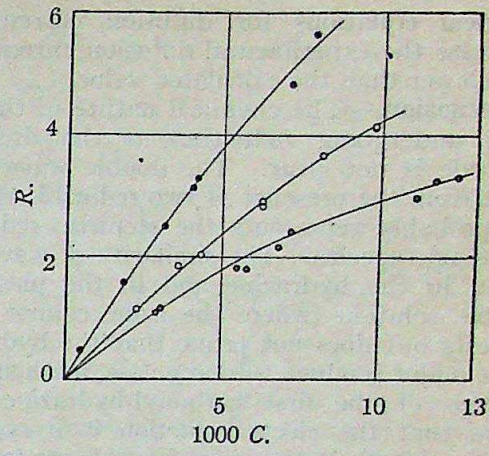

Fig. 3.—Reduction of aldehydes and ketones in hydrazine solution: ●, isobutyraldehyde; O, acetone; O, methyl n-amyl ketone.

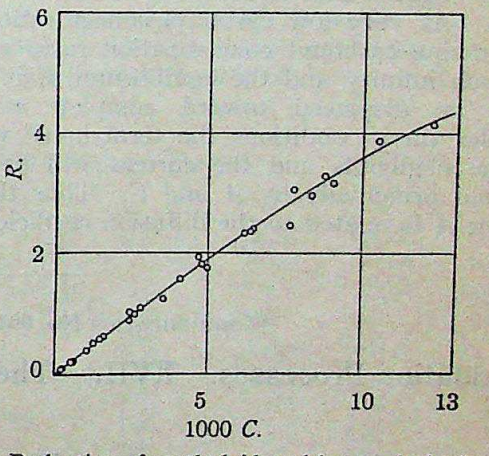

Fig. 4.—Reduction of methyl i-butyl ketone in hydrazine solution.

TABLE I

THE REDUCTION OF CARBONYL COMPOUNDS IN STANDARD HYDRAZINE SOLUTION: EMPIRICAL EQUATIONS RELATING R AND C. GENERAL EQUATION: $R = AC + BC^2$

Carbonyl compound	A	B	Mean deviation, %
Isobutyraldehyde	944	−36,300	4.5
Acetone	559	−15,100	2.4
Methyl i-butyl ketone	403	−4,960	4.9
Methyl n-amyl ketone	416	−12,900	4.4

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empirical equations for diffusion current. In each case the experimental diffusion current was much lower than the calculated value.

Discussion.—The chemical nature of the material undergoing reduction at the dropping electrode is not clear. The double wave could result from the presence of two reducible species, but probably represents the stepwise reduction of a single species. The similarity of waves obtained in the hydrazine and in the phenylhydrazine solution (where the azine cannot form) suggests but does not prove that the hydrazone is the major product. In any case, mathematical analysis of the first carbonyl-hydrazine wave shows that the electroreduction is irreversible, a value of 0.62 electron transferred being found.

The relatively low diffusion currents obtained at high concentrations and with carbonyl mixtures suggest that equilibrium exists in the system. At very low carbonyl concentrations the hydrazine–carbonyl concentration ratio will approach infinity and the equilibrium, if it exists, will be displaced toward complete reaction. Under these conditions the term in C^2 will become negligible and the current will be determined principally by A and C. Thus the constant A is related to the diffusion coefficient and the irreversibility factors, while B is related to the equilibrium constant of the reaction or reactions.

The mean deviation of all values for R is about 4% and is about three times the mean deviation of values for the chloride diffusion current. The increased deviation is due to the carbonyl wave, possibly because the system has not been adequately controlled. It is more probable, however, that the increased deviation is due to difficulties in locating precisely the inflection point between the carbonyl waves and to the possibility that the recorded wave, resulting from a dynamic instrument, does not accurately or consistently represent the rapidly changing electrode processes in the region of an inflection point.

Summary

It has been shown that aldehydes and ketones can be analyzed polarographically in acid hydrazine solution. The relationship between diffusion current and concentration has been determined for one aldehyde and three ketones over the range 0.0001 M to 0.01 M, and has been expressed by second degree equations. The precision of the method varies between 2 and 5%.

NEWARK, DELAWARE RECEIVED JANUARY 3, 1944

[COMMUNICATION NO. 963 FROM THE KODAK RESEARCH LABORATORIES]

Oxidation Processes. XVII.[1] The Autoxidation of Ascorbic Acid in the Presence of Copper

BY A. WEISSBERGER AND J. E. LUVALLE

Introduction

In the preceding paper of this series we reported on the autoxidation of *l*-ascorbic acid at *p*H from 4.7 to 9.2, in the presence of sufficient cyanide and thiocyanate to suppress the catalytic action of metals. Under these conditions, both the monovalent and the divalent ion of the acid participate in the reaction. With oxygen of atmospheric pressure, the divalent ion reacts 10^5 times faster than the monovalent ion. If the partial pressure of the oxygen is reduced to 1/5, the reaction rate of the divalent ion sinks in proportion to the oxygen concentration, but not the reaction rate of the monovalent ion. The latter ion undergoes a slow process before it reacts with the oxygen, probably forming a reactive radical in the interaction with dehydroascorbic acid. In the absence of cyanide and thiocyanate and in the presence of copper, the reaction rate of the monovalent ion is proportional to the oxygen concentration.[1] This shows that the metal-catalyzed autoxidation of the monovalent ion is more rapid than the slow process just mentioned.

The question arises whether the effect of the metal on the reaction of the monovalent ion explains fully the metal catalysis in the autoxidation of ascorbic acid, or whether the autoxidations of unionized ascorbic acid and divalent ion are likewise catalyzed by copper. This problem is treated in the present paper.

Materials and Methods

l-Ascorbic Acid.—Eastman Kodak Co. *l*-ascorbic acid was used.

Water was redistilled in an all-Pyrex still.

Oxygen in cylinders (Linde) was used.

Sodium *p*-Phenolsulfonate.—Eastman Kodak Co. sodium *p*-phenolsulfonate dihydrate was recrystallized several times from distilled water, which for the last two recrystallizations had been redistilled as stated above.

All other chemicals were Baker Analytical or General Chemical Company Reagent Grades.

Apparatus and techniques were those described in the preceding papers of this series, using the two-chamber reaction vessel.[2] The temperature was 20.03 ± 0.02°. Each volume read was corrected to a barometric pressure of 760 mm. The reaction mixtures had a volume of 50 ml. The buffers, present in a concentration of 0.20 molar, were monopotassium phosphate, potassium hydrophthalate, sodium acetate, dipotassium phosphate and sodium *p*-phenolsulfonate. They were adjusted to the proper *p*H with nitric acid or potassium hydroxide.

(1) Part XVI, Weissberger, LuValle and Thomas, THIS JOURNAL, 65, 1934 (1943). (On p. 1936, right column, line 15, it should read 0.001 *m* mole instead of 0.001 mole.)

(2) Weissberger, Mainz and Strasser, *Ber.*, 62, 1942 (1929).

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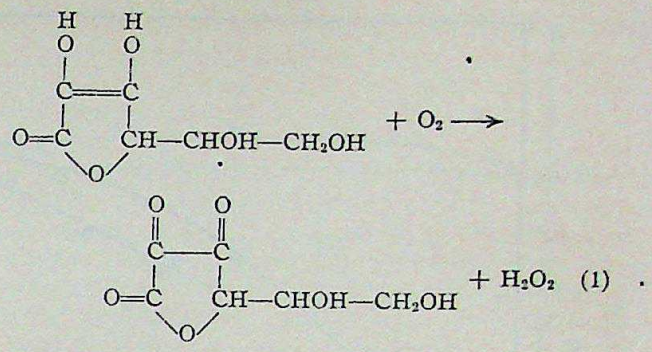
Before the start of the reaction, buffer and cupric nitrate in 45 ml. of water were placed in the lower chamber of the reaction vessel; the ascorbic acid in 5 ml. of water acidulated with 0.2 mmole of nitric acid was in the upper chamber.

Results and Discussion

The experimental results are collected in the table. The headings of the first five columns are the same as those in Table I of the preceding paper.[1] In the sixth column is listed the concentration of the solutions with respect to cupric nitrate as calculated from the amount of the salt added and the total volume of the reaction mixtures (50 ml.).

In column seven is listed the *total oxygen uptake*, a_{ob}, in mole O_2/mole ascorbic acid; a_{ob} is defined as the volume of oxygen absorbed after a time $t = 10\tau$ where τ is the time required for the absorption of 0.5 mole of oxygen per mole of ascorbic acid. If ascorbic acid reacts with oxygen forming dehydroascorbic acid and hydrogen peroxide according to equation 1



(1)

then theoretically one mole of oxygen will be absorbed per mole of ascorbic acid, provided the hydrogen peroxide neither reacts with ascorbic acid nor decomposes to oxygen and water. Either of the latter reactions might lower the total volume of oxygen absorbed to 0.5 mole, while a reaction of the peroxide with dehydroascorbic acid or its decomposition products would not affect this volume. The reaction of hydrogen peroxide with dehydroascorbic acid is very rapid in the

TABLE I

AUTOXIDATION OF ASCORBIC ACID, 0.00800 MOLE/LITER

Buffer 0.200 *M*	Initial *p*H	Final *p*H	P_{O_2}, mm.	Monovalent ascorbate ion, %/100	Metal added mole/l. × 10^6 $Cu(NO_3)_2$	a_{ob}. O_2/H_2A	k_1', min.$^{-1}$ × 10^5	k_1, min.$^{-1}$ × 10^3	k_{Cu}, min.$^{-1}$ × 10^3	k'_{Cu}, min.$^{-1}$
$KHCO_3$	9.32	9.14	740.8	0.9936	20.0	1.12	119	28.2	91	0.092
$KHCO_3$	9.31	9.15	733.0	.9936	20.0	1.11	129	28.2	101	.10
K_2HPO_4	7.49	7.54	730.5	.9995	20.0		170	0.484	170	.17
K_2HPO_4	7.01	7.07	730.3	.9986	20.0		153	.216	153	.15
KH_2PO_4	6.66	6.70	730.3	.9972	20.0		179	.158	179	.18
K_2HPO_4	6.19	6.24	737.4	.9915	20.0		125	.105	125	.13
K_2HPO_4	6.14	6.18	736.1	.9905	40.0	0.77	171	.100	171	
K_2HPO_4	6.12	6.15	736.8	.9901	20.0	.79	134	.0988	134	.13
K_2HPO_4	6.09	6.14	734.7	.9893	12.0	.81	108	.0958	108	
K_2HPO_4	6.09	6.20	733.6	.9893	4.00	.83	54.6	.0958	54.5	
K_2HPO_4	6.12	6.05	733.0	.9901	0.00		3.41	.0988	3.31	
K_2HPO_4	5.62	5.72	739.8	.9693	20.0		111	.0638	111	.12
NaO_2CCH_3	5.08	5.08	733.2	.9007	20.0	.80	90.8	.0398	90.8	.10
NaO_2CCH_3	3.87	3.86	736.2	.3595	20.0	.76	26.0	.0142	26.0	.072
KH_2PO_4	2.59	2.64	738.1	.0286	20.0		2.48	.0080	2.47	.087
$NaO_3SC_6H_4(p)OH$	9.32	9.29	732.9	.9936	20.0		43.0	29.0	14.0	.014
$NaO_3SC_6H_4(p)OH$	8.35	8.36	732.9	.9992	20.0		39.8	3.35	36.4	.036
$NaO_3SC_6H_4(p)OH$	7.95	7.89	734.8	.9996	200.0	.94	153	1.36	152	
$NaO_3SC_6H_4(p)OH$	7.94	7.93	733.1	.9996	160.0	.94	124	1.35	123	
$NaO_3SC_6H_4(p)OH$	7.95	7.89	730.2	.9996	120.0	.95	110	1.36	109	
$NaO_3SC_6H_4(p)OH$	7.94	7.95	728.5	.9996	80.0	.96	83.0	1.35	81.7	
$NaO_3SC_6H_4(p)OH$	7.92	7.88	723.9	.9996	40.0	.96	56.1	1.26	54.8	
$NaO_3SC_6H_4(p)OH$	7.93	7.88	734.4	.9996	20.0	1.00	30.2	1.30	28.9	.029
$NaO_3SC_6H_4(p)OH$	7.91	7.80	735.9	.9996	0.00	1.02	2.02	1.24	0.78	
$NaO_3SC_6H_4(p)OH$	7.87	7.77	736.6	.9996	20.0		33.9	1.13	32.8	.033
$KH(O_2C)_2C_6H_4$	5.42	5.50	740.8	.9521	20.0		72.8	0.0537	72.8	.076
$KH(O_2C)_2C_6H_4$	4.88	4.95	738.8	.8516	20.0		37.7	.0338	37.7	.044
$KH(O_2C)_2C_6H_4$	4.36	4.42	739.5	.6325	20.0		21.0	.0214	21.0	.033
$KH(O_2C)_2C_6H_4$	4.28	4.36	732.7	.5901	20.0		21.8	.0199	21.8	.037
$KH(O_2C)_2C_6H_4$	4.29	4.35	730.9	.5968	40.0		34.6	.0199	34.6	
					$AgNO_3$					
NaO_2CCH_3	5.12	5.17	736.5	.9090	20.0		2.54			
NaO_2CCH_3	5.10	5.08	740.2	.9052	00.0		2.27			

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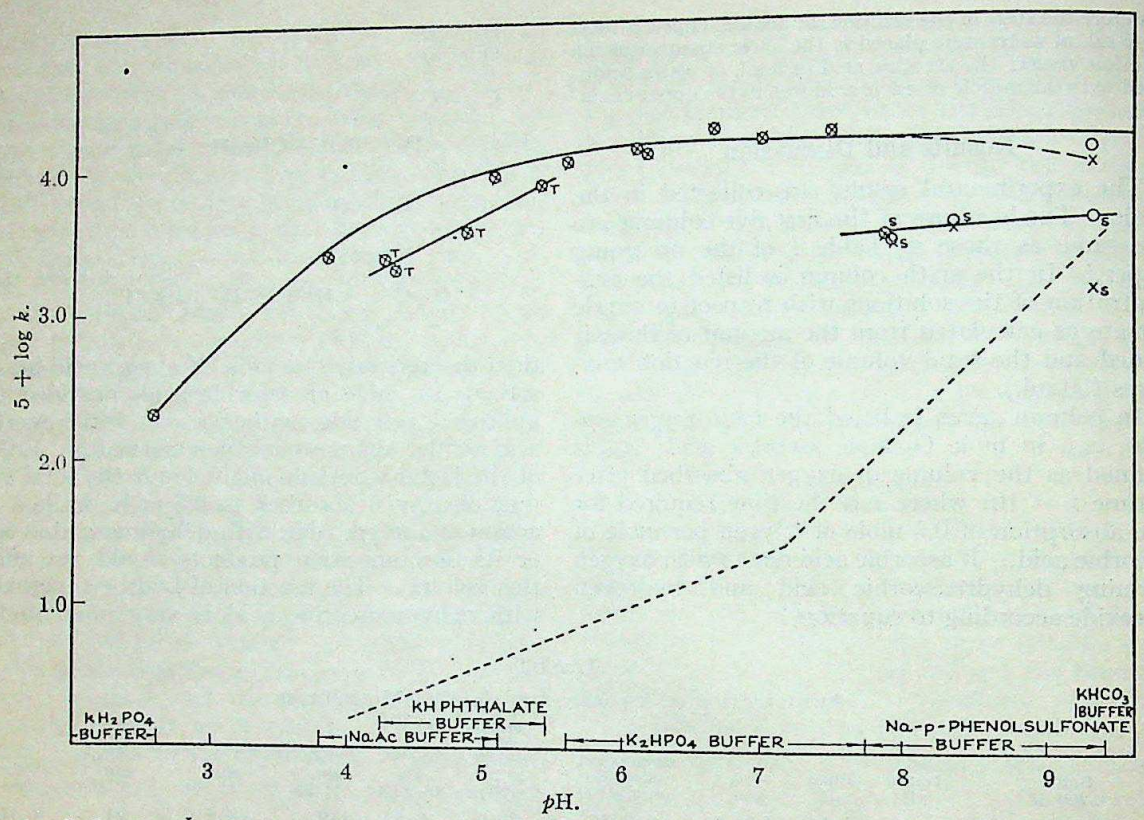

Fig. 1.—O, $5 + \log k^{I}$; ×, $5 + \log k_{Cu}$; . . . . . , $5 + \log k_1$; *T*, $C_6H_4(COO)_2HK$ buffer; *S*, $NaO_3SC_6H_4OH$ buffer.

alkaline range[3] in analogy to the common behavior of α-diketones.[2,4]

In the presence of copper the total uptake at *p*H 7.9 is close to the theoretical of eq. 1. At higher *p*H, a_{ob} is higher, 1.11 mole O_2 per mole of ascorbic acid at *p*H 9.3, presumably because decomposition products of dehydroascorbic acid absorb O_2.[1,5] At *p*H 7.8 to 6.2, the experiments were not observed sufficiently long to obtain a_{ob}. At *p*H 6.12 and down to *p*H 3.9, a_{ob} reaches only 80% of the theoretical value required by eq. 1, indicating that about 40% of the hydrogen peroxide decomposes to O_2 and H_2O, or 20% reacts with the ascorbic acid. Probably both reactions take place; the decomposition of hydrogen peroxide is catalyzed by cupric ion,[6] and the same catalysis has been suggested for the reaction of hydrogen peroxide with ascorbic acid.[7]

The plot of log $(a_{th}-x)$—where a_{th} is the theoretical volume of O_2 required by eq. 1 and x is the oxygen absorbed at the time t—against t is linear up to 80% of the theoretical uptake a_{th}, except for solutions of *p*H 5, which give straight lines for only 50% of the theoretical uptake.[8] This linearity justifies the calculation of a first-order reaction constant, k, by multiplication of the slope of the straight line with −2.303. The value of k corrected to an oxygen pressure of 760 mm. by multiplication with 760/(barometric pressure − P_{H_2O}) during the experiment is k^{I}. P_{H_2O}, the partial pressure of water at 20° is 17.5 mm.

The linearity of log $(a_{th} - x)$ *vs.* t shows in accordance with the literature,[9,1] that k is independent of the *concentration of ascorbic acid*. The dependence of the autoxidation rate on the *oxygen concentration* is reviewed in the introduction. The *dependence of log k^{I} on pH* of solutions to which is added 2×10^{-5} mole/liter of cupric nitrate, is shown in Fig. 1. The experimental points are marked by O. Those obtained in phosphate, acetate and carbonate buffer lie on a smooth curve. The rate in phthalate and *p*-phenolsulfonate buffer is lower than in phosphate, acetate and carbonate at the same *p*H.

The smooth log k^{I}/*p*H curve is discussed first. Barron, DeMeio and Klemperer[9a] as well as Schummer[9b] showed that ascorbic acid reacts

(3) Steinman and Dawson, THIS JOURNAL, 64, 1212 (1942).
(4) Weitz and Scheffer, *Ber.*, 54, 2327 (1921).
(5) Bowen, Davenport, Jeffrays and Warner, *J. Biol. Chem.*, 117, 237 (1937); Dodds, *Univ. of Pittsburgh Bull.*, 37, 84 (1941).
(6) Von Kiss and Lederer, *Rec. trav. chim.*, 46, 453 (1927).
(7) Hand and Greisen, THIS JOURNAL, 64, 358 (1942).
(8) One must wonder whether the experiments by Peterson and Walton, THIS JOURNAL, 65, 1212 (1943), justify the assumption of an autocatalytic reaction made by these authors. Their results might rather indicate a failure to keep the reaction mixture saturated with oxygen. This will depress the rate in the beginning of a reaction more than later on, because the volume of oxygen reacting per time unit is greatest at the start. For conditions of saturation with oxygen, see Weissberger, Mainz and Strasser, *Ber.*, 62, 1942 (1929); Weissberger and Thomas, THIS JOURNAL, 64, 1561 (1942).
(9) (a) Barron, DeMeio and Klemperer, *J. Biol. Chem.*, 112, 625 (1926); (b) Schummer, *Biochem. Z.*, 304, 1 (1940); (c) Dekker and Dickinson, THIS JOURNAL, 62, 2165 (1940).

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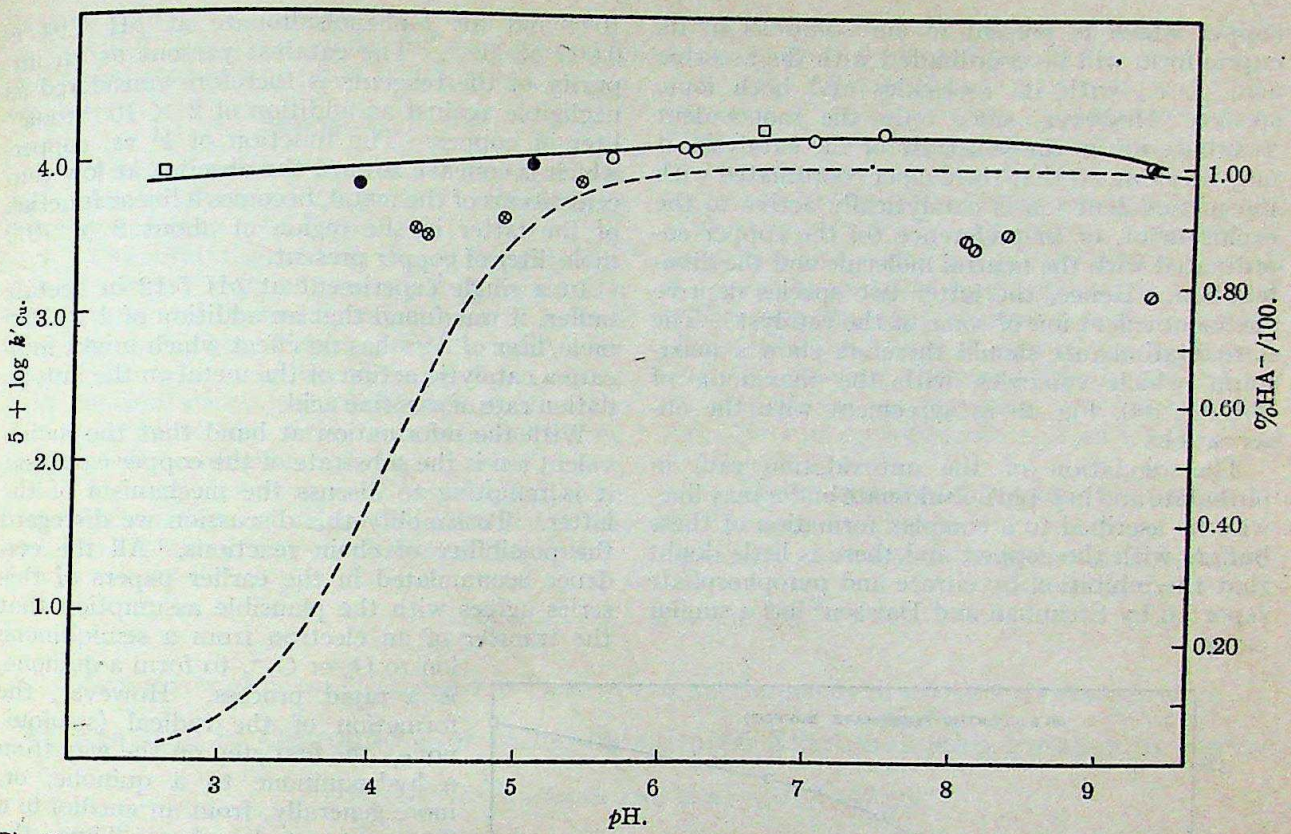

Fig. 2.— ———, $5 + \log k'_{Cu}$; — — — —, %HA⁻/100; ○, K_2HPO_4 buffer; □, KH_2PO_4 buffer; ●, $NaC_2H_3O_2$ buffer; ◑, $KHCO_3$ buffer; ⊕, $NaO_3SC_6H_4OH$ buffer; ⊗, $C_6H_4(COO)_2HK$ buffer.

with oxygen even under conditions which exclude the catalytic action of metals. The rate of this reaction as determined in the preceding paper of this series,[1] is given under k_1 in the table and log k_1 is represented by the dotted line in Fig. 1. If we assume that in the presence of copper the non metal-catalyzed reaction proceeds simultaneously with the copper-catalyzed, the rate of the copper-catalyzed reaction, $k_{Cu} = k^I - k_1$. At *p*H 2.59 to 7.73, k_1 is negligible in comparison with k^I, but at higher *p*H, log k_{Cu} differs appreciably from log k^I, as shown by Fig. 1, where x denotes log k_{Cu}.

In order to investigate whether copper catalyzes only the autoxidation of the monovalent ion or also that of the un-ionized acid and the divalent ion, we divide k_{Cu} by %HA⁻/100, *i. e.*, by the fraction of the monovalent ion,[1] at the respective *p*H, to obtain k'_{Cu}. The fraction %HA⁻/100 plotted against *p*H gives the dotted curve in Fig. 2, while log k'_{Cu} is represented by O and the solid line. The points corresponding to the smooth curve in Fig. 1 are approximately on a parallel to the abscissa. Such a parallelism should be expected if the *copper affects only the autoxidation of the monovalent ion of ascorbic acid and does not accelerate noticeably the autoxidation of the divalent ion or of the un-ionized acid.* According to these observations, the reactivity of the monovalent ion in the presence of 2×10^{-5} mole/liter of copper, k'_{Cu}, in the *p*H range 2.6 to 9.3 is 0.12 ± 0.03 min.$^{-1}$. It is 10^4 times greater than the reactivity of the monovalent ion in the absence of metal catalysis, k'.[1]

However, it must be noticed that the solid line in Fig. 2, which is drawn through the points corresponding to the smooth curve in Fig. 1, is not strictly straight and parallel to the abscissa, but provides for a flat maximum around *p*H 8. Although no measurements were made between *p*H 7.5 and 9.3 for lack of a suitable buffer, and although the rate at *p*H 9.3 is close to the limit of capacity of our apparatus,[8] this rate was ascertained by repeated measurements, and we believe that the maximum is real. It is readily explained as follows. The added copper, 2×10^{-5} molar, cannot be assumed to be present as atoms or free ions. No measurable solubility of copper atom could be found recorded in the literature. For cupric ion, according to Latimer's data,[10] the concentration of the saturated solution sinks below 2×10^{-5} at *p*H 6.5, and for cuprous ion the drop should occur around *p*H 4, caused in both cases by the precipitation of the respective hydroxides. Saturation phenomena were observed at neither of these *p*H values. On the other hand, cupric ion readily forms complexes with organic hydroxy compounds,[11] and

(10) Latimer, "Oxidation Potentials," Prentice-Hall, New York, N. Y., 1938, pp. 174, 175.

(11) (a) Kahlenberg, *Z. physik. Chem.*, **17**, 577 (1895); (b) F. J. Bates and associates, "Polarimetry, Saccharimetry and the Sugars," National Bureau Standards Circ. 440, 1942, p. 167.

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copper which is present in our solutions in its cupric form will be coördinated with the ascorbic acid, *i. e.*, with its molecules and both ionic species. However, since only the monovalent ascorbate ion is the substrate of the catalysis, it may be assumed that the copper coördinated with the monovalent ion is catalytically active to the exclusion of, or in preference to, the copper coördinated with the neutral molecule and the divalent ion. Hence, the latter two species deprive the monovalent ion of some of the catalyst. The autoxidation rate should therefore show a maximum which coincides with the maximum of $\%HA^-/100$, Fig. 2, in agreement with the observations.

The deviation of the autoxidation rate in phthalate and in *p*-phenolsulfonate buffer may likewise be ascribed to a complex formation of these buffers with the copper, and there is little doubt that the inhibition by citrate and pyrophosphate reported by Steinman and Dawson[3] has a similar cause.

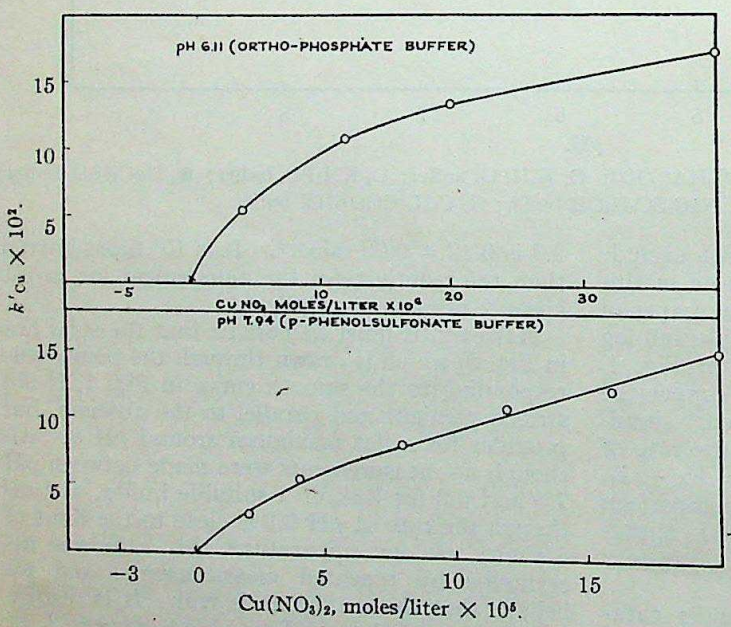

Fig. 3.

There remains to be discussed some scant experiments on the *dependence of k on the copper concentration*. In Fig. 3, k^I is plotted against the amount of copper added at *p*H 6.11 in phosphate and at *p*H 7.94 in *p*-phenolsulfonate buffer. The reaction rates at the same *p*H in the presence of cyanide and thiocyanate are used as the origin of the coördinates, and the reaction rates in the buffers, without addition of either cyanide and thiocyanate or copper, are marked by *X*. If one draws a smooth curve through all the points and the origin for a given *p*H, one can interpolate the amount of copper which would cause k^I to be raised from the origin to the value marked by *X*. This for phosphate at *p*H 6.11 is 0.03 × 10^{-5} and for *p*-phenolsulfonate at *p*H 7.94 is 0.005 × 10^{-5}. The catalyst present as an impurity of the reagents is therefore considered as negligible against an addition of 2 × 10^{-5} mole/liter of copper. The function of k^I *vs.* copper, which is concave toward the abscissa at low concentrations of the metal, becomes a linear function of the latter in the region of about 2 × 10^{-5} mole/liter of copper present.

In a single experiment at *p*H 5.12 in acetate buffer, it was found that an addition of 2 × 10^{-5} mole/liter of Ag^+ has no effect which might indicate a catalytic action of the metal on the autoxidation rate of ascorbic acid.

With the information at hand that the monovalent ion is the substrate of the copper catalysis, it is tempting to discuss the mechanism of the latter. To simplify this discussion we disregard the possibility of chain reactions. All the evidence accumulated in the earlier papers of this series agrees with the plausible assumption that the transfer of an electron from a semiquinone ion to O_2 or O_2^-, to form a quinone, is a rapid process. However, the formation of the radical (semiquinone), the first step on the way from a hydroquinone to a quinone, or, more generally, from an enediol to a diketone, can be slow. Thus, the dependence of k'_1 on O_2 indicated that in the autoxidation of the monovalent ascorbate ion in the absence of metals "the formation of an intermediate of semiquinone-like structure" is the rate-determining step.[1] Hence, it is a sufficient reason for the catalytic action of copper in the autoxidation of ascorbic acid, if the metal accelerates the reaction $HA^- \rightarrow A^- + H$.[12] This, as it is written, involving the elimination of hydrogen atom, is most improbable, while the sequence $HA^- \rightarrow HA + e$, $HA \rightleftharpoons H^+ + A^-$ presents a plausible process in which copper ion may act as electron acceptor. Correspondingly, the copper ion should undergo the change $Cu^{++} \rightarrow Cu^+$, or $Cu^+ \rightarrow Cu$. The second alternative is unlikely because it would lead to plating out of copper. On the other hand, Cu^{++}, as mentioned above, will be coördinated with the ascorbic acid. Hence, the monovalent ascorbate ion may change to the semiquinone-like radical by an electron transfer within the complex of Cu^{++} with the monovalent ion, $[Cu^{++}, HA^-] \rightarrow Cu^+$, HA. No indication was found in the literature[11b] for complex formation of Cu^+ with organic hydroxy compounds. Although radicals may

(12) Using the symbol H_2A for ascorbic acid, and, accordingly, A for dehydroascorbic acid, the semiquinone is written as HA and the semiquinone ion as A^-. The latter two species, related to each other by a simple acid ionization, *i. e.*, a fast process, are equivalent kinetically.

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behave differently, the unbracketed "complex" is probably unstable, while the liberated Cu^{+} ion is likely to undergo rapid oxidation to Cu^{++}.

Summary

1. The autoxidation rate of *l*-ascorbic acid in the presence of copper (2×10^{-5} mole/liter) is investigated from *p*H 2.59 to 9.31.

2. The results agree with the assumption that in the primary reaction, one mole of dehydroascorbic acid and of hydrogen peroxide is formed from one mole of ascorbic acid and oxygen.

3. The rate is independent of the ascorbic acid concentration, and, as shown in the preceding paper of the series, proportional to the oxygen concentration.

4. At very low copper concentrations, the rate increases faster than the concentration of the metal. At higher concentrations of the latter, the rate increase becomes proportional to the increase in the copper concentration.

5. The dependence of the rate on *p*H in the presence of copper has the appearance of being complex. However, analysis shows that neither the neutral acid nor the divalent ion, but *only the monovalent ion of l-ascorbic acid is the substrate of the copper catalysis*, and that the apparent irregularity in the dependence of the rate on *p*H is caused by complex formation of some of the buffers with the copper catalyst. A concentration of 2×10^{-5} mole/liter of copper, about 4 mg. of $Cu(NO_3)_2$ per liter, increases the reaction rate of the monovalent ascorbate ion by a factor of 10^4.

6. No corresponding effect of silver was found at *p*H 5.12.

7. The mechanism of the catalysis is discussed briefly.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

The Reaction of Dibromides of Mono-substituted Ethylenes with Potassium Iodide

BY DAVID PRESSMAN AND WILLIAM G. YOUNG

Iodide ion reacts with the dibromide of an olefinic compound to yield the original unsaturated compound, bromide ion and triiodide ion according to equation 1.[1]

$$RCHBrCH_2Br + 3I^- \longrightarrow 2Br^- + I_3^- + RHC{=}CH_2 \quad (1)$$

The reaction proceeds first order with respect to the dibromide concentration and also with respect to the iodide ion concentration in 99% methanol solution and is practically independent of the triiodide ion concentration.

We have shown that in the reactions of dibromides of *cis* and *trans* olefins with potassium iodide the reaction is slower for the dibromide from the *cis* olefin[2] and that the olefin produced is in its original stereoform in the case of the 2-butene dibromides.[3] The reaction takes place presumably through the attack by an iodide ion to remove a positive bromine atom as iodine bromide while, simultaneously, the electron pair which is left unshared by this removal attacks the carbon face opposite the remaining bromine atom forming a double bond and liberating a negative bromide ion.[3]

Our purpose in this research was to determine the reactivity of various mono-substituted ethylene dibromides with iodide ion. The reactions were studied in 99% methanol at two or more temperatures.

(1) R. T. Dillon, THIS JOURNAL, **54**, 952 (1932).
(2) W. G. Young, D. Pressman and C. D. Coryell, *ibid.*, **61**, 1640 (1939).
(3) S. Winstein, D. Pressman and W. G. Young, *ibid.*, **61**, 1645 (1939).

Experimental

Rates of Reaction.—The rate constants were obtained graphically by the use of equation 2

$$\mathrm{d}\log_{10}\frac{1-3b\varphi/a}{1-\varphi}\Big/\mathrm{d}t = \frac{a-3b}{2.303}k_{obs.} \quad (2)$$

where a and b are the initial iodide and dibromide concentrations respectively, φ is the fraction of dibromide reacted and t is the time in hours. The following corrections were made as discussed previously[2]: (a) correction to standard temperature of 45.00, 60.00, 75.00, 80.00 or 85.00°, (b) correction for activity of solvent (methanol preparations I, II, III are the same as those used previously[2]), (c) correction for salt effect, and (d) correction for solvent expansion.[4]

Preparation of Materials

1-Pentene dibromide was prepared by mixing slowly at 0° bromine with the 1-pentene obtained from ethylmagnesium bromide and allyl bromide. The product was fractionated through a Weston column and the fraction boiling at 84.5–85.5° at 15 mm. was used.

Acrylic Acid Dibromide.—The Eastman Kodak Co. product melting at 59–61° was used.

Styrene dibromide was prepared from styrene and bromine in carbon disulfide. The solvent was evaporated and the product recrystallized from alcohol; m. p. 74.0–74.5°.

Allylbenzene dibromide was prepared by brominating, in carbon tetrachloride, allylbenzene obtained from allyl bromide and phenylmagnesium bromide. The product was fractionated and the fraction boiling at 126° at 2 mm. was used.

Allyl Alcohol Dibromide.—The Eastman Kodak Co. product was refractionated and the fraction boiling 113–114° at 13 mm. was used.

(4) Corrections of 3.0, 4.8, 6.8, 7.6 and 8.1% were made at temperatures 45, 60, 75, 80 and 90°, respectively; (see ref. 2) Landolt–Börnstein, "Tabellen," Verlag von Julius Springer, Berlin, 1923, Vol. I, p. 278.

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TABLE I

REACTION RATE CONSTANTS AND HEATS OF ACTIVATION FOR THE REACTION OF $RCHBrCH_2Br$ WITH POTASSIUM IODIDE

Parent compound	R	k, obs.	Temp., °C.	KI, moles/l., [a]	Dibromide moles/l., [b]	k cor.[d]	k cor., KI = 0.25	Av. k l./mole hr.	Deviation, %	$\Delta H^{\ddagger}$, KI = 0.25
Ethylene	H	1.34[a]	74.93	0.22	0.022	1.54		(1.54)[e]		23.2
		0.299[a]	59.72	.22	.027	0.344		(.344)[e]		
Propylene	CH_3	.0582[a]	74.93	.22	.024	.0669		(.0669)[e]		25.2
		.0113[a]	59.72	.22	.022	.0130		(.0130)[e]		
1-Butene	C_2H_5	.0794[a]	74.93	.23	.034	.0913		(.0913)[e]		25.8
		.0148[a]	59.72	.22		.0171		(.0171)[e]		
Acrylic acid	COOH	3.985[b]	85.38	.243	.023	4.26	4.28	4.27	0.2	20.9[f]
		3.985[b]	85.38	.248	.023	4.26	4.26			
		1.665[b]	74.91	.252	.021	1.825	1.822	1.825	.2	
		1.665[b]	74.90	.251	.022	1.830	1.828			
		0.417[b]	79.46	.256	.025	0.468	0.466	0.467	.1	
		.416[b]	79.46	.252	.021	.467	.467			
		.1021[b]	44.75	.238	.023	.1100	.1108	.1109	.1	
		.1028[b]	44.75	.241	.025	.1103	.1109			
Allyl alcohol	CH_2OH	.0978[b]	74.90	.245	.027	.1075	.1090	.1079	1.0	25.2
		.0972[b]	74.91	.254	.027	.1070	.1068			
		.01905[c]	59.64	.248	.028	.02079	.02081	.02107	1.2	
		.01955[c]	59.64	.249	.023	.02131	.02133			
Allylbenzene	CH_2	.0915[c]	74.95	.278	.022	.0983	.0967	.0978	1.0	24.6
		.0915[c]	74.95	.242	.021	.0983	.0988			
		.01834[c]	59.64	.251	.020	.02000	.01998	.01987	0.6	
		.01811[c]	59.64	.252	.022	.01978	.01976			
Bromoethylene	Br	.0557[b]	85.37	.310	.026	.0591	.0571	.0581	1.7	25.0
		.0558[b]	85.37	.251	.028	.0592	.0591			
		.01930[b]	74.90	.255	.029	.02121	.02115	.02134	0.9	
		.01945[b]	74.90	.242	.028	.02141	.02152			
1-Pentene	C_3H_7	.0900	74.55	.242	.023	.1007	.1012	.1006	.6	24.8
		.0896	74.60	.248	.022	.0999	.1000			
		.01837[c]	59.64	.240	.020	.02000	.02012	.02015	.2	
		.01850[c]	59.64	.248	.020	.02016	.02018			
Styrene	C_6H_5	4.05[b]	85.36	.239	.023	4.34	4.37	4.34	.7	21.7[f]
		4.03[b]	85.36	.246	.023	4.30	4.31			
		2.657	80.12	.258	.025	2.880	2.868	2.868		
		1.612	74.55	.244	.021	1.796	1.802	1.811	.5	
		1.648	74.59	.261	.025	1.831	1.820			
		0.389	59.48	.249	.024	0.429	0.429	0.436	1.6	
		.3925[b]	59.48	.211	.028	.433	.442			
		.0860[b]	44.75	.251	.021	.0925	.0924	.0931	0.8	
		.0862[b]	44.75	.231	.021	.0926	.0937			

[a] These data were reported by Dillon using methanol which gave rate constants 7% lower than those obtained with the synthetic product (I) used as a standard in this work. [b] Synthetic methanol II, rates 2% lower than in methanol I. [c] Synthetic methanol III, rates same as in methanol I. [d] The constants have been corrected for reactivity of solvent, solvent expansion and to the temperatures 45.00, 60.00, 75.00, 80.00 or 85.00°. [e] These calculations were made from data reported by Dillon. Correction has not been made for the potassium iodide effect. [f] This value was obtained from slope of the curve in Fig. 2.

Bromoethylene Dibromide.—The Eastman Kodak Co. product was refractionated and the fraction boiling at 86.0–87.0° at 18 mm. was used.

Experimental Results

The pertinent date for the compounds studied are in Table I. There are also listed the values of the heats of activation calculated by the Arrhenius equation

$$\Delta H^{\ddagger} = RT^2 \mathrm{d} \ln k_{obs.}/\mathrm{d}t \qquad (3)$$

In Table II are given the observed relative values of the heats of activation $\Delta H^{\ddagger} - \Delta H_0^{\ddagger}$ and the entropies of activation $\Delta S^{\ddagger} - \Delta S_0^{\ddagger}$ (equation 4).[5]

$$\Delta S^{\ddagger} - \Delta S_0^{\ddagger} = \frac{\partial}{\partial T}\left(RT \ln \frac{k}{k_0}\right) \qquad (4)$$

$\Delta H_0^{\ddagger}$ and $\Delta S_0^{\ddagger}$ are, respectively, the heat and entropy of activation of the reference compound, ethylene dibromide.

(5) See L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., New York, N. Y., 1940, Chapter IV.

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TABLE II

RELATIVE ENTROPIES AND HEATS OF ACTIVATION FOR THE REACTION OF $RCHBrCH_2Br$ WITH POTASSIUM IODIDE

Parent compound	R	$k_{75°}$ l./mole hr.	$\Delta S^{\ddagger} - \Delta S_0^{\ddagger}$ cal./deg.	$\Delta H^{\ddagger} - \Delta H_0^{\ddagger}$ kcal.
Ethylene	H	1.54	0	0
Propylene	CH_3	0.0669	−0.5	2.0
1-Butene	C_2H_5	.0913	1.8	2.6
1-Pentene	C_3H_7	.1006	−0.8	1.6
Allylbenzene	$CH_2C_6H_5$	.0978	−1.5	1.4
Styrene	C_6H_5	1.811	−4.0	−1.5
Bromoethylene	Br	0.02134	−3.3	1.8
Allyl alcohol	CH_2OH	.1079	0.4	2.0
Acrylic acid	COOH	1.825	−6.3	−2.3

The observed effect of various substituents, R, on the reaction of $RCHBrCH_2Br$ with iodide ion is to increase the heat of activation in the order $COOH < C_6H_5 < H < C_6H_5CH_2 < C_3H_7 < Br < CH_2OH$, $CH_3 < C_2H_5$ and to increase the entropy of activation in the order: $COOH < C_6H_5 < Br < C_6H_5CH_2 < C_3H_7 < CH_3 < H < CH_2OH < C_2H_5$.

Discussion

The functions $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are in general relatively independent of temperature and are more reliable standards of comparison of reactivity than is the rate constant, since a sequence of order of reactivity as determined by the rate constant at any one temperature may be different at some other temperature. Empirically this occurs in the case of acrylic acid dibromide and styrene dibromide.[6] The rate constant of acrylic acid dibromide is larger than that of styrene dibromide at 45° but smaller at 85°.

However, in the reaction of potassium iodide with unsymmetrical dibromide such as styrene dibromide, even the observed heats of activation and the observed entropies of activation are not reliable bases of comparison of reactivity since they would be expected to be functions of temperature, aside from their general variation with temperature due to changes in the vibrational and rotational energy states with temperature. This arises from the fact that either bromine atom in an olefin dibromide molecule may be attacked by iodide ion and in the case of an unsymmetrical dibromide the two bromine atoms would be attacked at different rates. The rate of liberation of iodine is thus given by the equation

$$\begin{aligned} d(I_3^-)/dt &= (k_1 + k_2)(\text{Dibromide})(I^-) \\ &= k_{obs.}\ (\text{Dibromide})(I^-) \end{aligned} \quad (5)$$

where k_1 and k_2 are the rate constants for the attack of the individual bromine atoms by iodide ion and $k_{obs.}$ is the observed rate constant which is equal to the sum of k_1 and k_2.

The observed heat of activation $\Delta H^{\ddagger}$ is given then by equation 6.

$$d \ln (k_1 + k_2)/dT = \Delta H^{\ddagger}/RT^2 \quad (6)$$

(6) Similar cases have been pointed out by T. L. Davis and R. Heggie, *J. Org. Chem.*, **2**, 470 (1937).

Substituting for k_1 and k_2, their values as given in equations 7 and 8[7]

$$k_1 = \frac{kT}{h} e^{\Delta S_1^{\ddagger}/R} e^{-\Delta H_1^{\ddagger}/RT} \quad (7)$$

$$k_2 = \frac{kT}{h} e^{\Delta S_2^{\ddagger}/R} e^{-\Delta H_2^{\ddagger}/RT} \quad (8)$$

equation 9 is obtained.

$$d \ln \frac{kT}{h}\left(e^{\Delta S_1^{\ddagger}/R} e^{-\Delta H_1^{\ddagger}/RT} + e^{\Delta S_2^{\ddagger}/R} e^{-\Delta H_2^{\ddagger}/RT}\right) dT = \Delta H^{\ddagger}/RT^2 \quad (9)$$

Carrying out the indicated differentiation and neglecting the small term, $1/T$, gives equation 10.

$$\Delta H^{\ddagger} = \frac{\Delta H_1^{\ddagger} e^{(\Delta S_1^{\ddagger} - \Delta S_2^{\ddagger})/R} e^{(\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger})/RT} + \Delta H_2^{\ddagger}}{e^{(\Delta S_1^{\ddagger} - \Delta S_2^{\ddagger})/R} e^{(\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger})/RT} + 1} \quad (10)$$

As the temperature increases the apparent value $\Delta H^{\ddagger}$ approaches the value $(\Delta H_1^{\ddagger} e^{(\Delta S_1^{\ddagger} - \Delta S_2^{\ddagger})/R} + \Delta H_2^{\ddagger})/(e^{(\Delta S_1^{\ddagger} - \Delta S_2^{\ddagger})/R} + 1)$. This reduces to the average $(\Delta H_1^{\ddagger} + \Delta H_2^{\ddagger})/2$ if the entropy of activation is the same for the two reactions, *i. e.*, $\Delta S_1^{\ddagger} = \Delta S_2^{\ddagger}$. As the temperature decreases, the apparent value of $\Delta H^{\ddagger}$ approaches the smaller of the two values $\Delta H_1^{\ddagger}$ or $\Delta H_2^{\ddagger}$. We have adopted the convention that $\Delta H_1^{\ddagger}$ is the smaller.[8]

A more useful equation for discussion is obtained by subtracting $\Delta H_1^{\ddagger}$ from both sides of equation 10 to give equation 11.

$$\Delta H^{\ddagger} - \Delta H_1^{\ddagger} = \frac{\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger}}{e^{(\Delta S_1^{\ddagger} - \Delta S_2^{\ddagger})/R} e^{(\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger})/RT} + 1} \quad (11)$$

This equation shows that the difference between the observed value $\Delta H^{\ddagger}$ and the heat of activation for the reaction of either of the bromine atoms is a function of the relative values $(\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger})$ and $(\Delta S_2^{\ddagger} - \Delta S_1^{\ddagger})$ and of T and is independent of the absolute magnitude of $\Delta H^{\ddagger}$.

In Table III are given for several different assumed values of $\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger}$ and of $\Delta S_2^{\ddagger} - \Delta S_1^{\ddagger}$, the values at 75° of (a) $\Delta H^{\ddagger} - \Delta H_1^{\ddagger}$; (b) the rate of change of $\Delta H^{\ddagger}$ with temperature[9]; and (c) the fraction of the total reaction which is due to the bromine atom with the lower heat of activation,[10] $k_1/(k_1 + k_2)$. The assumed values of

(7) H. Eyring, *J. Chem. Phys.*, **3**, 107 (1935).

(8) Similar to $\Delta H^{\ddagger}$, $\Delta S^{\ddagger}$ is a function of T, $\Delta S_1^{\ddagger}$, $\Delta S_2^{\ddagger}$, $\Delta H_1^{\ddagger}$ and $\Delta H_2^{\ddagger}$.

(9) The rate of change of the observed heat of activation with temperature is given by equation 12.

$$\frac{d\,\Delta H^{\ddagger}}{dT} = \frac{(\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger})^2 e^{(\Delta S_1^{\ddagger} - \Delta S_2^{\ddagger})/R} e^{(\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger})/RT}}{RT^2(e^{(\Delta S_1^{\ddagger} - \Delta S_2^{\ddagger})/R} e^{(\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger})/RT} + 1)^2} \quad (12)$$

(10) This fraction is given by equation 13.

$$\frac{k_1}{k_1 + k_2} = \frac{e^{(\Delta S_1^{\ddagger} - \Delta S_2^{\ddagger})/R} e^{(\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger})/RT}}{1 = e^{(\Delta S_1^{\ddagger} - \Delta S_2^{\ddagger})/R} e^{(\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger})/RT}} \quad (13)$$

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TABLE III

APPARENT HEAT OF ACTIVATION, ITS RATE OF INCREASE WITH TEMPERATURE AND THE FRACTION OF THE REACTION WHICH IS DUE TO THE BROMINE ATOM WITH THE LOWER HEAT OF ACTIVATION AS FUNCTIONS OF $\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger}$ AND $\Delta S_2^{\ddagger} - \Delta S_1^{\ddagger}$ AT 75°

$\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger}$, cal. (assumed)	Value of $\Delta S_2^{\ddagger} - \Delta S_1^{\ddagger}$ (cal./deg.) (assumed) −4.6	0	4.6
	$\Delta H^{\ddagger} - \Delta H_1^{\ddagger}$ (cal.)		
700	25	260	550
1400	19	189	800
2100	10.4	100	700
2800	5.4	53	450
3500	2.3	23	220
	$d\Delta H^{\ddagger}/dT$ (cal./deg.)		
700	0.069	0.75	0.33
1400	.104	1.08	1.93
2100	.094	0.81	4.00
2800	.062	.60	4.30
3500	.032	.32	2.95
	$k_1/(k_1 + k_2)$		
700	0.96	0.73	0.21
1400	.99	.87	.43
2100	1.00	.95	.67
2800	1.00	.98	.84
3500	1.00	.99	.94

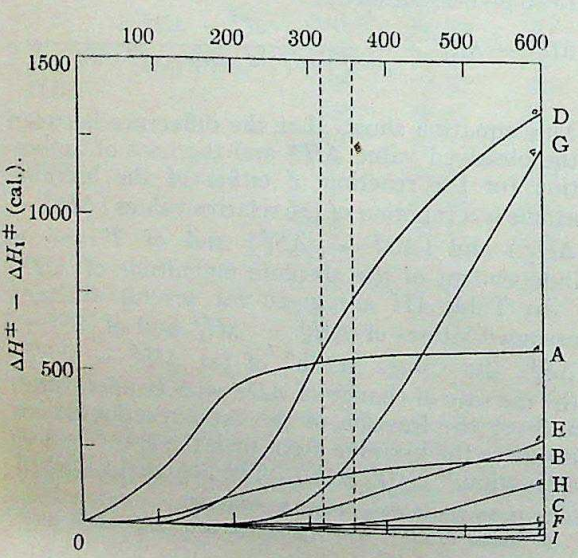

Fig. 1.—Plot of values of $\Delta H^{\ddagger} - H_1^{\ddagger}$ against absolute temperature for various assumed values of $\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger}$ and $\Delta S_2^{\ddagger} - \Delta S_1^{\ddagger}$:

Curve	$\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger}$, cal.	$\Delta S_2^{\ddagger} - \Delta S_1^{\ddagger}$, cal.
A	700	4.6
B	700	0
C	700	−4.6
D	2100	4.6
E	2100	0
F	2100	−4.6
G	3500	4.6
H	3500	0
I	3500	−4.6

$\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger}$ and $\Delta S_2^{\ddagger} - \Delta S_1^{\ddagger}$ used are of the same magnitude as was observed in changing substituents in symmetrically substituted ethylene dibromides.

Figure 1 shows plots of the apparent heat of activation relative to the lower of the individual values, $\Delta H_1^{\ddagger}$, as a function of temperature as calculated from equation 11 for several different assumed values of $\Delta H_2^{\ddagger} - \Delta H_1^{\ddagger}$ and of $\Delta S_2^{\ddagger} - \Delta S_1^{\ddagger}$. The temperature region in which our experiments were carried out is marked by dotted lines.

The calculated values in Table III and the plots of Fig. 1 show that the observed value, $\Delta H^{\ddagger}$, may be quite different from either of the values $\Delta H_1^{\ddagger}$ and $\Delta H_2^{\ddagger}$ which must be known before any quantitative theoretical consideration can be given to a discussion of the effect of structure on the reaction.

The calculated values of the rate of change of $\Delta H^{\ddagger}$ with temperature indicate that such a change would probably not be observed within the accuracy of our experiments. Experimentally, the heats of activation of the reactions of styrene dibromide and of acrylic acid dibromide appear to be constant over a range of 40°, as is shown by the straight line character of the plots of the logarithms of the reaction rate constants against the reciprocals of the absolute temperatures (Fig. 2).

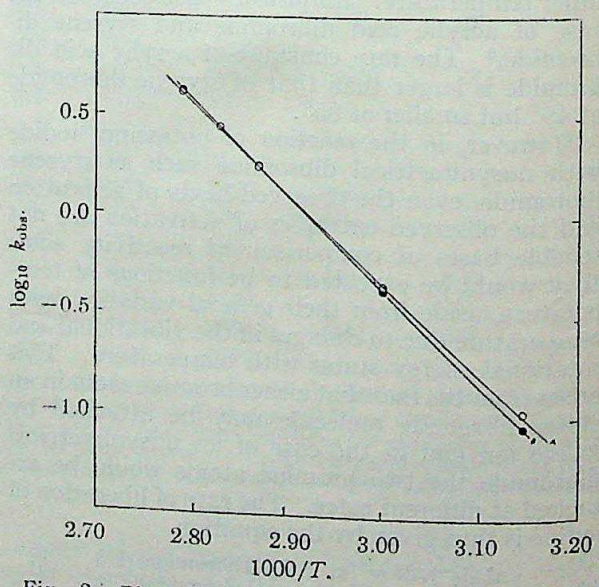

Fig. 2.—Plot of $\log_{10} k$ against reciprocal absolute temperature for acrylic acid dibromide ●, and for styrene dibromide ○.

The authors are indebted to Dr. C. D. Coryell for assistance in the calculation of the reaction rate constants.

Summary

The reaction rate constants and the heats and entropies of activation were determined for the

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reaction in 99% methanol of potassium iodide with monosubstituted ethylene dibromides, $RCHBrCH_2Br$ where R was C_3H_7, C_6H_5, $C_6H_5CH_2$, CH_2OH, COOH and Br.

It is shown that, since each of the bromine atoms can react and at a different rate and with a different heat of activation, no theoretical significance can be given to the effect of various substituents, R, on the observed values of the heats of activation and entropies of activation of the reaction of $RCHBrCH_2Br$ with potassium iodide.

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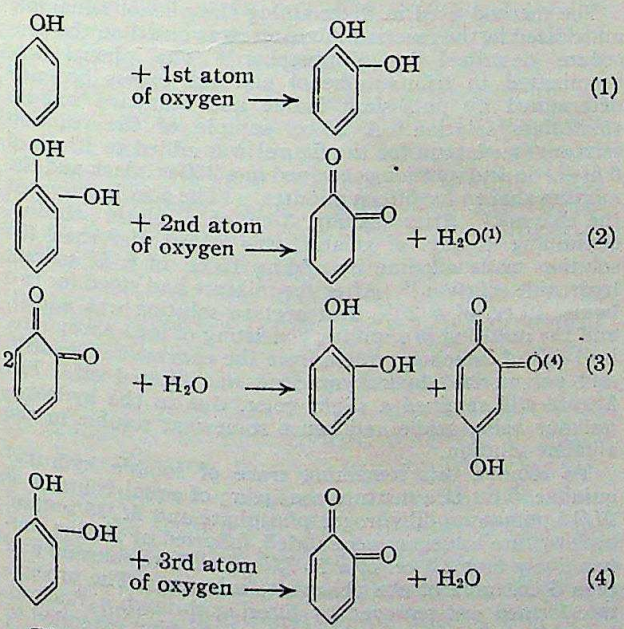
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

The Activity of Tyrosinase toward Phenol

BY RALPH C. BEHM AND J. M. NELSON

As shown by several investigators[1,2,3] the phenol oxidase, tyrosinase, possesses two essentially different enzymatic activities. It not only catalyzes the aerobic oxidation of many *o*-dihydric phenols to their corresponding *o*-quinones, but also catalyzes the introduction of a second hydroxyl group into several monohydric phenols, *ortho* to the hydroxyl group already present. These oxidation reactions are not simple, but involve several consecutive and concurrent reactions, especially when monohydric phenols constitute the substrate. Taking phenol and catechol as representing the two types of phenols, the final oxidation product in both instances is *p*-hydroxyquinone.[4] In the enzymatic oxidation of phenol at *p*H 6, 3 atoms of oxygen[5] are consumed per molecule of phenol oxidized.



The method usually used for estimating the activity of tyrosinase toward a monohydric phenol is based on determining the rate of oxygen uptake by means of a Warburg or Barcroft respirometer.[6] It is apparent, however, from what has been stated above, that only the first atom of oxygen is concerned with the enzyme's action on the monohydric phenol. The remaining two atoms of oxygen are consumed in the enzyme's action on the *o*-dihydric phenol. The question therefore arises: Can the rate of oxygen uptake serve as a true measure of the enzyme's activity toward a monohydric phenol?

To answer the latter question, it was decided to determine, instead of the rate of oxygen uptake, the rate of disappearance of the monohydric phenol from the reaction mixture. Such a method would be independent of all the accompanying reactions encountered in the oxygen uptake method. For the purpose a reaction mixture, consisting of the enzyme, phenol, buffer and water, was placed in a reaction vessel and air bubbled through the mixture. Samples were removed at regular time intervals and their phenol contents determined. The results obtained are shown as Curve I. Curve II represents the rate of oxygen uptake for a reaction mixture, identical in composition with the one used in following the rate of phenol disappearance. It will be observed that the two curves coincide within experimental error, showing that, at least when phenol is the monohydric phenol being oxidized by means of the enzyme, the concurrent reactions, equations (2), (3) and (4) must proceed at rates at least as great as the rate of the initial oxidation of the phenol (equation 1) and that, therefore, the rate of oxygen uptake can serve as a true measure of the enzyme's activity toward phenol.

Tyrosine preparations, depending on the method of preparation, often vary widely with respect to their relative activities toward monohydric and *o*-dihydric phenols. Therefore, it has become customary, in these Laboratories, to designate a preparation low in activity toward *p*-cresol compared to its activity toward catechol as a high catecholase preparation and a preparation high in *p*-cresolase activity as a high cresolase preparation.[7] Since in the present study phenol was used instead of *p*-cresol, it should be men-

(1) Pugh and Roper, *Biochem. J.*, **21**, 1370 (1927).
(2) Dalton and Nelson, THIS JOURNAL, **61**, 2946 (1939).
(3) Bordner and Nelson, *ibid.*, **61**, 1507 (1939).
(4) Wagreich and Nelson, *ibid.*, **60**, 1545 (1938).
(5) Unpublished results obtained in these Laboratories.
(6) Adams and Nelson, THIS JOURNAL, **60**, 2472 (1938).
(7) Parkinson and Nelson, *ibid.*, **62**, 1693 (1940).

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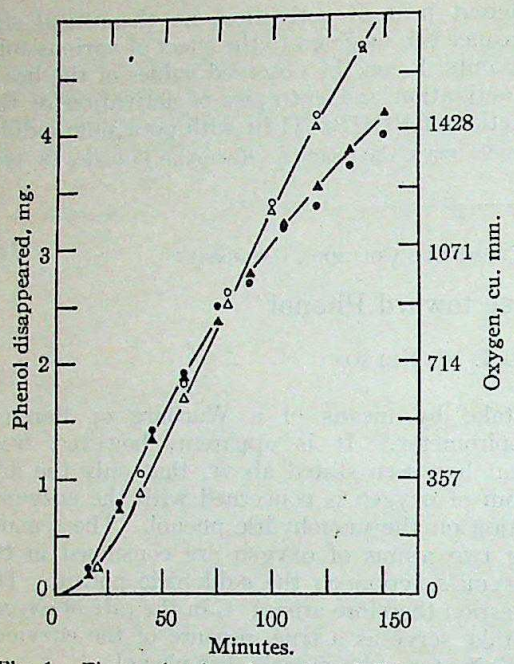

Fig. 1.—Figure showing the rates of disappearance of phenol and of oxygen uptake for the tyrosinase catalyzed aerobic oxidation of phenol at 25°. Warburg respirometer[8] was used in the oxygen uptake measurements. Curve II, triangles, shows the rate of oxygen uptake for a reaction mixture consisting of 2 cc. of $M/15$ phosphate buffer solution (*p*H 6.7), 1 cc. of phenol solution(20 mg.),[9] 1 cc. of gelatin solution (0.2 mg. of gelatin),[11] 1 cc. of a high catecholase preparation, containing 1.5 phenolase, 2.6 cresolase[6] and 32 catecholase units[12] (added at zero time from the side arm of the Warburg reaction flask) and sufficient water to make the final volume in the reaction vessel 8 cc. Curve I, circles, shows the rate of phenol disappearance from a reaction mixture similar to that for Curve II, except that 50 times the quantities of reactants were used. Curve IV, shaded triangles, shows the rate of oxygen uptake for a reaction mixture similar to that for Curve II, except 1 cc. of a high cresolase preparation, containing 1.5 phenolase, 1.3 cresolase, 17 catecholase units was used, and 1 cc. of water replaced the 1 cc. of gelatin solution. Curve III, shaded circles, shows the rate of disappearance of phenol from a reaction mixture similar to that used for the data represented by Curve IV, using, however, 50-fold quantities of the reactants. The reaction vessel used in determining the rate of disappearance of phenol consisted of a modified Reinder–Vles apparatus.[4] Briefly, the latter consisted of a 2-liter glass bottle provided with a rotating glass stirrer, so constructed that air was sucked into the reaction mixture. At suitable intervals 25-cc. samples were withdrawn and the phenol determined. Since both theoretically and experimentally, 1 mg. of phenol requires 357 c. mm. of oxygen for complete oxidation to the 3 atom stage, the data were plotted for purpose of comparison of the rates of phenol disappearance with the rate of oxygen uptake so that 357 c. mm. of oxygen uptake and 1 mg. loss of phenol had the same ordinate value in the graph. The tyrosinase preparations were obtained from the common mushroom, *Psalliota campestris*.

(8) Dixon, "Manometric Methods," Cambridge University Press, 1934.

(9) To obtain the maximum activity tyrosinase preparations, especially high cresolase, require optimum substrate concentrations.[10] The high catecholase preparation used for Curves I and II had an optimum phenol concentration of 2 mg. of phenol per 8 cc. of reaction mixture, while the high cresolase preparation (Curves III and IV) required about 20 mg. of phenol per 8 cc. Since the use of 20 mg. of phenol per 8 cc. of reaction mixture did not alter to any extent the activity of the high catecholase preparation, this concentration of substrate was used in all experiments.

(10) Gregg and Nelson, THIS JOURNAL, **62**, 2506 (1940).

(11) Gelatin was used to stabilize the tyrosinase preparation.[6]

(12) Miller, Mallette, Roth and Dawson, THIS JOURNAL, **66**, 514 (1944).

tioned that in the case of tyrosinase preparations, in which most of the concomitant protein has been removed, the phenolase activity is not very different from the *p*-cresol activity. (For units of activity of the preparations used in the investigation, see the legend for the accompanying figure.) The preparation used in obtaining the results represented by Curves I and II was a high catecholase.

The monohydric phenol activity being dependent on the reaction represented by equation (1) and the *o*-dihydric phenol activity depending on the reactions corresponding to equations (2), (3), and (4), it was decided to compare also the method, based on the rate of phenol disappearance, with that based on the rate of oxygen uptake, when a high cresolase was used instead of a high catecholase preparation. The results obtained are represented by Curves III and IV. It will be observed that again the linear portions of Curves III and IV—the portions of the curves used for determining the units of activity—practically superimpose. Therefore, the method based on the rate of oxygen uptake also is applicable (for high cresolase as well as for high catecholase preparations) for determining the activity toward phenol.

Experimental

The method used in determining the phenol remaining unoxidized in the reaction mixtures, was based on the procedure described by Koppeschar.[13] The phenol was brominated to tribromophenol and the excess bromine determined by potassium iodide and standard sodium thiosulfate solution. A 25-cc. sample of the reaction mixture (see legend for the figure) was added to 10 cc. of 6 M acetic acid solution contained in a 250-cc. flask and the mixture shaken for fifteen minutes. (The acid inactivated the enzyme.) After shaking, 3 cc. of a gelatin solution, containing 15 mg. of gelatin, was added and then the solution made alkaline by adding 15 cc. of 6 M sodium hydroxide solution.[14] After the mixture had stood for two hours, 10 cc. of a 20% lead acetate solution was added, and the resulting precipitate, consisting of lead phosphate, lead salt of catechol, protein from the enzyme and gelatin, and polymerized hydroxyquinone was filtered off. The filtrate still retained a slight color, due to the hydroxyquinone being acidic and hence somewhat soluble in the alkaline solution.

To remove this remaining trace of soluble hydroxyquinone, 5 cc. of a mixture consisting of equal volumes of $M/15$ potassium dihydrogen phosphate and $M/15$ sodium biphosphate solutions were added, followed by adding consecutively first 2.5 cc. of a 20% lead acetate solution and then 5 cc. more of the phosphate mixture. The precipitate formed was removed by filtering through a Büchner funnel in such a way that the stem of the filter extended to the bottom of the suction flask, to which 20 cc. of 6 M sodium hydroxide solution had been previously added. The purpose of this mode of filtering was to prevent any

(13) Koppeschar, *Z. anal. Chem.*, **15**, 233 (1876).

(14) In the alkaline solution, any incomplete oxidation of partly oxidized phenol, such as catechol or *o*-quinone, was converted by autoxidation into the final difficultly soluble polymerized hydroxyquinone. The presence of the gelatin seemed to aid the coagulation, probably by precipitation, of this final oxidation product.

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possible loss of phenol vapor, which is appreciable under the reduced pressure. To minimize, in the subsequent bromination of the phenol, the loss of bromine and to prevent[15] the bromination of any catechol still present, the last-mentioned mixture was cooled to −3° by the addition of 500 g. of chopped ice (prepared from distilled water). To the cold mixture 12.2 cc. of 0.1 *M* potassium bromate solution and 10 cc. of 15% potassium bromide solution were added and the mixture allowed to stand for twenty minutes. After the bromination had taken place, 10 cc. of a 25% solution of potassium iodide was added and the mixture allowed to stand in a dark place for fifteen minutes, after which the liberated iodine was determined by means of 0.1 *M* sodium thiosulfate solution.

In determinations involving small amounts of phenol (30 to 35 mg.) in the presence of large amounts of the final oxidation product the procedure was modified by using 5 cc. instead of 3 of the gelatin solution and twice as much lead acetate solution.

(15) Francis and Hill, THIS JOURNAL, 46. 2498 (1924).

The results of analyses made on prepared mixtures of phenol and catechol oxidation products had an average deviation of ±0.7%. The quantities of phenol found to be present at any time in the experiments corresponding to Curves I and II in the figure were therefore reliable to ±0.7%.

Summary

1. A method has been devised for determining the activity of tyrosinase toward phenol by determining the rate of disappearance of phenol from the reaction mixture.

2. A comparison of the direct phenol method with the oxygen uptake method, which is usually used, shows that the latter method is reliable for estimating the monohydric phenol activity of tyrosinase toward phenol.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

The Aerobic Oxidation of Phenol by Means of Tyrosinase

BY RALPH C. BEHM AND J. M. NELSON

When monohydric phenols, such as *p*-cresol,[1] phenol or *l*-tyrosine[2] are aerobically oxidized by means of tyrosinase, the reactions usually start with an initial lag. This induction period is overcome by the addition of a small amount of an *o*-dihydric phenol, such as catechol, to the reaction mixture.[1,2,3] Several explanations have been suggested as to how the *o*-dihydric phenol serves to decrease the induction period.[2,3,4] Since the enzyme also catalyzes the oxidation of *o*-dihydric phenols to their corresponding *o*-quinones, most of these explanations have been based on the view that the monohydric phenols are oxidized by the quinones. Bordner and Nelson,[1] however, have shown that the oxidation of the monohydric phenols to the *o*-dihydric state cannot be attributed to the quinones.

A theory for the oxidation of monohydric phenols by means of tyrosinase, which has several experimental facts in its favor, has been gradually taking shape in these laboratories. It is based on the idea that for tyrosinase to catalyze the oxidation of monohydric phenols, it must first be activated toward monohydric phenols, by simultaneously oxidizing an *o*-dihydric phenol.[1,5] This theory can be expressed briefly by reactions represented as shown beyond.

Some experimentally established facts, supporting the theory, are listed below and in the case of some of these a brief explanation has been added: (1) The fact that when phenol is enzymatically oxidized three atoms of oxygen are consumed per molecule of phenol oxidized is taken care of. (2) The addition of catechol decreasing the induction period and enabling the enzyme to catalyze the oxidation of phenol is accounted for by reactions (1) and (2). (3) Adding oxidizing agents, such as potassium ferricyanide, or the phenol oxidase, laccase, at the beginning of the reaction when phenol is oxidized by the enzyme lengthens the induction period.[1] These oxidizing agents would tend to deprive the enzyme of oxidizing catechol (reaction 2) and hence decrease the activation of the enzyme toward phenol. Less activation at the beginning of the reaction would slow down reaction (1) and lengthen the induction period. (4) Benzenesulfinic acid added initially to the reaction mixture when *p*-cresol or phenol is oxidized by the enzyme greatly lengthens the induction period.[1,6] Benzenesulfinic acid combines with *o*-quinone[1,6] and consequently would eliminate reaction (3). Elimination of reaction (3) would mean less catechol being formed and oxidized and hence less activation. Less activation, as pointed out in 3, would lengthen the induction period. (5) The length of the induction period has been found to decrease with increase in *p*H.[1] The *o*-quinone disappears faster as its aqueous solution becomes more alkaline.[7] The latter means the rate of reaction (3) increases with increase in *p*H and hence catechol is returned to the solution and oxidized faster. As a result the enzyme is activated faster, the rate of reaction (1) increased and the induction period shortened. (6) In the present study it has been found that the addition of a reducing agent such as ascorbic acid shortens the induction period. Since the

(1) Bordner and Nelson, THIS JOURNAL, 61, 1507 (1939).
(2) Califano and Kertesz, *Nature*, 142, 1036 (1938).
(3) Onslow and Robinson, *Biochem. J.*, 22, 1327 (1928).
(4) Richter, *ibid.*, 28, 901 (1934).
(5) Gregg and Nelson, THIS JOURNAL, 62, 2506 (1940).
(6) Pugh and Raper, *Biochem. J.*, 21, 1370 (1927).
(7) Dawson and Nelson, THIS JOURNAL, 60, 245 (1938).

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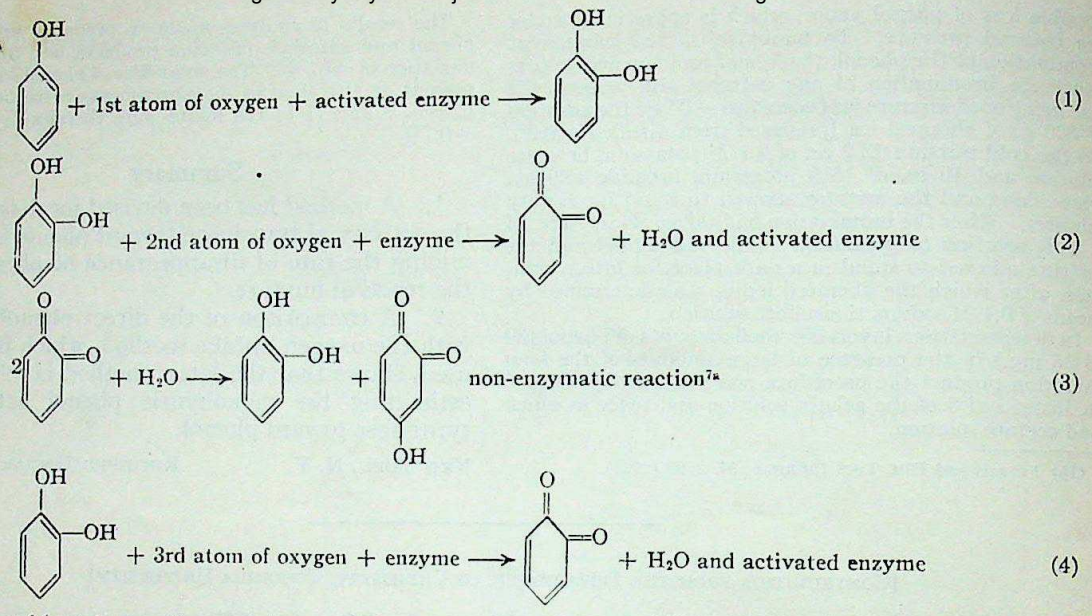

ascorbic acid reduces the *o*-quinone formed in reaction (2), more catechol would be formed and oxidized. As a result the enzyme would be activated faster and increase the rate of reaction (1). In other words, the induction period would be shortened. (7) When 4,5-dimethylphenol (xylenol) is oxidized by means of tyrosinase the induction period is long.[8] Due to positions 4 and 5 being occupied, the 4,5-dimethylquinone cannot undergo reaction (3) and less of the catechol compound is returned to the reaction mixture than when phenol constituted the substrate. The oxidation of less *o*-dihydric phenol amounts to less activation, slower rate for reaction (1) and consequently a longer induction period. (8) The fact that no preparation of tyrosinase, free of *o*-dihydric phenol activity, has ever been prepared also can be taken as evidence supporting the above theory.

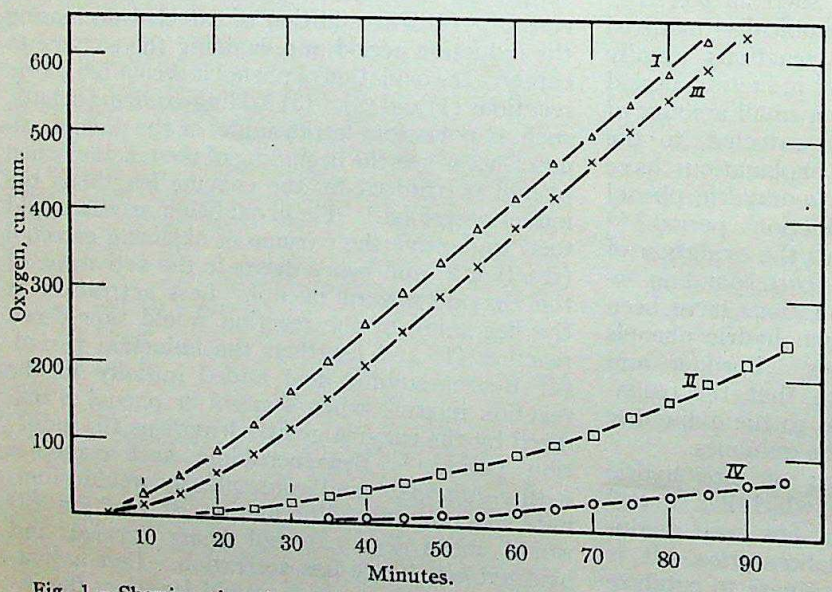

Fig. 1.—Showing that the oxidation of phenol by means of tyrosinase is more dependent on the oxidation of *o*-dihydric phenol than is the oxidation of *p*-cresol: Warburg respirometer; temperature 25°; *p*H 7.0. Reaction mixture for Curve I: 4 cc. of *M*/15 phosphate buffer, 1 cc. of gelatin solution (5 mg. of gelatin), 2 cc. of *p*-cresol (8 mg. *p*-cresol), and 1 cc. of mushroom tyrosinase containing 0.85 *p*-cresolase unit.[12] Reaction mixture Curve II: same as for Curve I, except 4 cc. of *M*/15 sodium borate buffer used in place of the phosphate buffer (final *p*H 7). Reaction mixtures for Curves III and IV, similar to those for Curves I and II, respectively, except 2 cc. of a phenol solution (8 mg. of phenol) was used in place of the *p*-cresol.

That the activation of tyrosinase toward monohydric phenols is transitory and requires the simultaneous oxidation of an *o*-dihydric phenol, *i. e.*, reaction (1) can only occur if at the same time reaction (2) is taking place, is indicated by the following experiment. A hundred times the amount of catechol necessary to prevent the induction period was first oxidized completely by the enzyme (catechol is oxidized very rapidly by tyrosinase[9]). Immediately afterward phenol was added. The enzymatic oxidation of the phenol, however, started

(7a) Wagreich and Nelson, THIS JOURNAL, **60**, 1545 (1938).

(8) Cushing, Dissertation, Columbia University, 1942.

(9) Nelson, *Cold Spring Harbor Symposia on Quantitative Biology*, **7**, 148 (1939).

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with a lag period showing that the activation caused by the previous oxidation of the catechol had disappeared.

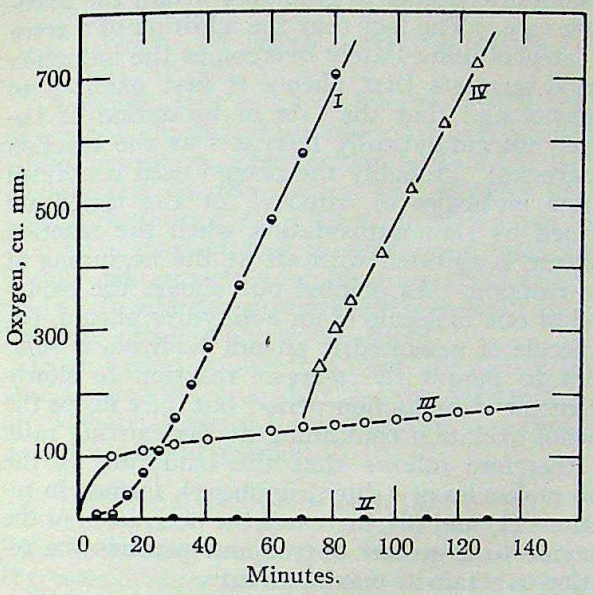

Fig. 2.—Showing that the oxidation of one molecule of catechol per molecule of phenol oxidized does not activate tyrosinase sufficiently to enable the reaction to overcome the induction period, nor to increase the existing rate of oxidation when an excess of phenol–enzyme complex is present in the reaction mixture. Warburg respirometer was used[10]; temp. 25°. Curve I represents the rate of oxygen uptake (rate of phenol disappearance from the reaction mixture[11]) when phenol was oxidized by means of tyrosinase. Reaction mixture for Curve I: 1 cc. of phenol solution (5 mg. of phenol), 2 cc. of *M*/15 phosphate buffer (*p*H 6.7), 1 cc. of gelatin solution (0.2 mg.),[11a] 1 cc. of a high catecholase preparation of mushroom tyrosinase containing 1.1 phenolase[12] and 22.8 catecholase[13] units[13a] and sufficient water to make the final reaction volume equal to 8 cc. Curve II shows that benzene sulfinic acid, initially present, prevents the enzymatic oxidation of the phenol. Reaction mixture for Curve II: same as for Curve I, except it also contained 3 mg. of sodium benzene sulfinate. Curve III shows that the addition of a small amount of catechol overcomes the inhibiting action of the benzenesulfinic acid. Reaction mixture for Curve III: same as for Curve II, except 0.2 mg. of catechol was added at zero time.[14a] The addition of 20 mg. of phenol to the reaction mixture corresponding to Curve III, after the reaction had been in progress for seventy minutes, failed to increase the rate of oxygen uptake. Although the concentration of the phenol–enzyme complex must have been increased considerably when the 20 mg. of phenol was added, the presence of the sulfinic acid, preventing reaction (3) from taking place, left only the one molecule of catechol, formed in reaction (1), to be oxidized per molecule of phenol oxidized. The oxidation of this one molecule of catechol was only able to activate the enzyme to such an extent that the existing rate of oxygen uptake could continue. As soon, however, as 0.2 mg. of catechol was added with the 20 mg. of phenol, after the reaction had been in progress for seventy minutes, enough catechol was oxidized, per molecule of phenol oxidized, to raise the rate of oxygen uptake to the maximum rate, Curve IV, determined by the enzyme operating at a phenol concentration equivalent to the optimum phenol concentration.

As already mentioned, the influence of benzenesulfinic acid, initially present, on the oxidation of phenol prevents the reaction from starting, but only lengthens the induction period when *p*-cresol is the substrate. This difference shown by the two monohydric phenols suggests that the enzyme requires more activation, *i. e.*, a greater rate of *o*-dihydric phenol oxidation (reaction (2)) in the case of the enzymatic oxidation of phenol than when *p*-cresol is being oxidized. That such is actually the case is indicated by the results shown in Fig. 1. The two monohydric phenols were oxidized by means of the enzyme in the presence and absence of boric acid. It will be noticed that the oxidation of the phenol was retarded more by the boric acid than that of the *p*-cresol. It is well known that boric acid tends to combine with *o*-dihydric phenols and therefore would tend to reduce the amount of *o*-dihydric phenol oxidized in reaction (2). If the phenol oxidation requires more activation of the enzyme than does the *p*-cresol oxidation, then it follows that the presence of the boric acid would affect the phenol oxidation the most.

The data in Fig. 2 show that the oxidation of one molecule of catechol (reaction (2)) per molecule of phenol oxidized only permits the enzymatic oxidation of phenol to proceed at the existing rate. When benzenesulfinic acid is present at the beginning of the reaction and the rate of the phenol oxidation is zero, the rate remains zero (Curve II). On the other hand, if the reaction is progressing in the presence of the sulfinic acid and the rate is not zero (Curve III) then the rate will continue at this rate, even though the concentration of the phenol–enzyme complex is increased by the addition of a large amount of phenol to the reaction mixture. The latter rate of oxygen uptake can only be increased by also adding a small amount of catechol (Curve IV). This constant rate of phenol oxidation, in the presence of benzene sulfinic acid, irrespective of the concentration of the phenol–enzyme complex, indicates that the one molecule of catechol formed in reaction (1) (reaction (2) being prevented from taking place by the sulfinic acid) does not give rise to sufficient activation to increase the existing rate of oxidation of the phenol. On the other hand (see Fig. 4, Bordner and Nelson[1]),

(10) Dixon, "Manometric Methods," Cambridge University Press, 1934.

(11) Behm and Nelson, THIS JOURNAL, **66**, 709 (1944).

(11a) Gelatin used to stabilize the enzyme preparation.

(12) Adams and Nelson, THIS JOURNAL, **60**, 2472 (1938).

(13) Miller, Mallette, Roth and Dawson, *ibid.*,, **66**, 514 (1944).

(13a) The enzyme preparation had an optimum phenol concentration of less than 5 mg. of phenol per 8 cc. reaction mixture.[14] The phenolase units were determined by the same method as used for cresolase units.

(14) Gregg and Nelson, THIS JOURNAL, **62**, 2506 (1940).

(14a) Besides removing the *o*-benzoquinone, as it is formed in reaction (2), the sulfinic acid also competes with the phenol for the enzyme, *i. e.*, it is a competitive inhibitor as shown in Fig. 3. Therefore, the rate of oxygen uptake shown by Curve III, after the induction period (zero rate) was overcome by the addition of the 0.2 mg. of catechol, is the maximum rate. The reason the maximum rate (Curve III) was much less than the maximum rate shown by Curve I was due to the sulfinic acid, as a competitive inhibitor, lowering the concentration of the phenol–enzyme complex.

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when *p*-cresol is oxidized in the presence of sulfinic acid the oxidation of one molecule of homocatechol per molecule of *p*-cresol oxidized (Reaction (2)) causes enough activation of the enzyme to permit the rate of oxidation to gradually increase and overcome the induction period, although more slowly than when no sulfinic acid is present.

The question may arise: How can tyrosinase initiate the oxidation of a monohydric phenol, if it first has to be activated by catalyzing the oxidation of an *o*-dihydric phenol? The induction period shows that some product is formed autocatalytically which enables the oxidation of the monohydric phenol to gradually attain the maximum rate. The fact that the addition of a trace of catechol immediately overcomes the induction period suggests that phenol is first oxidized to catechol and that the rate of formation of the latter autocatalytically increases as the reaction progresses. Probably the phenol used contained a few molecules of catechol, or the latter are formed by slow autoxidation when the reaction mixture is agitated with air at the beginning of the reaction. As pointed out above, the oxidation of one molecule of an *o*-dihydric phenol, per molecule of monohydric phenol oxidized, is sufficient to permit the *p*-cresol reaction to slowly overcome its induction period but only keeps the phenol oxidation continuing at the existing rate. It therefore follows that the oxidation of the two molecules of *o*-dihydric phenol, formed in reactions (1) and (3), increases the activation of the enzyme to a greater degree and permits the reaction to attain its maximum rate.

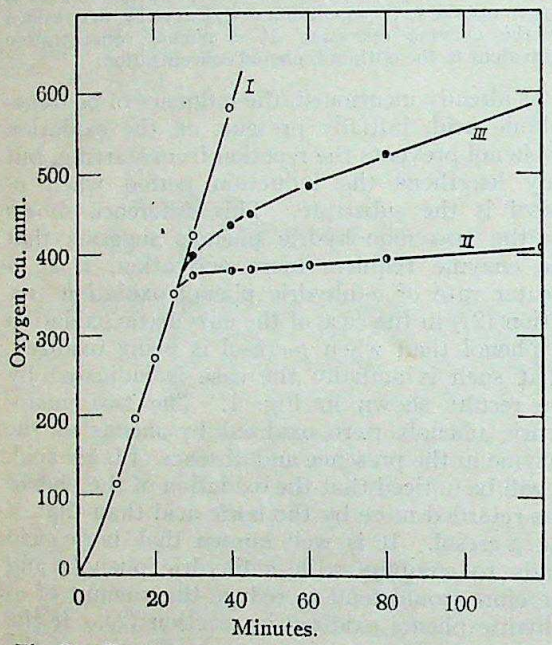

Fig. 3.—Showing that benzenesulfinic acid behaves as a competitive inhibitor toward phenol in the aerobic oxidation of phenol by means of tyrosinase. Curve I shows the rate of oxygen uptake for a reaction mixture consisting of 2 cc. of *M*/15 phosphate buffer *p*H 6.7, 1 cc. of phenol solution (20 mg.), 1 cc. of gelatin solution (0.2 mg.), 1 cc. of a high catecholase preparation containing 1.3 phenolase[12] units and 28.3 catecholase units,[13] and sufficient water to make the total volume in the reaction vessel 8 cc. The same curve was obtained if 1 cc. of phenol solution contained only 5 mg. of phenol. In each case the reaction had been in progress for ten minutes before the manometers of the Warburg respirometer were closed at "zero" time. Curve II shows the effect of addition of 35 mg. of sodium benzenesulfinate at time = 25 minutes to a reaction mixture similar to that for Curve I, using 5 mg. of phenol. Curve III shows the effect of addition of 35 mg. of sodium benzenesulfinate at time = 25 minutes to a reaction mixture similar to that for Curve I, using 20 mg. of phenol. The slope of the constant rate achieved after the addition of sulfinate in the experiment represented by Curve II (using 5 mg. of phenol) is 0.38 cu. mm. of oxygen uptake per minute; that of the experiment represented by Curve III (using 20 mg. of phenol) is 1.67 cu. mm. of oxygen uptake per minute. The change in slope, caused by the four-fold variation in phenol concentration in the presence of a constant amount of sodium benzenesulfinate, is 4.4. In view of the fact that experience in these laboratories has shown that benzenesulfinate has practically no effect on the rate of the enzymatic oxidation of catechol (the primary agent in this system) the retarding effect of the sulfinate on the phenol oxidation seems best explained on the basis that it displaces phenol from the enzyme; or in other words, benzenesulfinic acid behaves as a competitive inhibitor for phenol in the aerobic oxidation of phenol by means of tyrosinase.

Concerning the nature of the activation of tyrosinase toward monohydric phenols caused by the enzymatic oxidation of an *o*-dihydric phenol little is known. As shown by Bordner and Nelson, the oxidation of the monohydric phenols cannot be attributed to quinones or hydrogen peroxide formed in the oxidation of the *o*-dihydric phenols. That any other oxidation product of the *o*-dihydric phenols is responsible for the monohydric phenol also seems to be excluded as is indicated by the following experiment. Phenol was oxidized by means of the enzyme in the absence and presence of a relatively large amount of catechol and the rate of phenol disappearance from the reaction mixture followed in both instances by the method of Behm and Nelson.[11] The results indicated that the oxidation of the added catechol exerted practically no influence on the rate of disappearance of the phenol, except to eliminate the induction period.

Summary

Additional evidence is presented supporting the view that for tyrosinase to catalyze the oxidation of a monohydric phenol, the enzyme must catalyze simultaneously the oxidation of an *o*-dihydric phenol.

To overcome the induction period, when phenol is acted on by tyrosinase, it is necessary for the enzyme to catalyze simultaneously the oxidation of more than one molecule of catechol per molecule of phenol oxidized.

To increase the existing rate in the oxidation of phenol, when the latter is lower than the maximum, it is necessary to oxidize simultaneously more than one molecule of an *o*-dihydric phenol per molecule of phenol oxidized.

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[CONTRIBUTION FROM THE AMMONIA DEPARTMENT OF E. I. DU PONT DE NEMOURS & COMPANY, INC.]

Analytical Procedures Employing Karl Fischer Reagent. X. The Determination of Aliphatic Hydroxy Amines (Amino Alcohols)[1]

BY DONALD MILTON SMITH, J. MITCHELL, JR., AND WALTER HAWKINS

The acidimetric methods for the determination of alcoholic hydroxyl usually are based on acetylation involving acetyl chloride[2,3] or on some modification of the Verley and Bölsing acetic anhydride procedure.[4] These methods are subject to a marked loss in sensitivity where the sample contains considerable amounts of water or acids. In addition primary and secondary amines interfere, often to a variable extent.

In an earlier publication from this Laboratory[5] an esterification procedure for the determination of alcoholic hydroxyl was described, depending upon the general reaction

$$ROH + CH_3COOH = CH_3COOR + H_2O$$

This technique, employing boron trifluoride as the esterification catalyst, has been extended to include hydroxyamines. As in the previous case the water liberated in the above reaction, which is equivalent to the hydroxyl esterified, is determined by direct titration with Karl Fischer reagent. Since the reaction of the amine group with the acid or boron trifluoride does not involve water, no interference is encountered.

The new procedure is applicable to aliphatic mono- and polyhydric hydroxyamines in general, including branched chain types and such aromatic hydroxyamines as have the hydroxyl group attached to an aliphatic side chain. The method is applicable also to the determination of hydroxyl in the presence of ammonia or amines. Aminophenols, however, do not react completely.

Experimental

Reagents.—The esterification reagent is prepared by dissolving about 200 g. of boron trifluoride gas[6] in sufficient Merck C. P. glacial acetic acid to make one liter of solution. Dry Baker C. P. or Eastman Kodak No. 214-H pyridine may be used without further purification. Karl Fischer reagent is prepared as indicated in an earlier publication.[7]

Analytical Procedure.—The sample, containing up to 0.1 equivalent of hydroxyl, is weighed into a 50-ml. glass-stoppered volumetric flask about one-third filled with glacial acetic acid. (It is usually safer to chill the flask containing the acetic acid before addition of the sample.) The solution is made up to volume with more acetic acid. Five ml. (using calibrated pipet) of the sample solution is transferred to a 250-ml. glass-stoppered volumetric flask[8] and 20 ml. of the esterification reagent added. The flask is stoppered tightly and together with a control containing 20 ml. of reagent and 5 ml. of acetic acid, is placed in a water-bath or oven at 70 ± 2° for two hours. At the end of this time the flasks are removed and allowed to cool to room temperature spontaneously. Ten ml. of dry pyridine is added to each and the mixture titrated with Karl Fischer reagent.

After correction for the water in acetic acid, esterification reagent and pyridine, the millimoles of water present after reaction less the water originally present, are equal to the milliequivalents of free hydroxyl in the sample.

The water originally present may be obtained by titrating 5 ml. of the original acetic acid solution with Fischer reagent. A correction for the water present in the acetic acid is obtained by titrating a 5-ml. portion and correcting to the volume of acid actually present in the sample solution.

Analytical Results

The experimental results obtained with twelve hydroxyamines are given in Table I. With the exception of the mono- and diethanolamines the trade products were used without further purification.

Aminophenols do not esterify completely under the conditions of the general procedure; *m*-aminophenol reacted only about 40%.

The precision and accuracy average about ±0.3%, comparing favorably with the earlier hydroxyl procedure.[5]

TABLE I

ANALYTICAL DATA FOR HYDROXYAMINES

Substance	Found, wt. % Hydroxyamine	H_2O	Total
Monoethanolamine (6)[a]	99.8 ± 0.1	0.1	99.9
Diethanolamine (4)	99.9 ± 0.1	.0	99.9
Triethanolamine[b] (4)	99.9 ± 0.1	.0	99.9
Diisopropanolamine (2)	100.1 ± 0.1	.7	100.8
Triisopropanolamine (2)	95.0 ± 0.4	.2	95.2
2-Amino-2-methyl-1-propanol[c] (4)	99.6 ± 0.2	.3	99.9
Hydroxyethyl ethylenediamine (2)	97.8 ± 0.3	.6	98.4
2-Amino-2-methyl-1,3-propanediol[c] (4)	99.5 ± 0.4	.0	99.5
2-Amino-2-ethyl-1,3-propanediol[c] (4)	89.9 ± 0.5	.4	90.3
2-Amino-1-butanol[c] (4)	96.5 ± 0.3	1.6	98.1
Tris-(hydroxymethyl)-aminomethane[c] (4)	99.2 ± 0.2	.0	99.2
Ethylphenylethanolamine (2)	96.7 ± 0.2	.4	97.1

[a] Figures in parentheses represent number of determinations. [b] Eastman Kodak Chemical. [c] Commercial Solvents Company, all others Carbide & Carbon chemicals.

The analytical method was developed through a study of the esterification of carefully purified

(1) Presented in part before the Division of Analytical and Micro Chemistry at the Pittsburgh Meeting of the American Chemical Society, September 9, 1943.

(2) Smith and Bryant, THIS JOURNAL, 57, 61 (1935).

(3) Christensen, Pennington and Dimick, *Ind. Eng. Chem. Anal. Ed.*, 13, 821 (1941).

(4) Verley and Bölsing, *Ber.*, 34, 3354 (1901).

(5) Bryant, Mitchell and Smith, THIS JOURNAL, 62, 1 (1940).

(6) Obtained in cylinders from the Ohio Chemical Company, Cleveland, Ohio.

(7) Smith, Bryant and Mitchell, THIS JOURNAL, 61, 2407 (1939).

(8) Where convenient the sample, containing up to 10 milliequivalents of hydroxyl, may be weighed directly into the 250-ml. volumetric flask. In this case 5 ml. of glacial acetic acid should be added to the cooled flask containing the sample before addition of the reagent.

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mono- and diethanolamines, using various concentrations of boron trifluoride in acetic acid with ten milliequivalents of hydroxyl. Results obtained are shown in Table II.

TABLE II

EFFECT OF CONCENTRATION OF BF_3 ON ESTERIFICATION OF ETHANOLAMINE

	—% Reaction of —OH group—		
	50 g. BF_3/l.	100 g. BF_3/l.	200 g./l.
Monoethanolamine	38	96	99.8
Diethanolamine	79	96	99.9

It is interesting to note that in the experiment using 50 g. of boron trifluoride per liter the reaction of diethanolamine was considerably greater than the monoethanolamine.

Interfering Substances.—The new hydroxyl procedure is unfavorably affected by aldehydes and ketones, acetals and ketals as indicated in an earlier publication.[5]

Orthoesters react quantitatively. The reaction apparently is general, probably following the equation

$$RC(OR')(OR')(OR') + 2CH_3COOH \longrightarrow RCOOR' + 2CH_3COOR' + H_2O$$

Five Eastman Kodak Co. orthoesters were mixed with the 100 g. of catalyst and heated for two hours at 60° and at 67°. Analytical results are summarized in Table III.

TABLE III

ANALYTICAL DATA ON ORTHOESTERS

Substance	Found, wt. %
Ethyl orthoformate	97.6 ± 0.4
Methyl orthoacetate	99.4 ± 0.3
Methyl orthopropionate	97.4 ± 0.0
Methyl ortho-*n*-butyrate	97.1 ± 0.0
Methyl ortho-*n*-valerate	92.2 ± 0.3

Summary

1. A specific quantitative method for the determination of hydroxyamines has been described. The method is based on quantitative esterification and subsequent titration of the water liberated with Karl Fischer reagent.

2. The method is applicable to the determination of hydroxyl in the presence of ammonia or amines.

3. Analytical results are reported for twelve amino alcohols.

4. The method is quantitative for samples containing a large excess of water.

5. Orthoesters react quantitatively with the acetic acid in the esterification reagent.

WILMINGTON, DELAWARE RECEIVED JANUARY 26, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

The Reaction between Cyclic β-Diketones and Grignard Reagents. II. 8,8-Dimethylperinaphthindandione-7,9[1]

BY T. A. GEISSMAN AND LESTER MORRIS

The reaction between cyclic β-diketones and Grignard reagents has been studied in a few cases only, and in none of these cases has the cleavage of the diketone been observed, normal addition of the reagent to the carbonyl groups having occurred.[2] This behavior is in marked contrast to that of many open-chain diketones, which are cleaved by the action of Grignard reagents according to the partial equation

$$-CO-C(R)(R)-CO- + R'MgX \longrightarrow -COR' + \left(-COC(R)(R)\right)MgX$$

When the ketone represented by —COR′ is capable of further reaction with the reagent a tertiary alcohol is the final product.

In the present work the study has been extended to include a diketone in which the diketonic function is a part of a six-membered ring: 8,8-dimethylperinaphthindandione-7,9 (I). The reaction of this compound with phenylmagnesium bromide has been carried out under a variety of conditions and three products have been isolated and characterized. None of these is the expected cleavage product.

8,8-Dimethylperinaphthindandione-7,9 was prepared by the methylation (in two steps) of perinaphthindandione-7,9.[3] It has been described by Freund and Fleischer,[4] who prepared it by the condensation of naphthalene with dimethylmalonyl chloride under the influence of aluminum chloride, followed by manual separation of the crystals of the three possible isomers, all of which were produced. An unsuccessful attempt was made in the present work to prepare the monomethyl derivative by the condensation of ethyl propionate with methyl 1,8-naphthalate; although the expected product was formed the yield was very low.

By a suitable control of the experimental con-

(1) Presented before the American Chemical Society, Fall Meeting, 1942, at Buffalo, N. Y.

(2) Geissman and Tulagin, THIS JOURNAL, **63**, 3352 (1941), and other references there cited.

(3) Errera, *Gazz. chim. ital.*, **41**, I, 190 (1911); *Chem. Centr.*, **82**, II, 1633 (1911).

(4) Freund and Fleischer, *Ann.*, **399**, 203 (1913).

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ditions the reaction between the diketone (I) and phenylmagnesium bromide can be made to yield as the predominant product any of three substances. These are the normal monoaddition compound (II), the normal diaddition compound (III) and a compound which is formed by normal addition to one of the carbonyl groups followed by 1,4-addition (into the naphthalene ring) to the other (IV).

The monoaddition product (II) was formed when one mole of phenylmagnesium bromide was added at 0° to the diketone. The compound was converted into a methyl ether (V) and a monochloro compound (VI) when it was treated with hydrogen chloride in methanol and benzene, respectively.

The action of excess phenylmagnesium bromide upon the diketone at 25° led to the formation of the normal diaddition product (III). An attempt to convert this compound into the dimethyl ether by treating it with hydrogen chloride in methanol resulted in the formation of a substance to which has been assigned the structure of the endoxo compound VII, formed by transannular dehydration of the diol. The oxide (VII) liberated no gas and consumed no reagent when treated with methylmagnesium iodide in the "Grignard machine."

When an excess of phenylmagnesium bromide was added to the diketone at the temperature of boiling benzene, the principal product was a substance (IV) different from I and II. It formed a monomethyl ether (VIII) in acidic methanol, showed one active hydrogen and one carbonyl group in the "Grignard machine" and formed a monochloro compound (IX) when treated with anhydrous hydrogen chloride in benzene. These observations definitely exclude the possibility that it is the isomeric diaddition product corresponding to III, of which a *cis* and a *trans* form can exist. It was at first assumed, on the basis of carbon–hydrogen analyses, that IV was isomeric with III. Since IV is not the cleavage product (which has been synthesized independently[5]) and is not a glycol, the only reasonable assumption was that it was the product of 1,2- and 1,4-addition to the carbonyl groups. The product formed in such a way, however, would be a dihydronaphthalene derivative and would be expected to show considerable reactivity toward oxidizing agents and bromine. The compound (IV) is quite resistant to attack by such reagents and thus it appears that it has lost the two hydrogen atoms which would be present in the direct product of a 1,4-addition into the naphthalene nucleus. Such an aromatization, occurring either during the course of the initial reaction or in the isolation process, has been observed in analogous cases.[6]

The compound which would be expected if cleavage of the diketone had occurred (X) has been synthesized by an independent method.[5] It is not identical with any of the products obtained by the action of phenylmagnesium bromide on I.

8,8-Dimethylperinaphthindandione-7,9 is one more example of a cyclic β-diketone which does not undergo cleavage upon reaction with a Grignard reagent. Except for the reaction leading to the product IV its behavior parallels that of 2,2-dimethyl-1,3-diketohydrindene.[2] No observation made in the present work offers a basis for modifying or extending the discussion of the reaction of cyclic β-diketones and Grignard reagents, presented in the previous paper of this series.[2] The present results serve to emphasize the influence of the spatial disposition of the β-diketone function upon the course of its reaction with a Grignard reagent.

(5) Geissman and Morris, THIS JOURNAL, 63, 1111 (1941).

(6) Fuson and Speck, *ibid.*, 64, 2446 (1942).

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Experimental

Dimethyl 1,8-Naphthalate.[7]—A solution of 116 g. of naphthalic anhydride (recrystallized from concentrated nitric acid) in 670 ml. of a solution of 224 g. of potassium hydroxide in two liters of absolute methanol was placed in a 3-necked flask fitted with two dropping funnels. Into one of the dropping funnels was placed the remainder of the alcoholic potassium hydroxide solution and into the other was placed 373 ml. of dimethyl sulfate. The two reagents were run in simultaneously in a 4:1 ratio, with stirring and cooling of the flask contents. After all of the reagents had been added the potassium methyl sulfate was removed by filtration and the filtrate cooled in ice–salt. The product was collected and the filtrate diluted with water to precipitate the remainder. The second crop was recrystallized from methanol and combined with the first crop. The yield was 143 g. (89%), m. p. 102° (reported,[7] 25% yield, m. p. 102–103°).

The condensation of ethyl propionate with methyl 1,8-naphthalate in the presence of sodium resulted in the formation of a very small amount of 8-methylperinaphthindandione-7,9.

Perinaphthindandione-7,9.[3]—A mixture of 100 g. each of pulverized naphthalic anhydride, 100 g. of freshly fused zinc chloride and 200 g. of ethyl malonate was heated at 170–175° for four hours, with occasional stirring to break up a hard crust which formed around the edges of the mass. The mixture became yellow, then brown, and largely liquefied as the reaction progressed. The mixture was cooled and stirred with 500 ml. of 0.1 *N* hydrochloric acid, ground in a mortar with a fresh portion of acid and then shaken with two further portions. The resulting brown, granular material was stirred with 600 ml. of 4 *N* sodium hydroxide and the mixture filtered. The deep red filtrate was acidified, the bright yellow precipitate collected, redissolved in alkali and reprecipitated. Crystallization of the product from glacial acetic acid yielded 65 g. of brownish-yellow granular crystals, m. p. 247°, dec. Reported,[3] turns brown at 250°, melts toward 265°.

8-Methylperinaphthindandione-7,9.—To a solution of 2.5 g. of sodium in 150 ml. of absolute alcohol was added 14 g. of perinaphthindandione-7,9 and 14 ml. of methyl iodide. A heavy-walled bottle equipped with a pressure-tight closure was used. The bottle was heated before sealing and sealed when vapors of the contents began to escape. It was then heated at 100° for four hours. After cooling, the contents of the bottle were filtered. The filtrate was concentrated on the water-bath, cooled, and to the resulting solution eight volumes of 4 *N* sodium hydroxide were added. The undissolved solid (a mixture of O-methyl ether and dimethylated products) was removed and the filtrate acidified. The yellow precipitate was redissolved in alkali, reprecipitated, and recrystallized from ethanol. The yield of orange-yellow product, m. p. 183–185°, was 60%.

Anal. Calcd. for $C_{14}H_{10}O_2$: C, 80.0; H, 4.8. Found: C, 79.8; H, 4.8.

8,8-Dimethylperinaphthindandione-7,9 (I).—In a 500-ml., three-necked flask fitted with a reflux condenser, stirrer and dropping funnel were placed 30 ml. of anhydrous acetone, 8 ml. of methyl iodide and 12 g. of the monomethyl compound. A solution of 1.3 g. of sodium in the minimum quantity of absolute methanol was added over a period of three hours under reflux and with constant stirring. The final mixture was concentrated on the water-bath until most of the solvents had been removed and to the residue was added dilute sodium hydroxide solution. A crystalline material separated. This was removed and recrystallized from ligroin (b. p. 95–100°), affording long, light yellow needles of the dimethyl compound mixed with a small amount of tiny rosets of the O-methyl ether. The latter could be separated easily by shaking the dried crystals on a piece of wire gauze, the coarse needles of the desired product being retained and the fine needles of the impurity passing through. The yield of final material, m. p. 99–101°, was 30–40% (m. p. reported[4] 100–101°).

(7) Graebe, *Ann.*, **340**, 247 (1905).

2,4-Dinitrophenylhydrazone of I.—A solution of the diketone and 2,4-dinitrophenylhydrazine in alcohol, containing a few drops of hydrochloric acid, was boiled for twenty minutes. On cooling a dark purple material separated. Recrystallization of this crude product from ethyl acetate–petroleum ether afforded brown-red crystals, m. p. 208–210°.

Anal. Calcd. for $C_{21}H_{16}O_5N_2$: C, 62.4; H, 4.0. Found: C, 62.3; H, 4.0.

The Reaction of the Diketone (I) with Phenylmagnesium Bromide. One Mole of C_6H_5MgBr at 0°: 7-Phenyl-7-hydroxy-8,8-dimethylperinaphthindanone-9 (II).—To a solution of 3.3 g. of the diketone (I) in a mixture of 50 ml. of benzene and 10 ml. of ether, cooled in an ice-bath, was slowly added exactly one equivalent of an ether solution of phenylmagnesium bromide. A deep purple complex separated. After two hours the mixture was hydrolyzed with iced ammonium chloride solution and subjected to steam distillation. The involatile residue was recrystallized from alcohol, yielding 1.3 g. of II and, from the mother liquors, 1.5 g. of unchanged I. In later runs it was found that extending the time of the reaction to six to eight hours gave better yields of II. The product formed colorless prisms, m. p. 190°.

Anal. Calcd. for $C_{21}H_{18}O_2$: C, 83.4; H, 6.0. Found: C, 83.2; H, 5.8.

The compound gave a cherry-red solution in concentrated sulfuric acid. Attempts to prepare a dinitrophenylhydrazone were not successful.

7-Phenyl-7-methoxy-8,8-dimethylperinaphthindanone-9 (V).—The conversion of II into its methyl ether was readily brought about by adding a drop of concd. hydrochloric acid to its solution in boiling methanol and allowing the solution to cool. The ether separated in iridescent needles, m. p. 214–216°.

Anal. Calcd. for $C_{22}H_{20}O_2$: OCH_3, 9.8. Found: OCH_3, 9.8.

7-Phenyl-7-chloro-8,8-dimethylperinaphthindanone-9 (VI).—Anhydrous hydrogen chloride was passed through a solution of 0.1 g. of II in 6 ml. of dry benzene for three hours. Evaporation of the solvent left a clear glass. This was dissolved in a little benzene and the solution allowed to evaporate slowly; large, cubical crystals were deposited. The compound melted at 156°, dec.

Anal. Calcd. for $C_{21}H_{17}OCl$: Cl, 11.1. Found: Cl, 10.9.

Excess C_6H_5MgBr at Room Temperature: 7,9-Diphenyl-7,9-dihydroxy-8,8-dimethylperinaphthindane (III).—To a solution of 3.2 g. of the diketone (I) in 100 ml. of benzene, cooled in an ice-bath, was added an ether solution of three equivalents of phenylmagnesium bromide. The purple complex which formed persisted after three hours, so the mixture was allowed to come to room temperature. The purple color disappeared and a clear red-violet solution resulted. After four hours the solution was decomposed with iced ammonium chloride and the mixture steam distilled. The residue was recrystallized from ligroin, forming colorless prisms, m. p. 168°.

Anal. Calcd. for $C_{27}H_{24}O_2$: C, 85.2; H, 6.4; active H, 2. Found: C, 85.2; H, 6.2; active H (Grignard machine), 2.0.

The glycol gives a deep blue-violet color in concd. sulfuric acid, forming a dark, resinous mass.

7,9-Diphenyl-7,9-endoxo-8,8-dimethylperinaphthindane (VII).—A solution of the glycol (III) in methanol containing a trace of hydrochloric acid was boiled for a short time and cooled. Colorless crystals separated, m. p. 134°.

Anal. Calcd. for $C_{27}H_{22}O$: C, 89.5; H, 6.1. Found: C, 89.4; H, 5.9.

The compound liberated no gas in the Grignard machine.

Excess C_6H_5MgBr at 80°: 1,7-Diphenyl-7-hydroxyperinaphthindanone-9 (IV).—To a solution of 3.0 g. of the diketone (I) in 100 ml. of boiling benzene was slowly (two hours) added a solution of three equivalents of phenylmagnesium bromide in ether. A purple complex separated

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at first but later disappeared with the formation of a clear, light red solution. The solution was cooled, decomposed with iced ammonium chloride and steam distilled. Recrystallization of the residue from alcohol yielded colorless needles, m. p. 238–239°. From the mother liquors was isolated a small amount of the glycol (III), identified by m. p. and conversion into VII.

Anal. Calcd. for $C_{27}H_{22}O_2$: C, 85.7; H, 5.9; active H, 1; carbonyl, 1. Found: C, 85.5; H, 6.1; active H, 0.96; carbonyl (addition), 1.05.

The compound gives a red-violet color in concd. sulfuric acid. It does not react with bromine in acetic acid or carbon tetrachloride nor with cold potassium permanganate solution in acetone. It is reduced by hydriodic acid (in boiling acetic acid) with the formation of a compound, m. p. 157°, which was obtained in small amounts only and was not further characterized.

1,7-Diphenyl-7-methoxy-8,8-dimethylperinaphthindanone-9 (VIII).—The ether was formed when a solution of IV in boiling methanol was treated with a trace of hydrochloric acid and allowed to cool. It formed colorless crystals, m. p. 224°.

Anal. Calcd. for $C_{28}H_{24}O_2$: C, 85.7; H, 6.2; OCH_3, 7.8. Found: C, 85.4; H, 6.3; OCH_3, 7.9.

1,7-Diphenyl-7-chloro-8,8-dimethylperinaphthindanone-9 (IX).—Anhydrous hydrogen chloride was passed into a solution of 0.2 g. of IV in warm, anhydrous benzene, containing a few granules of calcium chloride. Evaporation of the benzene left a colorless oil which crystallized slowly when dissolved in benzene–petroleum ether and allowed to stand. The chloro compound melted at 158–162°, dec.

Anal. Calcd. for $C_{27}H_{23}OCl$: C, 81.3; H, 5.8; Cl, 8.9. Found: C, 81.1; H, 5.7; Cl, 9.4.

Summary

A study has been made of the reaction between phenylmagnesium bromide and 8,8-dimethylperinaphthindandione-7,9. The diketonic function was not cleaved under any of the conditions used. Three products were obtained, two of which were the result of normal addition to either one or both of the carbonyl groups, the other being the result of 1,2-addition to one of the carbonyl groups and 1,4-addition to the other.

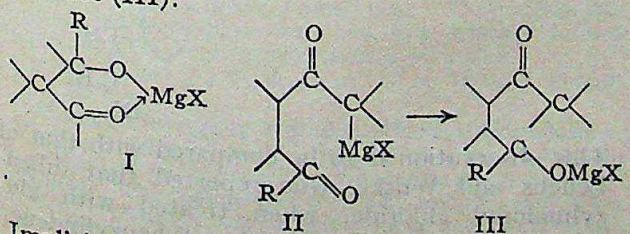
LOS ANGELES, CALIFORNIA RECEIVED JANUARY 6, 1944

[CONTRIBUTION FROM DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA, LOS ANGELES]

The Reaction between Cyclic β-Diketones and Grignard Reagents. III. 2-Methyl-2-benzoylhydrindone

BY T. A. GEISSMAN AND VSEVOLOD TULAGIN

It has been shown in a number of instances that β-diketones in which the two carbonyl groups are members of a four-,[1] five-,[2] or six-membered[3] ring undergo normal addition when treated with Grignard reagents. This behavior is in contrast to that of many open-chain β-diketones, which are readily cleaved by alkyl- and arylmagnesium halides.[4] Among the possible explanations for this difference in behavior are[2] (1) that for cleavage to occur it must be necessary for a coördination complex such as I to form after the first mole of reagent adds, and (2) that the cleavage product (II) which would be expected in the case of a cyclic β-diketone is incapable of existence because of its readiness, for steric reasons, to reform the monoaddition product (III).

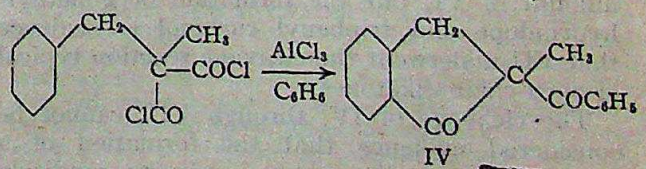


I II III

Implicit in the second explanation is the assumption that there is no bar to the initiation of cleavage, but only that it cannot proceed to such an extent as to allow a second mole of reagent to add to the resulting carbonyl group to yield an enolate–carbinolate. It is to be remarked that the conditions under which a β-diketone is allowed to react with a Grignard reagent will have an effect upon the nature of the reaction, and that a discussion of the presence or absence of cleavage in any case must take into account whether or not the reaction was carried out under conditions which would be expected to favor cleavage.

In the present paper are described the results of a study of the reaction between phenylmagnesium bromide and a β-diketone in which the carbonyl groups are disposed in such a way that chelation in the monoaddition product can occur, but in which the spatial arrangement of the groups is such that the sequence indicated by II→III could also occur.

2-Methyl-2-benzoylhydrindone (IV) was prepared by the treatment of methylbenzylmalonyl chloride with aluminum chloride in benzene solution. Simultaneous ring closure and condensation occurred smoothly to form IV in good yield.



IV

The structure of IV was proved by its cleavage with alkali to benzoic acid and 2-methylhydrindone, and by the nature of the products formed when it reacted with phenylmagnesium bromide.

(1) Wedekind and Miller, *Ber.*, **44**, 3285 (1911).
(2) Geissman and Tulagin, THIS JOURNAL, **63**, 3352 (1941).
(3) Geissman and Morris, *ibid.*, **66**, 716 (1944).
(4) Kohler and Erickson, *ibid.*, **53**, 230 (1931).

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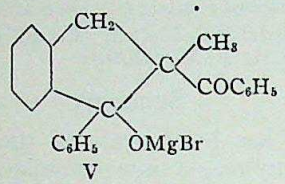
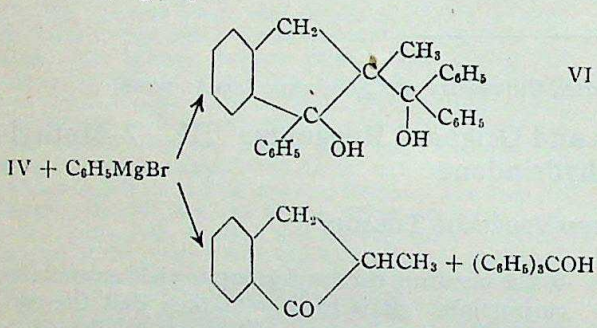
It was anticipated that the cyclic carbonyl group of IV would be the more reactive, and that the monoaddition compound V would arise as the first product of the reaction of IV with phenylmagnesium bromide.



V

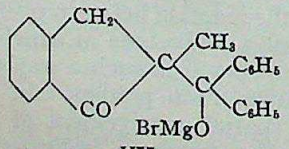
This compound (V) fulfils the conditions which should lead to cleavage if a chelated intermediate is a sufficient condition for cleavage. The reaction actually went in two ways, resulting in diaddition to form the glycol (VI), and cleavage into products which could only have arisen as the result of an initial attack of the reagent at the *benzoyl* group.



VI

The relative amounts of the products isolated indicated that about one-fifth of the total amount of reaction followed the route leading to cleavage, the remainder leading to VI.

The initial products formed by the attack of phenylmagnesium bromide on IV would be the monoaddition compounds V and VII



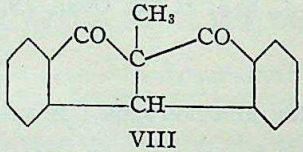
VII

It is clear from the products isolated that the subsequent reaction of V involved the addition of a second mole of the reagent to yield VI (after hydrolysis). The further reaction of VII may have led in part to the formation of an additional amount of VI, but the formation of 2-methylhydrindone and triphenyl carbinol is evidence that VII underwent the cleavage reaction typical of open-chain diketones.

The cleavage of IV, through VII, cannot be considered evidence that the formation of a chelated intermediate is a necessary condition for cleavage, since this case parallels that of a simple open-chain β-diketone. The lack of cleavage through the intermediate V does prove, however, that the formation, or possibility of formation, of a chelated intermediate is not a sufficient condition for cleavage. The question of the necessity for such an intermediate in the cleavage reaction must be examined in a different way, but it can be said that in no case so far examined in which such an intermediate cannot form has cleavage been observed.

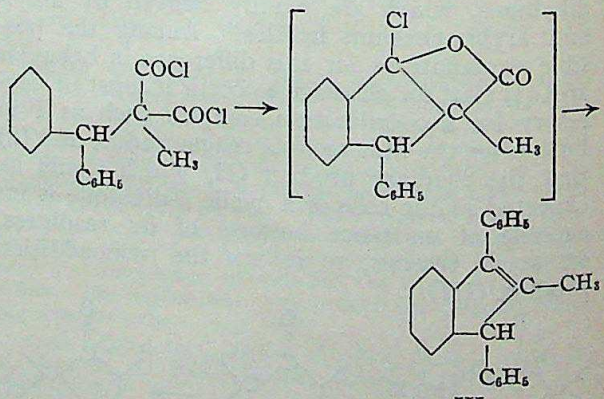
Preliminary to the preparation and study of IV attempts were made to prepare two other diketones in which the carbonyl groups are disposed in such a way that it appeared (from models) that a coördinated complex such as I could form, but in which the conditions for the reaction II→III were also present. These experiments were unsuccessful, but will be described briefly because of certain features of interest in the synthetic work done.

The preparation of the diketone VIII was attempted by the sequence: diethyl benzalmalo-



VIII

nate + phenylmagnesium bromide→diethyl benzhydrylmalonate[5]→diethyl methylbenzhydrylmalonate→methylbenzhydryl malonic acid→chloride, and ring-closure of this to yield VIII. The only product isolated in attempts to bring about this ring closure resulted when the reaction was carried out in benzene solution. It was a crystalline substance the analysis of which corresponded to the formula $C_{22}H_{18}$. This compound is assumed to have arisen as follows, and to have the structure IX



IX

This observation is to be compared with that of Leuchs and Wutke, who reported that dibenzylmalonyl chloride, when treated with aluminum chloride, yielded 1-chloro-2-benzylindene.[6] Thomas[7] has reported other, analogous cases.

The preparation of the diketone X was attempted in the following way: dibenzylacetic

(5) Kohler, *Am. Chem. J.*, **34**, 134 (1904).

(6) Leuchs and Wutke, *Ber.*, **46**, 2428 (1913).

(7) Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Am. Chem. Soc. Monograph, Reinhold Publishing Co., New York, N. Y., 1941, pp. 237–239.

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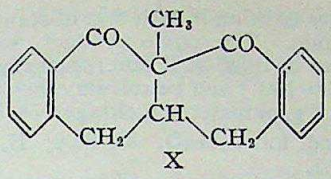

X

acid→β,β-dibenzylpropionic acid (by the Arndt–Eistert reaction)→3-benzyltetralone→ethyl 3-benzyltetralone - 2 - glyoxylate → ethyl 3 - benzyltetralone - 2 - methyl - 2 - glyoxylate → ethyl 3 - benzyltetralone - 2 - methyl - 2 - carboxylate → acid, followed by ring closure to yield XI. Difficulties were encountered in attempts to hydrolyze ethyl 3-benzyltetralone-2-methyl-2-carboxylate to the corresponding acid, and the synthesis was finally abandoned in favor of studies on the diketone IV.

Experimental

Methylbenzylmalonic Acid.—Absolute alcohol was added in small portions to a suspension of 8 g. of powdered sodium in 50 ml. of boiling, dry benzene, until a clear solution was obtained. The solvents were removed at 100° and 22 mm., and to the dry sodium ethoxide was added a solution of 90 g. of ethylbenzylmalonate in 150 ml. of dry benzene. The mixture was treated with 70 g. of methyl iodide and allowed to stand overnight. After the addition of water, the benzene layer was separated and the benzene removed under reduced pressure. The residue was dissolved in a solution of 40 g. of sodium hydroxide in 60 ml. of water and 300 ml. of alcohol and the solution refluxed for twenty-four hours. The resulting suspension was dissolved in 1 liter of water, the alcohol removed by distillation, the aqueous solution decolorized and acidified. The oily acid was taken up in ether and after the removal of the ether, crystallized from benzene. The product weighed 60 g. (80%); m. p. 139.5–140° (literature[8] 135°).

2-Methyl-2-benzoylhydrindone (IV).—A suspension of 20 g. of methylbenzylmalonic acid in a mixture of 50 ml. of dry benzene, 50 g. of thionyl chloride and 3 drops of pyridine was allowed to stand, with occasional agitation, until all of the solid had dissolved. The solution was evaporated and to the residual oil was added 12 g. of phosphorus pentachloride and a few ml. of benzene. After thirty minutes the volatile material was removed at 22 mm. and 100°, the residue taken up in 50 ml. of dry benzene, and 40 g. of aluminum chloride added in small portions. Hydrogen chloride was evolved and the solution changed through red to a deep violet. After standing overnight, the mixture was decomposed with ice and hydrochloric acid, the benzene layer separated and evaporated and the residue distilled at 3 mm. Most of the material distilled at 195–197° as a light yellow oil which crystallized when rubbed with a few drops of acetic acid. The material was crystallized from dilute methanol, from which it formed large clumps of colorless needles, m. p. 62.5–63.5°.

Anal. Calcd. for $C_{17}H_{14}O_2$: C, 81.6; H, 5.6. Found: C, 81.3; H, 5.7.

Alkaline Cleavage of 2-Methyl-2-benzoylhydrindone.—A mixture of 5 g. of the diketone, 5 g. of sodium hydroxide and 10 ml. of water was refluxed overnight and then steam-distilled. The residue was acidified; upon cooling it deposited crystals of benzoic acid: m. p. and mixed m. p., 120–121°; neutral equivalent found, 123; calculated, 122. The steam distillate contained 2-methylhydrindone as a light yellow, mobile oil from which were prepared an oxime, m. p. 103–104.5 (literature[9] 104–106°), a *p*-nitrophenylhydrazone, m. p. 171–172° (literature[9] 167–168°), and a 2,4-dinitrophenylhydrazone, m. p. 213–215°.

The Reaction of 2-Methyl-2-benzoylhydrindone with Phenylmagnesium Bromide.—A solution of phenylmagnesium bromide in equal parts of ether and benzene was added dropwise to a refluxing solution of 4 g. of the diketone in 50 ml. of dry benzene. The first mole of the reagent caused the formation of a gummy, orange-yellow precipitate which dissolved as a second mole was slowly added, a clear yellow solution resulting. The addition of the first two moles of reagent took an hour; a third mole was then added all at once to insure the completion of the reaction. The resulting solution was refluxed for two hours, cooled and decomposed with ice and hydrochloric acid. The solvents were removed by steam distillation. The semi-crystalline residue remaining was crystallized from toluene, yielding 3.9 g. of colorless crystals, m. p. 214–215°. This material (VI) is readily soluble in hot acetone, acetic acid, benzene and toluene, but only slightly soluble in these solvents in the cold.

Anal. Calcd. for $C_{29}H_{26}O_2$: C, 85.9; H, 5.9. Found: C, 85.8; H, 6.2.

The mother liquor from which VI had crystallized was evaporated and the residue taken up in hot acetone. An additional amount of VI separated; this was removed and the solution cooled to 0°. On standing, the solution deposited 1.3 g. of triphenylcarbinol, m. p. (after recrystallization) and mixed m. p. 159–162°. In order to isolate 2-methylhydrindone, another sample of 8 g. of the diketone was treated as above; the benzene layer, separated after decomposition with ice and ammonium chloride, was cooled to remove VI and then distilled through a small helix-packed column. The last traces of benzene were removed at 100° and 22 mm. and the residue steam-distilled. The light yellow oil present in the steam distillate was converted into a 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. 214–215°.

Oxidation of the Diol (VI).—A suspension of 2 g. of VI in a solution of 20 ml. of concentrated nitric acid in 60 ml. of water was refluxed for one hour. The resulting dark red oil was taken up in ether, the ether solution washed with water and with sodium bicarbonate solution, dried and evaporated. The residue was distilled at 3 mm., yielding an oily distillate which crystallized when seeded with benzophenone. The material melted, alone or mixed with benzophenone, at 48–49°. It formed a 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. with an authentic sample of benzophenone 2,4-dinitrophenylhydrazone, 235–237°. The yield was 48%, based upon unrecovered diol.

The sodium bicarbonate extract of the original ether solution was acidified and extracted with ether. From the ether solution was isolated 210 mg. of *o*-benzoylbenzoic acid: neutral equivalent found, 227; calculated, 228. It melted at 126–128° and did not depress the m. p. of an authentic sample of *o*-benzoylbenzoic acid. It formed a hydrate, m. p. 93–94°, identical with an authentic sample.

There was no neutral fraction other than that represented by benzophenone and no ether-soluble acid other than *o*-benzoylbenzoic acid.

Methylbenzhydrylmalonic Acid.—A solution of 58 g. of ethyl benzhydrylmalonate in 600 ml. of dry ether was stirred with 4 g. of sodium wire until all of the metal had disappeared. A solution of 55 g. of methyl iodide in 50 ml. of ether was then added dropwise during thirty minutes and the mixture allowed to stand overnight. Water was added and the layers separated. The crude ester weighed 60 g.; it was not purified before saponification.

A solution of 53 g. of the ester, 100 g. of sodium hydroxide, 200 ml. of water and 300 ml. of alcohol was heated on the steam-bath for one hour. The thick crystalline magma was dissolved by the addition of 150 ml. of water and the resulting solution refluxed for twenty hours. After dilution with water the solution was acidified; the dark brown oil which separated crystallized on standing at 0°. The crude acid was recrystallized from dilute acetic acid. It formed nearly colorless prisms, m. p. 143–145° with gas evolution. The yield was 26.5 g.

Anal. Calcd. for $C_{17}H_{16}O_4$: C, 71.8; H, 5.7; neut. eq., 142. Found: C, 71.9; H, 6.0; neut. eq., 140.

Attempted Ring Closure of Methylbenzhydrylmalonyl Chloride.—(A) In benzene solution: to a solution of 5 g.

(8) Conrad and Bischoff, *Ann.*, **204**, 177 (1880).

(9) Auwers and Auffenberg, *Ber.*, **52**, 107 (1919).

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of the acid in benzene was added 5 g. of phosphorus pentachloride. After thirty minutes the benzene and phosphorus compounds were removed on the water-bath at 20 mm. and to the residue, dissolved in 50 ml. of benzene, was added 6 g. of aluminum chloride in small portions. The initial yellow color slowly changed to red in the course of several hours. After twenty-four hours the mixture was decomposed with ice and hydrochloric acid, the benzene layer separated, dried and evaporated. The residue was distilled at 2 mm., yielding a light yellow distillate which crystallized from dilute acetic acid. There was obtained 0.81 g. of colorless crystals, m. p. 91–92°. The compound was not soluble in cold, concentrated sulfuric acid, very soluble in ligroin and slightly soluble in acetone.

Anal. Calcd. for $C_{22}H_{18}$: C, 93.6; H, 6.4. Found: C, 93.2; H, 6.6.

When stannic chloride was used in place of aluminum chloride the same compound was formed.

(B) In carbon bisulfide: No crystalline material could be isolated when carbon bisulfide was used as the solvent in place of benzene.

β,β-Dibenzylpropionic Acid.—A solution of 15 g. of dibenzylacetic acid, 18 g. of thionyl chloride, 3 drops of pyridine and 60 ml. of dry benzene was allowed to stand for an hour at room temperature. The solution was evaporated at 22 mm. and 100°, the residue taken up in 50 ml. of dry benzene and treated with a dried solution of diazomethane, prepared from 30 g. of nitrosomethylurea, in ether. After an hour the solution was filtered and the solvents removed under reduced pressure. The residue crystallized as orange needles. Recrystallized from 90% methanol, the diazoketone formed pale yellow needles, m. p. 72–74°; yield, 15 g. (90%).

Anal. Calcd. for $C_{17}H_{16}ON_2$: C, 77.3; H, 6.1. Found: C, 76.9; H, 6.2.

The recrystallized diazoketone was dissolved in 100 ml. of anhydrous ethanol and treated with 3 g. of dry silver oxide. On warming to 50° a vigorous evolution of nitrogen occurred and the solution was cooled. The solution was then warmed at 60° for an hour and filtered. Five grams of potassium hydroxide was added and after three hours at room temperature the silver oxide which had precipitated was removed and the solution refluxed for thirty minutes. Water was added, the alcohol removed by distillation and the solution acidified. The precipitated acid was extracted with ether and, after removal of the ether, crystallized from dilute acetic acid. The product melted at 85–86°; the yield was 13.1 g. (91%, based on the diazoketone).

Anal. Calcd. for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1; neut. eq., 254. Found: C, 80.0; H, 7.1; neut. eq., 255.

The acid was also prepared through the Reformatsky reaction starting with ethyl bromoacetate and dibenzyl ketone, the hydroxy ester being dehydrated to the unsaturated ester, the latter saponified and the acid reduced with Raney nickel at 150° and 1700 lb. The over-all yield was 15% of a product identical with that prepared as described above.

3-Benzyltetralone.—Five grams of β,β-dibenzylpropionic acid was converted into its chloride with thionyl chloride and cyclized by treating it with 8 g. of stannic chloride in benzene solution. The crude product, isolated in the usual way, was distilled at 2 mm., then crystallized from ligroin (b. p. 90–100°) and petroleum ether (b. p. 30–60°). The yield was 4 g. of material melting at 54–56°.

Anal. Calcd. for $C_{17}H_{16}O$: C, 86.4; H, 6.8. Found: C, 86.6; H, 7.1.

Methyl 3-Benzyltetralone-2-glyoxalate.—Dry sodium methoxide was prepared from 1.5 g. of sodium and absolute methanol, and to it was added 15 g. of dimethyl oxalate and 50 ml. of dry benzene. A solution of 15.5 g. of 3-benzyltetralone in 15 ml. of benzene was added dropwise, and the mixture allowed to stand overnight. Water was added, the benzene layer separated and evaporated, and the residue crystallized from methanol. There was obtained 14 g. of colorless needles, m. p. 85–87°.

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.6; H, 5.6. Found: C, 74.4; H, 5.7.

Methyl 3-Benzyltetralone-2-carboxylate.—The glyoxylic ester was mixed with 20 g. of powdered soft glass (previously treated with aqua regia, water, alkali and then thoroughly washed) and the mixture heated for twenty minutes at 175°. The product was extracted with acetone, the acetone removed, and the residue recrystallized from methanol. Large colorless needles, m. p. 77–78°, were obtained. The yield was quantitative.

Anal. Calcd. for $C_{19}H_{18}O_3$: C, 77.6; H, 6.1. Found: C, 77.3; H, 6.3.

Methyl 2-Methyl-3-benzyltetralone-2-carboxylate.—To the dry sodium methoxide prepared from 0.46 g. of sodium was added a solution of 5.9 g. of methyl 3-benzyltetralone-2-carboxylate in 25 ml. of dry benzene. When the solid had dissolved, 6 g. of methyl iodide was added and the solution allowed to stand overnight. After the addition of water and ether, the ether layer was separated, dried and evaporated. The residue crystallized from methanol, yielding a first crop of 4.4 g. of material, m. p. 114–115°, and a second crop of 0.7 g. of slightly less pure material. The total yield was 5.1 g. (84%).

Anal. Calcd. for $C_{20}H_{20}O_3$: C, 77.9; H, 6.5. Found: C, 77.5; H, 6.7.

Summary

The reaction between phenylmagnesium bromide and 2-methyl-2-benzoylhydrindone follows two courses, leading to products derived from (a) diaddition to the carbonyl groups and (b) cleavage. Cleavage occurs only when the initial attack by the reagent is on the extracyclic carbonyl group.

It is postulated that the ability of the monoaddition product to form an intramolecular coordination complex is not a sufficient condition for cleavage.

LOS ANGELES, CALIF. RECEIVED JANUARY 6, 1944

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Preparation of 24-Keto and 24-Hydroxycholesterol and Certain Derivatives[1]

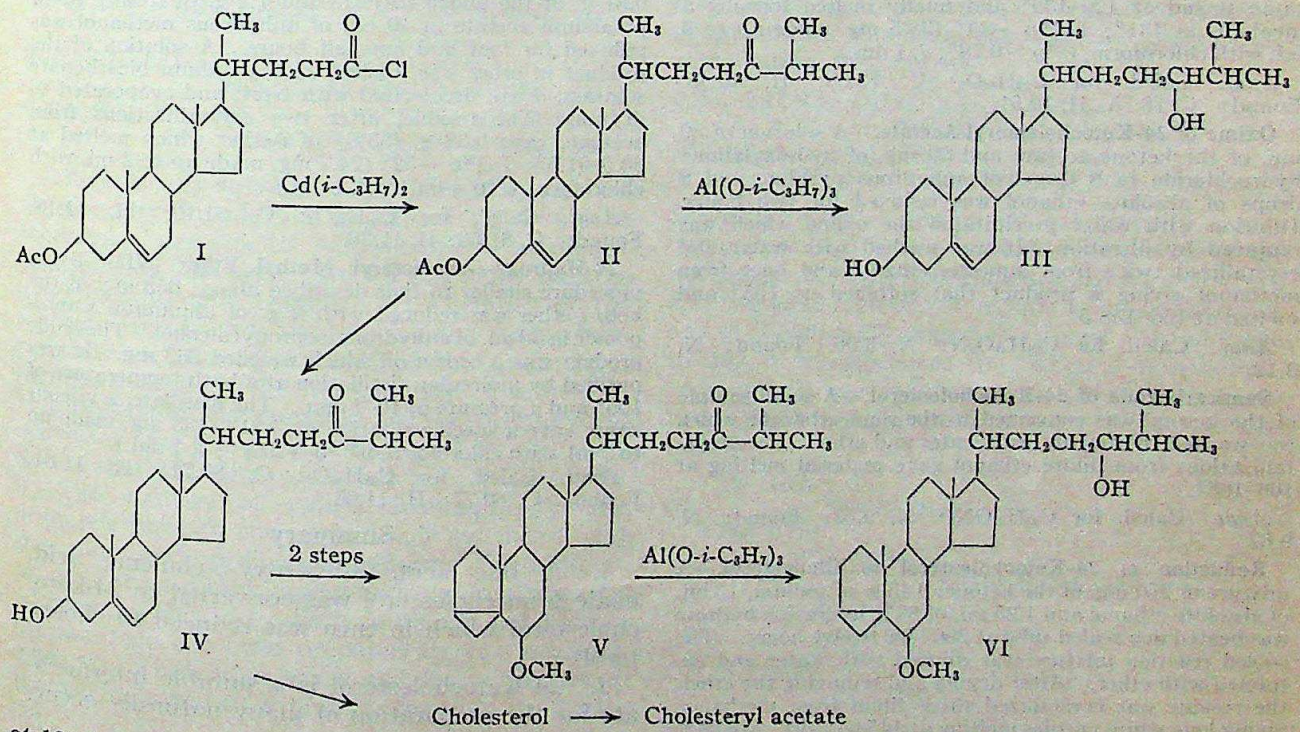
BY BYRON RIEGEL AND IRVING ALLAN KAYE

The structures of the side chains of sterols have been elucidated chiefly by degradative studies. Surprisingly little has been done to establish more definitely these structures by resyntheses from degraded products containing the 3-hydroxyl group and the 5,6-double bond.[2]

The carbon skeletons of naturally occurring sterols differ only in the substituents at the 24-position. Thus, a suitable intermediate for the preparation of sterols having various side chains would be 24-ketocholesterol (IV). This intermediate will also permit further study of the stereochemical contribution of the side chain to the optical rotation. An excellent method for the preparation of this compound involves the reaction of diisopropylcadmium with 3-acetoxy-5-cholenyl chloride[2d] (I). 24-Ketocholesterol melts at 137–138.5° and has a specific rotation of −37°. Its semicarbazone, acetate and the acetate oxime were prepared.

Cholesterol was obtained directly from 24-ketocholesterol by a modified Wolff–Kishner reduction of the carbonyl group. The Clemmensen and the ordinary Wolff–Kishner reductions gave tarry products. Reduction of the ketone (II) by means of aluminum isopropoxide gave 24-hydroxycholesterol (III). Intermediates from which the 24-hydroxyl group might be removed by dehydration were sought. Attempts to make the 3-monoacetate by partial acetylation gave only the diacetate or starting material.

Use was then made of the so-called *i*-ether configuration as a method for the specific protection of the 3-hydroxyl group. The tosylate of 24-ketocholesterol, when heated in a-buffered methanol solution, gave 24-keto-*i*-cholesteryl methyl ether (V) which melted at 90.5–91.5° and gave a specific rotation of +52°. This ketone (V) in the presence of aluminum isopropoxide was reduced to 24-hydroxy-*i*-cholesteryl methyl ether. The conversion of some of these compounds to other naturally occurring sterols is now being studied.



The authors wish to thank the Rockefeller Foundation for financially supporting this work.

Experimental[3]

24-Ketocholesterol (IV).—The 3-acetoxy-5-cholenyl chloride[2d] prepared from 25 g. of 3-acetoxy-5-cholenic acid[4] (m. p. 183–185°) was not isolated but was dissolved in dry benzene and then added to a diisopropylcadmium solution. The latter solution was made from 14.65 g. of magnesium, 125 g. of isopropyl bromide, anhydrous ether and 88 g. of

(1) Original manuscript received August 10, 1943.

(2) (a) H. Wieland and R. Jacobi, *Ber.*, **59**, 2064 (1926); (b) F. Reindel and K. Niederländer, *Ann.*, **522**, 218 (1936); (c) E. Fernholz, *Ber.*, **69**, 1792 (1936); (d) S. Kuwada and M. Yogo, *J. Pharm. Soc. (Japan)*, **57**, 963 (1937).

(3) All melting points are corrected. Analyses by Dr. T. S. Ma, University of Chicago.

(4) The authors wish to express their appreciation to Dr. Erwin Schwenk of the Schering Corporation for a generous quantity of this acid.

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anhydrous cadmium bromide. The reaction mixture, after standing overnight, was worked up in the usual way and the product was saponified with methanolic potassium hydroxide. The ether soluble material from the saponification was crystallized three times from petroleum ether (Skellysolve C, b. p. 85–100°). A yield of 11.19 g. (46%) of large clumps of hard needles, melting at 134.5–135.5°, was obtained. More material was recovered from the mother liquors by forming the semicarbazone of the crude ketone. The semicarbazone was washed well with water, dried and decolorized by extraction with ether in a Soxhlet extractor. The white powdery product was hydrolyzed, dissolved in ether, and decolorized with Norit. Removal of the ether and crystallization from Skellysolve C gave 1.57 g. (7%) of material melting at 134–135.5°. After three more crystallizations of the ketone from aqueous methanol, it melted at 137–138.5°; $[\alpha]^{26}D$ −37° (19.6 mg. made up to 2 ml. with chloroform, $\alpha^{26}D$ −0.36°; *l*, 1 dm.).

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.94; H, 11.07. Found: C, 80.87; H, 11.02.

24-Ketocholesteryl Acetate (II).—The interaction of the acid chloride with the cadmium Grignard reagent gave considerable esterification which is difficult to understand. However, from the reaction mixture the 24-ketocholesteryl acetate could be isolated by means of Girard's reagent-T. Even after two crystallizations from methanol and two more from 95% ethanol it gave a peculiar melting point. It melted at 127.5–128° but did not become fluid, then became turbid at 129–130° and finally melted forming a meniscus at 131°; $[\alpha]^{26}D$ −41° (38.5 mg. made up to 2 ml. with chloroform, $\alpha^{26}D$ −0.78°; *l*, 1 dm.).

Anal. Calcd. for $C_{29}H_{46}O_3$: C, 78.68; H, 10.48. Found: C, 78.75; H, 10.51.

Oxime of 24-Ketocholesteryl Acetate.—A solution of 50 mg. of the ketone acetate and 50 mg. of hydroxylamine hydrochloride in 8 drops of anhydrous pyridine and 8 drops of absolute ethanol was refluxed for two hours. Dilution with water precipitated the oxime which was removed by filtration. It was washed with water and crystallized twice from aqueous ethanol and once from methanol giving a product that softened at 155° and melted at 156–158.5°.

Anal. Calcd. for $C_{29}H_{47}O_3N$: N, 3.06. Found: N, 3.12.

Semicarbazone of 24-Ketocholesterol.—A small sample of the ketone was converted to the semicarbazone which was washed thoroughly with water and ether. Two crystallizations from dilute ethanol gave material melting at 166–168°.

Anal. Calcd. for $C_{28}H_{47}ON_3$: N, 9.52. Found: N, 9.67.

Reduction of 24-Ketocholesterol to Cholesterol.—A mixture of 250 mg. of the ketone, 0.45 g. of sodium, 15 ml. of absolute ethanol and 1.25 ml. of 85% hydrazine hydrate was heated in a sealed tube at 200° for twelve hours. The cooled reaction mixture was diluted with water and extracted with ether. After drying and removing the ether, the residue was crystallized three times from methanol, giving long white needles melting at 145.6–146.1°; $[\alpha]^{28.5}D$ −36° (27.5 mg. made up to 2 ml. with chloroform, $\alpha^{28.5}D$ −0.50°; *l*, 1 dm.). It gave a mixed m. p. of 144–145.8° when mixed with an authentic sample of cholesterol (m. p. 150–151°).

The acetate was prepared by heating 90 mg. of the above product with 3 ml. of acetic anhydride. After removing the acetic anhydride, the residue was crystallized once from methanol and twice from dilute ethanol. It melted at 113–114°, gave no depression in m. p. when mixed with an authentic sample of cholesteryl acetate and gave a specific rotation of −46° (6.8 mg. made up to 2 ml. with chloroform, $\alpha^{28}D$ −0.15°; *l*, 1 dm.).

24-Hydroxycholesterol (III).—A solution of 0.5 g. of 24-ketocholesteryl acetate and 5 g. of aluminum isopropoxide in 75 ml. of anhydrous isopropyl alcohol was refluxed for three hours. About one-half of the solvent was removed by slow distillation, 75 ml. more of anhydrous isopropyl alcohol was added and again distilled slowly until removed. The reaction mixture was cooled and decomposed by adding 50 ml. of dilute hydrochloric acid. The product was removed by filtration and crystallized from dilute methanol giving 470 mg. (94%) of material melting at 166–169°.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.54; H, 11.52. Found: C, 80.55; H, 11.97.

Diacetate.—When the above diol was treated with acetic anhydride the diacetate was obtained readily. After two crystallizations from aqueous ethanol and two from methanol, it softened at 93° and melted at 95–96°.

Anal. Calcd. for $C_{31}H_{50}O_4$: C, 76.50; H, 10.36. Found: C, 76.75; H, 10.44.

24-Ketocholesteryl *p*-Toluenesulfonate.—Following the method of Freudenberg and Hess,[5] 1 g. of 24-ketocholesterol gave 1.1 g. (82%) of tosylate. From low boiling petroleum ether, it formed small, hard crystals which softened at 115° and melted at 119–120° (dec.); $[\alpha]^{26}D$ −35° (23.5 mg. made up to 2 ml. with chloroform, $\alpha^{26}D$ −0.42°; *l*, 1 dm.).

Anal. Calcd. for $C_{34}H_{50}O_4S$: C, 73.60; H, 9.08. Found: C, 74.28; H, 9.34.

24-Keto-*i*-cholesteryl Methyl Ether (V).—A solution of 0.81 g. of the above tosylate and 1.2 g. of freshly fused potassium acetate in 40 ml. of anhydrous methanol was refluxed for four and one-half hours. A solution of the product in ether was washed with a sodium bicarbonate solution, dried, decolorized with Norit and evaporated to dryness. The residue, after two crystallizations from acetone, gave 0.32 g. (53%) of *i*-ether which melted at 90.5–91.5°; $[\alpha]^{26}D$ +52° (24.7 mg. made up to 2 ml. with chloroform, $\alpha^{26}D$ +0.64°; *l*, 1 dm.).

Anal. Calcd. for $C_{28}H_{46}O_2$: C, 81.10; H, 11.18. Found: C, 81.50; H, 11.28.

24-Hydroxy-*i*-cholesteryl Methyl Ether (VI).—By a procedure similar to that described above, 658 mg. of the keto *i*-ether was reduced with 2 g. of aluminum isopropoxide in 60 ml. of anhydrous isopropyl alcohol. The crude product was a brown oil which weighed 563 mg. It was purified by molecular distillation at a bath temperature of 106° and a pressure of 10^{-4} mm. The distillate, a viscous sirup, gave a specific rotation of +31° (133 mg. made up to 2 ml. with chloroform, $\alpha^{27.5}D$ +2.07°; *l*, 1 dm.).

Anal. Calcd. for $C_{28}H_{48}O_2$: C, 80.71; H, 11.61. Found: C, 80.77; H, 11.66.

Summary

1. A bile acid, 3-hydroxy-5-cholenic acid, made from cholesterol was converted to 24-ketocholesterol which in turn was reduced to cholesterol.

2. 24-Ketocholesterol is a suitable intermediate for the preparation of many naturally occurring sterols.

3. Reduction of the 24-keto group, by the Meerwein–Ponndorff method, gave 24-hydroxycholesterol.

4. The 3-hydroxyl group of these compounds can be protected for some reactions by the excellent method of conversion to their *i*-ethers.

5. Several other derivatives of these steroids are reported.

EVANSTON, ILLINOIS RECEIVED FEBRUARY 15, 1944

(5) K. Freudenberg and H. Hess, *Ann.*, **448**, 128 (1926).

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Basically Substituted Aliphatic Nitriles and their Catalytic Reduction to Amines[1]

BY FRANK C. WHITMORE, HARRY S. MOSHER,[2] ROBERT R. ADAMS,[3] ROBERT B. TAYLOR, EARL C. CHAPIN,[3] CHARLES WEISEL AND WILLIAM YANKO[3,4]

In the course of our work on basically substituted heterocyclic compounds it became necessary to prepare a group of aliphatic substituted diamines. This paper is a report on the more successful of these experiments. Since it was necessary to produce rather large amounts of these compounds, the phthalimide synthesis which has been used most often for this purpose was judged unsuitable and it was finally decided to use the reduction of basically substituted nitriles to obtain these amines. The general procedures used are represented by the following equations, where R may be hydrogen, alkyl or bound in a heterocyclic ring system.

$$R_2NH + CH_2{=}CHCN \longrightarrow R_2NCH_2CH_2CN \quad (I)$$

$$2R_2NH + ClCH_2CH_2CH_2CN \longrightarrow R_2NCH_2CH_2CH_2CN + R_2NH{\cdot}HCl \quad (II)$$

$$Et_2N(CH_2)_nOH + CH_2{=}CHCN \xrightarrow{NaOMe} Et_2N(CH_2)_n{-}O{-}CH_2CH_2CN \quad (III)$$

$$R_2N(CH_2)_nCN + 2H_2 \longrightarrow R_2N(CH_2)_{n+1}NH_2 \text{ and } [R_2N(CH_2)_{n+1}]_2NH + NH_3 \quad (IV)$$

The basically substituted propionitriles are best obtained by the addition of ammonia, primary, or secondary amines to acrylonitrile.[5] Although this method has been used for the same purpose by Holcomb and Hamilton,[6] no studies of the reaction itself and the mechanism have been published. Structural proof of the products is furnished first by the non-identity of α-diethylaminopropionitrile prepared by the cyanohydrin synthesis and the product obtained by the addition of diethylamine to acrylonitrile, and secondly by the identity of γ-diethylaminopropylamine prepared through the phthalimide synthesis[7] and the compound obtained by reducing the addition product from diethylamine and acrylonitrile. In addition to this, β-(γ-diethylaminopropylamino)-propionitrile has been prepared by two separate methods as indicated below and the properties of the products and their picrates found to be identical.

$$\left.\begin{array}{l} Br{-}CH_2CH_2CN + H_2N(CH_2)_3NEt_2 \\ CH_2{=}CHCN + H_2N(CH_2)_3NEt_2 \end{array}\right\} \rightarrow NCCH_2CH_2NH(CH_2)_3NEt_2 \quad (V)$$

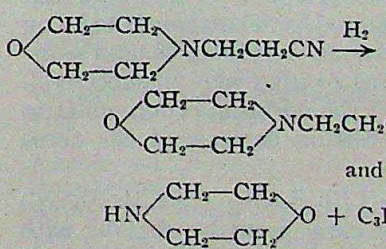
Thus the mechanism by which the addition takes place probably involves a typical 1,4-addition.

From the following experimental evidence it is apparent that the reaction is reversible. When the higher β-dialkylaminopropionitriles are heated near their boiling points for any length of time, they slowly decompose to give some of the dialkylamine. This is especially true in the case of diethanolamine, addition of which to acrylonitrile gives a viscous liquid from which is readily obtained the crystalline picrate of β-diethanolaminopropionitrile. Attempted distillation of this reaction product, however, gives back all of the diethanolamine used as starting material and leaves only a non-distillable polymer. If, however, the addition compound is reduced without distillation, a fair yield of γ-diethanolaminopropylamine, which can be distilled without decomposition, is obtained.

$$CH_2{=}CHCN + (HOCH_2CH_2)_2NH \rightleftharpoons (HOCH_2CH_2)_2NCH_2CH_2CN \quad (VI)$$

$$(HOCH_2CH_2)_2NCH_2CH_2CN + 2H_2 \longrightarrow (HOCH_2CH_2)_2NCH_2CH_2CH_2NH_2$$

Secondly, when equal molar amounts of a secondary amine and acrylonitrile react, some of the unreacted starting materials are always recovered and the yield is never as high as when an excess of one of the starting materials is used. In addition to this, it was observed that when β-morpholinopropionitrile was reduced at an elevated temperature (190°) a 35% yield of morpholine was obtained.



$$\xrightarrow{H_2} \text{(45\%)} \quad \text{and} \quad \text{(55\%)} \quad (VII)$$

Although this may be explained by hydrogenolysis, it can equally well be explained on the basis of a reversal of the morpholine–acrylonitrile–β-morpholinopropionitrile equilibrium at the elevated temperature. Finally the spontaneous polymerization of β-aminopropionitrile on standing to give a polymer and ammonia can best be explained by assuming its disproportionation into acrylonitrile and ammonia followed by the polymerization of the acrylonitrile.

$$H_2NCH_2CH_2CN \rightleftharpoons NH_3 + CH_2{=}CHCN \longrightarrow \text{Polymer} + NH_3 \quad (VIII)$$

The ease with which the various amines react

(1) Presented before the Organic Division of The American Chemical Society at Detroit, April 12, 1943.

(2) The material herein presented is taken in part from a thesis submitted by Harry S. Mosher to The Pennsylvania State College in partial fulfillment of the requirements for the Ph.D. degree.

(3) Parke, Davis and Company Research Fellow 1942–43.

(4) Present address: Monsanto Chemical Company, Dayton, Ohio.

(5) (a) Hoffmann and Jacobi, U. S. Patents 1,992,615 and 2,017,537; (b) Roh and Wolff, German Patent 641,597.

(6) Holcomb and Hamilton, THIS JOURNAL, 64, 1309–1311 (1942).

(7) Shriner and Hickey, *ibid.*, 61, 888 (1939).

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with acrylonitrile is interesting. Piperidine is the most reactive and the solution should be cooled during the addition; morpholine is next in activity, being only slightly less reactive than piperidine; diethylamine is the most reactive of the dialkylamines employed but its rate of addition is very much slower than that for either of the two above cyclic bases and no noticeable heat is evolved on mixing with acrylonitrile. The rate of addition of the remaining dialkylamines decreases progressively with the length and size of the alkyl groups and the formation of β-[di-(2-ethylhexylamino]-propionitrile was only 77% complete after heating di-(2-ethylhexyl)-amine and acrylonitrile together for 360 hours at 100°. That the rate of addition is not a function of the basic strength of the addenda is shown by the relative reactivities of diethylamine, piperidine and morpholine (whose ionization constants are, respectively, 1.2×10^{-3}, 1.6×10^{-3} and 2.4×10^{-6})[8] but apparently is more dependent upon the size and shape of the entering molecule.

In the case of certain heterocyclic and aromatic amines a catalyst was necessary. Thus methylaniline did not react with acrylonitrile in a sealed tube at 200° in the absence of a catalyst nor did any reaction take place between the two when refluxed in dioxane in the presence of benzyltrimethylammonium hydroxide. But in the presence of hydrated copper sulfate at 180° the desired β-(methylphenylamino)-propionitrile was produced. Likewise carbazole would not react without a catalyst but in the presence of benzyltrimethylammonium hydroxide, the reaction proceeded vigorously. Neither copper bronze, copper sulfate, small amounts of sulfuric acid, nor benzyltrimethylammonium hydroxide would catalyze the addition of tetrahydroquinoline to acrylonitrile but in acetic acid solution a good yield of the addition product was obtained.[9] All attempts to bring about a reaction between acrylonitrile and anisidine, 2-aminopyridine or urea were unsuccessful.

The special case of the addition of ammonia to acrylonitrile[5] is interesting because of the three possible products.

$H_2NCH_2CH_2CN$ $HN(CH_2CH_2CN)_2$ $N(CH_2CH_2CN)_3$

When the reaction is carried out by shaking with aqueous ammonia, the secondary and tertiary amines predominate but when the reaction takes place in a seven molar excess of liquid ammonia at about 40°, a 22% yield of the primary amine and a 64% yield of the secondary amine result with very little of the completely substituted product. The data indicate that the addition of β-aminopropionitrile to acrylonitrile takes place approximately 20 times faster than the corresponding addition of ammonia. The reduction of a similar reaction mixture resulted in a 20% yield of trimethylenediamine.

(8) Ingram and Luder, THIS JOURNAL, 64, 3043 (1942).

(9) The use of acetic acid as solvent for this reaction was made at the suggestion of Dr. J. B. Dickey of Eastman Kodak Company.

The group of amines which contain an ether linkage were obtained by the method of Bruson and Riener[10] by the action of acrylonitrile on a basically substituted alcohol such as diethylaminoethanol in the presence of sodium methoxide (Equation III). The yields with diethylaminoethanol and γ-diethylaminopropanol were 79.5 and 75.4%, respectively, while that for the secondary alcohol, 1-diethylamino-4-pentanol,[11] was 66%.

The γ-aminobutyronitriles were all obtained in excellent yields by the reaction of secondary amines with γ-chloro- or γ-bromo-butyronitriles according to the method employed by Utermohlen and Hamilton,[12] and Strukov.[13] Their yields were greatly improved by the use of a solvent.

The reduction of the nitriles to amines was usually accomplished with Raney nickel catalyst at temperatures of 90–130° and hydrogen pressures of 67 to 270 atmospheres. This was found to be superior to platinum at lower pressures or to reduction at higher temperatures. A typical example is the hydrogenation of β-morpholinopropionitrile, 4.8 moles of which was reduced without solvent in twenty minutes at 120° and 1400 lb. per sq. in. pressure to give a 60% yield of γ-morpholinopropylamine. The reduction of nitriles has been studied extensively[14] and is known to produce as a by-product the secondary amine as well as the primary amine (Equation IV) in which it seems quite certain that the mechanism envolves the reaction of a part of the primary amine which has been produced, with the intermediate imine.[15] The formation of similar triamines has been reported by Mannich and Margotte,[16] in a patent by Münch and Schlichting,[17] by Winans and Adkins,[15] and Magidson[13] has also used such an amine in the synthesis of an acridine derivative.

These secondary amines were normally observed in each of our reductions when sufficiently large runs were made and constituted 5 to 32% yields. The γ-aminobutyronitriles gave uniformly higher yields of the secondary amines than the corresponding propionitriles; thus γ-piperidinobutyronitrile gave a 54% yield of the primary amine and a 31% yield of the secondary amine.

$$C_5H_{10}NCH_2CH_2CH_2CN \nearrow C_5H_{10}NCH_2CH_2CH_2CH_2NH_2 \quad 54\%$$
$$\searrow [C_5H_{10}NCH_2CH_2CH_2CH_2]_2NH \quad 31\%$$
(IX)

(10) Bruson and Riener, THIS JOURNAL, 65, 23 (1943).

(11) Furnished through the courtesy of the Winthrop Chemical Company.

(12) Utermohlen and Hamilton, THIS JOURNAL, 63, 156 (1941).

(13) Strukov, *Khim. Farm. Prom.*, 332-(1933); *C. A.*, 28, 3714 (1934).

(14) Adkins, "Reactions of Hydrogen with Organic Compounds Over Chromium Oxide and Nickel Catalysts," University of Wisconsin Press, 1937.

(15) Winans and Adkins, THIS JOURNAL, 55, 4167 (1933).

(16) Mannich and Margotte, *Ber.*, 68B, 273–278 (1935).

(17) Münch and Schlichting, German Patent 561,156, Dec. 10, 1932.

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while β-piperidinopropionitrile gave a 45% yield of primary amine and a 17% yield of the secondary amine under the same conditions. The reduction can be controlled and the yield of primary amine increased by carrying out the hydrogenation in the presence of ammonia,[18] thus reversing the reaction which produces the secondary amine. By this method the 45% yield of γ-piperidinopropylamine reported above was raised to 68.5%, the 54% yield of γ-diethylamiopropylamine raised to 72% and the 60% yield of γ-morpholinopropylamine raised to 70.6%. It was likewise found possible to increase the yield of secondary amine by performing the reduction of the nitrile in the presence of an excess of the primary amine. Thus when an equal molar mixture of γ-diethylaminopropylamine and β-diethylaminopropionitrile was reduced, a 28% yield of the di-(γ-diethylaminopropyl)-amine was obtained in contrast to the 13% yield found when the hydrogenation was carried out in the normal manner or the 5% yield obtained when carried out in the presence of ammonia. It is apparent that this reduction may be controlled within limits to produce either a larger or smaller yield of primary or secondary amine depending upon which product is most desired. It is believed that the yields of the primary products can be increased in almost every case if hydrogen pressures of 250 to 300 atmospheres are employed and larger amounts of ammonia introduced. Tables I and II give the nitriles and amines which were prepared along with boiling points, indices, yields, melting points of the picrate derivatives and the observed and calculated neutralization equivalents. All of the propionitriles with the one exception noted were made from acrylonitrile, while all of the butyronitriles were prepared from γ-chlorobutyronitrile. The reductions were all carried out catalytically with approximately 10 g. of Raney nickel per mole of nitrile. All boiling points are within a one degree range and all melting points within a one-half degree range unless otherwise noted.

A representative group of seven sulfanilamide derivatives was prepared from these aliphatic amines by shaking in acetone solution over a saturated potassium carbonate solution with acetylsulfanilyl chloride. Because of the strongly basic character of the aliphatic amines, it was impossible to obtain the products by using pyridine or pyridine-acetone as solvents and only red, unworkable solutions resulted in these cases. These sulfanilamide derivatives are given in Table III along with melting points, yields, and the melting points of the acetyl derivatives. Compounds similar to these have been reported by Drozdov[19] and Walker.[20]

Experimental

Preparation of β-Aminopropionitriles.—The addition of secondary amines to acrylonitrile has already been described in patents[5] and by Holcomb and Hamilton.[6] The general procedure used here is illustrated by the preparation of β-diethylaminopropionitrile. Fractionated acrylonitrile, b. p. 77.2° (732.4 mm.), $n^{20}D$ 1.3911, 424 g. (8.0 moles) and diethylamine, 1000 g. (13.7 moles) were mixed and warmed at 50° for twenty-four hours and after standing at room temperature for two days, the excess diethylamine was removed at atmospheric pressure and the residue distilled through a modified Claisen flask to give 970 g. of material boiling from 119 to 120° at 70 mm. pressure; $n^{20}D$ 1.4351 to 1.4353, yield 97%. Another run in which the reactants were mixed in mole to mole ratio, heated on the steam-bath for eight hours, and immediately distilled at atmospheric pressure (b. p. 196–198° at 737 mm.), resulted in a 74% yield. A third experiment in which 355 g. of diethylamine (5 moles) was added to 500 g. of commercial acrylonitrile (9.5 moles) with some cooling over a period of ten minutes and the reaction mixture refluxed for one-half hour, set in the refrigerator overnight and distilled, resulted in a 93% yield of β-diethylaminopropionitrile boiling between 104 and 106° at 35 mm. pressure. This product can be titrated to a sharp end-point with hydrochloric acid using methyl orange as the indicator; equivalent weight calculated, 126.2; found 126.1. It forms a picrate which is readily recrystallized from methanol–acetone mixture and melts sharply at 85°. In general it seems that a better yield results if the reaction is allowed to reach equilibrium at room temperature before the final distillation. For the same reason the product should be distilled more or less rapidly at a low temperature if possible. A slow, careful fractionation through an efficient fractionating column is a distinct disadvantage in the case of the higher dialkylamino derivatives since dissociation into the original reactants results.

β-[Di-(γ-diethylaminopropyl)-amino]-propionitrile.—In a 500-ml. flint glass bottle was mixed 26 g. (0.107 mole) of di-(γ-diethylaminopropyl)-amine and 32 g. (0.6 mole) of acrylonitrile along with 0.1 g. of copper bronze. The flask was stoppered and heated at 100° for twenty-four hours, allowed to stand at room temperature for a like period, and distilled to give 24.6 g. (78% yield) of product, b. p. 145° (5 mm.), $n^{20}D$ 1.3640.

β-(γ-Diethylaminopropylamino)-propionitrile.—This compound was made by two different methods; *i. e.*, by the addition of γ-diethylaminopropylamine to acrylonitrile in 79.4% yield and by the reaction of β-bromopropionitrile[21] with γ-diethylaminopropylamine in 76.4% yield by the same method as described for the preparation of γ-piperidinobutyronitrile.

β-(β′-Diethylaminoethoxy)-propionitrile.—To a mixture of 220 g. (1.88 moles) of diethylaminoethanol and 2.3 g. of sodium methoxide in a 1-liter flask equipped with a thermometer, stirrer and dropping funnel was added 100 g. (189 moles) of acrylonitrile over a one-half hour period while the temperature was kept at 25°. The reaction mixture was stirred for a short while longer, allowed to stand overnight, 4.2 ml. of concd. sulfuric acid cautiously added, the solution filtered, and the filtrate distilled to give 260 g. (80% yield); b. p. 140–145° (25 mm.), $n^{20}D$ 1.4430. With the secondary alcohol, 1-diethylamino-4-pentanol,[11] the reaction did not proceed as rapidly and a yield of only 66% was obtained.

The Reaction of Ethylamine with Acrylonitrile.—Acrylonitrile, 106 g. (2 moles), was added to a 70% aqueous solution of ethylamine, 200 g. (3 moles), over a period of two hours while the temperature was kept below 30°. The reaction mixture was stirred at room temperature for five hours and finally heated on the steam-bath for one hour. After the reaction mixture had stood overnight, the water was removed by adding 50 g. of anhydrous potassium carbonate and separating the aqueous layer. The product was purified by distillation to give 176.9 g., b. p. 92–95° (30 mm.), $n^{20}D$ 1.4318–1.4322; yield 90.4% of β-ethyl-

(18) Schwoegler and Adkins, THIS JOURNAL, 61, 3499 (1939).

(19) Drozdov and Starrovskaya, *J. Gen. Chem.*, (U. S. S. R.) 9, 1642–1646 (1939).

(20) Walker, *J. Chem. Soc.*, 686–692 (1940).

(21) The β-bromopropionitrile used in this work was obtained in 95.2% yield by bubbling dry hydrogen bromide through acrylonitrile at room temperature according to the method of Moureu, *Chem. Zentr.*, 92, I, 442 (1921).

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TABLE I

BASICALLY SUBSTITUTED NITRILES

No.	Nitrile	Yield, %	Properties: B. p. °C.	B. p. Mm.	$n^{20}D$	Picrate M. p., °C.	Neut. eq. Calcd.	Neut. eq. Found	Reduction[a] conditions: Moles	Temp., °C.	Press., atm.
1	β-Aminopropionitrile[b]	22[c]	66–69	5	1.4396	178	70.0	70.3	5.0	90	120
2	Di-(β-cyanoethyl)-amine[h]	64[c]	165	4	1.4640	Oil	123.0	123.3			
3	β-Diethylaminopropionitrile[e]	95	196	735	1.4356	85	126.2	126.1	6.3	100	83
									1.7	100	85
									4.0	130	85
4	β-Ethylaminopropionitrile[d]	90.4	92	30	1.4318	163	98.1	98.1	1.3	115	107
5	Di-(β-cyanoethyl)-ethylamine	60	200–202	30	1.4591	170	[f]		1.1	116	95
6	β-Di-*n*-propylaminopropionitrile[g]	88	116	20	1.4381	111	154.2	154.3	0.7	95	3
7	β-Di-*n*-butylaminopropionitrile[g]	91	141	20	1.4423	75	182.3	182.5	0.6	95	3
8	β-Di-*n*-amylaminopropionitrile[e]	89	159–161	19	1.4457	Oil	[h]				
9	β-Di-*n*-hexylaminopropionitrile[e]	85	145–146	2	1.4483	Oil	[i]				
10	β-Piperidinopropionitrile	93	129–130	30	1.4697	160	138.2	138.3	1.3	110	117
									8.5	100	120
11	β-Morpholinopropionitrile[e]	95	149	20	1.4710	139.5	140.2	140.1	4.8	130	95
									2.7	105	200
									4.0	190	90
12	γ-Diethylaminobutyronitrile[j]	86	101–103	21	1.4351	69–70	140.2	140.1	2.3	105	150
13	γ-Piperidinobutyronitrile[j]	87	127–129	25	1.4653	117	152.2	151.9	2.7	100	107
14	γ-Morpholinobutyronitrile	70	148–150	25	1.4665	152–153	154.2	154.6	1.8	125	80
15	β-Diethanolaminopropionitrile[k]					108–109			0.5	105	133
16	Di-(β-cyanoethyl)-ethanolamine[k]					137–138					
17	Bis-(β-cyanoethyl) ether[l]								0.9	100	240
18	β-(γ′-Diethylaminopropylamino)-propionitrile	79.4[m] 76.4[n]	163–165	25	1.4573	123	91.5	91.5	0.4	120	100
19	α-Diethylamino-γ-[di-(β′-cyanoethyl)-amino]-propane	8.8	233–235	25	1.4709	166–167	118.1	118.1			
20	β-[Di-(γ′-diethylaminopropyl)-amino]-propionitrile	70	153	3	1.4640	157–158	[f]		1.9	100	250
21	β-(β′-Morpholinoethylamino)-propionitrile	81.5	183	20	1.4817	176.5	[f]		1.5	118	250
22	β-(γ′-Morpholinopropylamino)-propionitrile	76	178–180	9	1.4819	148–149	98.6	98.1	1.5	105	215
23	β-(β′-Diethylaminoethoxy)-propionitrile	79.5	145	25	1.4430	75	170.2	169.0	1.5	105	74
24	β-(γ′-Diethylaminopropoxy)-propionitrile	75.4	148–150	25	1.4440	Oil	184.2	184.1	0.5	105	135
25	β-(δ′-Diethylamino-α-methylbutoxy)-propionitrile	66	125–130	3	1.4456	Oil	211.3	209.3	0.9	103	80
26	γ-(Methylphenylamino)-propionitrile	25	175–177	29	[o]	118	[f]				
27	N-(β-Cyanoethyl)-carbazole[p]	85.4	Solid, m. p. 155.5°			[q]	[f]		0.1	103	68
28	N-(β-Cyanoethyl)-tetrahydroquinoline	75.5	192	10	1.5780	172	[f]		0.9	118	70
									0.3	120	90

[a] Approximately 10 g. of Raney nickel catalyst used per mole of nitrile reduced. [b] See ref. 5a. [c] This yield represents only one of two products isolated in the reaction. [d] Mentioned in a paper presented by Dr. M. T. Leffler at the Medicinal Section of the American Chemical Society in Detroit, April 14, 1943. [e] See ref. 6. [f] This compound was only slightly water soluble and a satisfactory end-point could not be obtained by titration. [g] See Burckhalter, Jones, Holcomb and Sweet, THIS JOURNAL, 65, 2012 (1943). [h] Calcd. for $C_{13}H_{26}N_2$: N, 14.0. Found: N, 13.7. [i] Calcd. for $C_{15}H_{34}N_2$: N, 11.7. Found: N, 11.6. [j] See ref. 12. [k] This compound decomposes on distillation at 1 mm. press. into the starting amine and polymerized acrylonitrile. [l] See ref. 10. [m] Synthesized from acrylonitrile and γ-diethylaminopropylamine. [n] Synthesized from β-bromopropionitrile and γ-diethylaminopropylamine. [o] See the experimental for the conditions used in this reaction. [p] See ref. 5b. [q] Does not form a picrate derivative.

aminopropionitrile. Equivalent weight calculated: 98.15, found 98.15. When a 70% ethylamine solution, 130 g. (2 moles), was added to an excess of acrylonitrile, 250 g. (4.7 moles), and the warm mixture heated on the steam-bath for two hours and worked up as indicated above, a 60% yield (180.5 g.) of di-(β-cyanoethyl)-ethylamine, b. p. 202–205° (30 mm.), $n^{20}D$ 1.4585–1.4591 was obtained.

The Reaction of Diethanolamine and Acrylonitrile.—Freshly distilled diethanolamine (52.6 g., 0.5 mole) was mixed with acrylonitrile (160 g., 3 moles) and the heterogeneous mixture shaken until homogeneous. After this reaction mixture had stood at room temperature for eight hours, the excess acrylonitrile was removed under vacuum. The residue (77.5 g.) corresponded to an increase in weight of 0.47 mole of acrylonitrile. A sample of the reaction product formed a picrate in alcohol which on recrystallization melted at 108–109°. The picrate of diethanolamine is completely soluble in alcohol but when crystallized from ether–alcohol mixture, melts at 108.8–109.0°. A mixture of these two picrates melted, however, at 94–97°. The addition product from the diethanolamine and acrylonitrile was reduced in 100 ml. of ethanol using Raney nickel catalyst and hydrogen at an average pressure of 133 atmospheres and a temperature of 105–110°. Separation by distillation was somewhat difficult because of the viscous nature of the product. Constant-index constant-boiling material 31.4 g., was obtained at 158° (2 mm.) and $n^{20}D$ 1.4975 which had an equivalent weight of 84.1 as compared

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TABLE II

REDUCTION PRODUCTS OF BASICALLY SUBSTITUTED NITRILES

No.	Reduction conditions: Time, hr.	Solvent	Products	Yield, %	Properties: B. p. °C.	B. p. Mm.	$n^{20}D$	Picrate M. p., °C.	Neut. eq. Calcd.	Neut. eq. Found
1	4.0	B	Trimethylenediamine[b]	23[c]	138	735	1.4600	178	35.0	36.1
3	0.5	A	γ-Diethylaminopropylamine[d]	54[a]	168	735	1.4355	194	65.0	65.3
			Di-(γ-diethylaminopropyl)-amine	15[a]	107	3	1.4541	153–154	81.3	81.0
	6.0	D	γ-Diethylaminopropylamine	42[a]						
			Di-(γ-diethylaminopropyl)-amine	29[a]						
	0.8	C	γ-Diethylaminopropylamine	72[a]						
			Di-(γ-diethylaminopropyl)-amine	5[a]						
4	0.2	E	γ-Ethylaminopropylamine	74	156	735	1.4441	193	51.1	51.6
5	0.5	D	Di-(γ-aminopropyl)-ethylamine	16	135	20	1.4709	197–199	53.1	53.4
6	3.0	A	γ-Di-*n*-propylaminopropylamine[g]	49	94	20	1.4435	181	79.1	80.0
7	3.0	A	γ-Di-*n*-butylaminopropylamine[g]	32	121	20	1.4462	188	93.2	93.7
10	2.5	C	γ-Piperidinopropylamine[h]	68.5	205	730	1.4750	209–210	71.1	71.2
	0.5	A	γ-Piperidinopropylamine	56.4[i]						
			Di-(γ-piperidinopropyl)-amine	10[i,a]	153	2	1.4916	193	89.2	89.7
11	0.5	A	γ-Morpholinopropylamine[e]	60	219	733	1.4762	166	72.1	72.1
	1.5	H	γ-Morpholinopropylamine	70.6						
			Di-(γ-morpholinopropyl)-amine	10[a]	185	5	1.4918	213–215	90.8	90.8
	1.1	A	γ-Morpholinopropylamine	43.5						
			Morpholine	35						
12	4.5	A	δ-Diethylaminobutylamine[j]	51	85–88	18	1.4462	155–156	72.2	72.2
13	9.0	A	δ-Piperidinobutylamine[j]	53.8	118–120	25	1.4756	160.5	78.1	77.9
			Di-(δ-piperidinobutyl)-amine	32[a]	220–225	25	1.4898	202–203	98.5	98.1
14	0.7	A	δ-Morpholinobutylamine	62[a]	122	20	1.4760	148	79.1	79.3
			Di-(δ-morpholinobutyl)-amine	23.8	200–202	3	1.4900	136	99.8	100.4
15	1.5	F	γ-Diethanolaminopropylamine	40[i]	158	2	1.4975	157–158	81.1	81.2
17	1.0	F	Bis-(γ-aminopropyl)-ether	29	113	32	1.4618	Oil	67.1	66.1
18	0.3	F	γ-(γ′-Diethylaminopropylamino)-propylamine	51	142–144	25	1.4630	197–198	62.4	62.3
			Di-[γ-(γ′-diethylaminopropylamino)-propyl]-amine	31[a]	253–260	25	1.4710	197	71.8	71.4
20	0.5	E	γ-[Di-(γ′-diethylaminopropyl)-amino]-propylamine	52	155–165	3	1.4662	162.5	75.1	75.2
21	1.0	H	γ-(β′-Morpholinoethylamino)-propylamine	57.5	120–123	2	1.4870	208	62.4	62.6
22	2.0	D	γ-(γ′-Morpholinopropylamino)-propylamine	45.2	137–140	1.5	1.4878	205	67.1	67.0
23	1.0	A	γ-(β′-Diethylaminoethoxy)-propylamine	56.7	118–122	25	1.4498	Oil	87.1	87.2
			Di-[γ-(β′-diethylaminoethoxy)-propyl]-amine	23.8[a]	175	3	1.4582	Oil	110.5	110.5
24	0.8	A	γ-(γ′-Diethylaminopropoxy)-propylamine	57.4	130–132	25	1.4500	Oil	94.1	93.6
			Di-[γ-(γ′-diethylaminopropoxy)-propyl]-amine	28.2[a]	182	3	1.4581	Oil	119.8	118.6
25	0.4	A	γ-(δ′-Diethylamino-α-methylbutoxy)-propylamine	50.5	80–83	2	1.4492	88–89	108.1	107.8
			Di-[γ-(δ′-diethylamino-α-methylbutoxy)-propyl]-amine	23[a]	210–215	3	1.4580	Oil	138.4	137.9
26	2.0	E	γ-(Methylphenylamino)-propylamine	63	171–172	40		189	[k]	
27	2.0	G	N-(γ-Aminopropyl)-carbazole	70.5	228	3	Solid	206–207	[l]	
28	0.7	H	N-(γ-Aminopropylamino)-tetrahydroquinoline	82	132–135	3	1.5828		[f]	

A, No solvent. B, Liquid ammonia, 69 moles, used as solvent. C, The nitrile was saturated with ammonia at room temperature and approx. 15 atm. press. prior to hydrogenation. D, One mole equivalent of γ-diethylaminopropylamine used as solvent in the reduction. E, Approximately 150 ml. of sat. alc. ammonia solution used as solvent. The reduction was carried out in approx. 100 ml. of abs. alc. G, Reduced in 600 ml. of dioxane. H, Reduced in a solution of 40 ml. of liquid ammonia and 150 ml. of abs. alc. [a] This yield represents only one of two products isolated in the reduction. [b] See Fischer and Kock, *Ber.*, **17**, 1799 (1881). [c] This yield was obtained upon the reaction of a large excess of liquid ammonia with acrylonitrile and the reduction of the reaction mixture in liquid ammonia solvent. [d] See ref. 7. [e] See ref. 6. [f] This compound was only slightly soluble in water and a satisfactory end-point could not be obtained by titration. [g] See Burkhalter, Jones, Holcomb and Sweet, THIS JOURNAL, **65**, 2012 (1943). [h] See ref. 24. [i] Combined yield on the addition and reduction. [j] See ref. 12. [k] Calcd. for the hydrobromide salt, $C_{10}H_{17}N_2Br$, m. p. 120°: Br, 32.7. Found: Br, 32.8. [l] Calcd. for the hydrochloride salt, $C_{15}H_{17}N_2Cl$, m. p. 273°: Cl, 13.6. Found: Cl, 13.6.

to the theoretical value of 81.1. It forms a picrate in alcohol which melts at 156.5–157.5° after recrystallization from acetone–ethyl acetate. When an attempt was made to distill the acrylonitrile diethanolamine addition product, a 67% recovery of material which was identified by its boiling point, picrate derivative, and equivalent weight as diethanolamine was obtained. The major portion of the remaining material was non-distillable residue.

9-(γ-Aminopropyl)-carbazole.—An intimate mixture of 167 g. of carbazole[22] and 250 ml. of acrylonitrile was cooled in an ice-bath and then made to react by the addition of 2 cc. of 40% solution of benzyltrimethylammonium hydroxide to the well stirred mixture. Upon the addition of the catalyst a vigorous reaction ensued; the mixture warmed up and the pasty mass partially solidified. The mixture was heated on the steam-bath for one hour and upon cooling a mass of crystals separated from the solution. These were removed by filtration and added to a second crop of crystals obtained by concentrating the mother liquors. The yield was 188 g. (85.4%); m. p. 155.5°. Recrystallization from acetone did not raise the melting point. 9-(β-Cyanoethyl)-carbazole, 150 g., was reduced catalyti-

(22) Carbazole "95%" was furnished through the courtesy of Reilly Tar and Chemical Company.

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cally by dissolving in 600 ml. of warm dioxane, adding 20 g. of Raney nickel and shaking at 118° in the presence of 67 atmospheres pressure of hydrogen for one and one-half hours. The dioxane was removed from the reduction mixture by distillation at atmospheric pressure and the residue distilled to give 107 g. of 9-(γ-aminopropylamino)-carbazole, b. p. 228–30° (3 mm.). The first fraction of this material melted at 47° and the last at 48°. The product forms a picrate, m. p. 206–207° after two crystallizations from alcohol, and a hydrochloride, m. p. 273° after recrystallization from 95% ethanol. *Anal.* Calcd. for $C_{15}H_{17}N_2Cl$: Cl, 13.59. Found: Cl, 13.62.

The Reaction of Methylaniline and Acrylonitrile.—When a mixture of 27 g. of acrylonitrile and 53 g. of methylaniline was sealed in a tube and heated at 180° for four hours and the reaction mixture distilled, all of the methylaniline was recovered unchanged. But when the identical reaction was performed in the presence of 1 g. of hydrated copper sulfate, only 18 g. of the methylaniline was recovered and 20 g. of β-(methylphenyl)-propionitrile, b. p. 175–7° (20 mm.), was obtained. This product is too water insoluble to titrate to a satisfactory end-point. It forms a well-defined picrate melting at 118°. When a mixture of 50 g. of methylaniline, 1 ml. of a 40% solution of benzyltrimethylammonium hydroxide and 100 ml. of dioxane was heated to 90–100° and 25 g. of acrylonitrile added dropwise over a period of one and one-half hours and the solution refluxed for an additional eight hours, no reaction took place and 47 g. of the methylaniline and 22 g. of the acrylonitrile were recovered unchanged.

The Reaction of Tetrahydroquinoline with Acrylonitrile.—The heating of a mixture of tetrahydroquinoline and acrylonitrile in the presence of a small amount of copper–bronze, copper sulfate, and sulfuric acid at 160° for four hours gave no appreciable reaction; 81% of the tetrahydroquinoline and 60% of the acrylonitrile were recovered. The remaining material was either very high boiling or a non-distillable residue. A basic catalyst was also found to be inadequate for bringing about the reaction. A mixture of 133 g. of tetrahydroquinoline, 100 ml. of acrylonitrile and 2 ml. of a 40% solution of benzyltrimethylammonium hydroxide was refluxed for ten hours, during which time the temperature of the boiling mixture rose from 88 to 120°. On cooling a polymer separated. The methanol extracts of this reaction mixture gave an 82% recovery of tetrahydroquinoline upon distillation. At the suggestion of Dr. J. B. Dickey, the reaction was carried out in acetic acid. A solution of 133 g. of tetrahydroquinoline and 100 g. of acetic acid was heated to 125° and 100 g. of acrylonitrile dropped in over a period of three hours. After the addition of the first mole, the temperature dropped to 108°. The mixture was heated at reflux for six hours. Neutralization of the reaction mixture with a saturated solution of potassium carbonate in the cold, extraction with 3, 100-ml. portions of chloroform, and distillation of the dried extracts gave 140.4 g. (75.5% yield) of N-β-cyanoethyltetrahydroquinoline, b. p. 192° (10 mm.), $n^{20}D$ 1.5780.[23]

γ-Aminobutyronitriles.—γ-Diethylaminobutyronitrile and γ-morpholinobutyronitrile have been prepared by Utermohlen and Hamilton[12] but in only fair yields. The following is an example of the general procedure used in the preparation of these compounds. In a 5-liter flask equipped with stirrer, condenser, and dropping funnel was placed a solution of 600 g. (7 moles) of piperidine in a mixture of 500 ml. of dry benzene and 100 ml. of chloroform. To the refluxing solution was added a total of 310 g. (3 moles) of γ-chlorobutyronitrile[24] over a one-half hour period. The reaction mixture, after refluxing five hours was then allowed to stand overnight and the crystals of piperidine hydrochloride removed by filtration. These were washed with ether and the ether washings and the benzene–chloroform filtrate containing most of the γ-piperidinobutyronitrile were combined and distilled from a short Vigreux column until the temperature reached 108°. The residue was cooled and a second crop of piperidine hydrochloride collected and washed with ether. The total amount of piperidine hydrochloride was 350 g. or 96% of the theoretical amount. The filtrate and ether washings were combined, the ether removed by distillation and the residue vacuum distilled to obtain 393 g. (86.2% yield) of product, b. p. 129–131° (25 mm.), $n^{20}D$ 1.4653. In the preparation of γ-diethylaminobutyronitrile, γ-bromobutyronitrile was substituted for the γ-chlorobutyronitrile; yield 86%.

Reduction of the Nitriles.—The reduction of basically substituted nitriles has been carried out using sodium and alcohol–toluene by Strukov[13] and Utermohlen and Hamilton,[12] and catalytically by Münch and Schlichting[17] using nickel on Kieselguhr and by Schwoegler and Adkins[14] using Raney nickel. After trying platinum oxide at low pressures and platinum oxide in the presence of acetic anhydride and discarding these methods, the method of Adkins was followed. The general procedure employed is illustrated by the preparation of δ-piperidinobutylamine which follows.

δ-Piperidinobutylamine.—In a 1300-ml. capacity Adkins hydrogenation bomb was placed 390 g. of γ-piperidinobutyronitrile and 10 g. of Raney nickel catalyst under 109 atmospheres pressure of hydrogen. The bomb was heated to 100° and shaken for one and one-half hours after which time the absorption of hydrogen had ceased and was approximately 90% of the theoretical. A large amount of ammonia was evolved when the bomb was opened. The reduction mixture was transferred to a modified Claisen flask and distilled to give 215 g. (53.8% yield) of δ-piperidinobutylamine; b. p. 120–122° (25 mm.), $n^{20}D$ 1.4756 and 118.4 g. (31.2% yield) of di-(δ-piperidinobutyl)-amine; b. p. 195–200° (5 mm.), $n^{20}D$ 1.4898. The total combined yield was 85%.

γ-Piperidinopropylamine and Di-(γ-piperidinopropyl)-amine.—β-Piperidinopropionitrile was prepared by mixing 10 moles each of acrylonitrile and piperidine with cooling and allowing the mixture to stand overnight. This was used in the two subsequent experiments without purification. γ-Piperidinopropionitrile, 1180 g. (8.55 moles), was reduced at 120° and 109 atmospheres pressure in the presence of 60 g. of Raney nickel catalyst. The theoretical amount of hydrogen had been absorbed in thirty-five minutes; the product was fractionated through a 12-plate column to give 543 g. (45% over-all yield) of constant-boiling (203–204°), constant-index ($n^{20}D$ 1.4750) γ-piperidinopropylamine[25] and 135.5 g. (19% over-all yield) of di-(γ-piperidinopropyl)-amine; b. p. 205–207° (17 mm.), $n^{20}D$ 1.4911–1.4917, picrate m. p. 190–192°. A 200-g. portion of the same crude β-piperidinopropionitrile as used above was reduced in the presence of 20 g. of Raney nickel catalyst after first saturating the nitrile with ammonia (at 8 atmospheres pressure). Hydrogen absorption had ceased after three hours at 1500 lb. per sq. in. pressure and 100° and was approximately 90% of the theoretical. The product was fractionated through a 12-plate column to give 137 g. (66.8% over-all yield) of γ-piperidinopropylamine.

γ-Morpholinopropylamine.—A mixture of 150 ml. of absolute ethanol, 371 g. of β-morpholinopropionitrile, 50 cc. of liquid ammonia and 25 g. of Raney nickel was reduced by shaking in the presence of 200 to 280 atmospheres pressure of hydrogen at a temperature of 105°. The theoretical amount of hydrogen was absorbed in one and one-half hours. Distillation of the reduction mixture gave 270 g. (70.6% yield) of γ-morpholinopropylamine; b. p.

(23) Dr. J. B. Dickey, private communication, has described a similar experiment using sulfuric acid as solvent and heating on the steam-bath for 65 hours which resulted in a 73% yield of N-β-cyanoethyl-7-methyltetrahydroquinoline.

(24) This material was the crude γ-chlorobutyronitrile made in 70.4% yield according to a slight modification of the directions of Charles F. H. Allen, "Organic Syntheses," Collected Vol. I, second edition, 1941, p. 156. This product as obtained here is approximately 15% γ-bromobutyronitrile and 85% γ-chlorobutyronitrile. The yield is raised from the reported 40–47% to 68–70% by extracting the reaction mixture with four portions of chloroform instead of one as recommended. The crude material is quite satisfactory for this reaction but may readily be separated into its components by fractionation through a 12-plate laboratory column.

(25) Blicke, Burke and Leonard, THIS JOURNAL, 62, 3316 (1940).

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129–132° (40 mm.), $n^{20}D$ 1.4763–1.4769. A higher boiling product, b. p. 185° (5 mm.), $n^{20}D$ 1.4923–1.4924, proved to be di-(γ-morpholinopropyl)-amine; yield 36 g. (10%).

γ-Diethylaminopropylamine.—In a similar manner 4 moles of β-diethylaminopropionitrile which had been saturated with ammonia at 7 atmospheres pressure (by attaching an ammonia tank to one of the leads of the bomb and shaking it for one-half hour) was reduced to give a 72% yield of γ-diethylaminopropylamine; b. p. 167.5–167.7° (735 mm.), $n^{20}D$ 1.4419, d^{20} 0.8254, picrate m. p. 193.5–194.0°, phenylurea derivative m. p. 66–67°, and phenylthiourea derivative m. p. 116.5–117.0°. The mixed melting point of this last substance with the phenylthiourea derivative obtained from γ-diethylaminopropylamine made by the phthalimide synthesis according to Shriner and Hickey[7] was 116.0–116.5°. Molecular refraction calculated, 41.89; observed, 41.71. The higher boiling fraction, 150–155° (15 mm.), 25 g. (5% yield), is di-(γ-diethylaminopropyl)-amine, $n^{20}D$ 1.4541; equivalent weight calculated, 81.3; found, 81.0; picrate m. p. 153.4°.

N¹-(γ-Morpholinopropyl)-sulfanilamide.—To a solution of 28.2 g. (0.2 mole) of γ-morpholinopropylamine in 150 cc. of acetone which was contained in a separatory funnel over a solution of 33 g. of potassium carbonate dissolved in 30 cc. of water was added a total of 50 g. (0.21 mole) of *p*-acetylaminobenzenesulfonyl chloride with intermittent shaking over a period of one and one-half hours. Upon completion of the addition, a white crystalline solid separated which was filtered and washed three times with 50-cc. portions of water to remove potassium carbonate and potassium chloride. The filtrate was concentrated to 100 ml. and on cooling a second crop was collected. These crystals were dried and recrystallized from acetone–water mixture to give 62.5 g. of product which melted sharply at 97°; yield 91.5%. The acetyl derivative was hydrolyzed by heating on the steam-bath with 20% hydrochloric acid for three and one-half hours. The cold hydrolysis mixture was carefully neutralized to the equivalence point with sodium hydroxide and cooled in the refrigerator overnight. The crystallized cake was recrystallized from an acetone–water mixture to give a total of 39.8 g. of N¹-(γ-morpholinopropyl)-sulfanilamide, m. p. 47–50°. On recrystallizing from acetone–ether an anhydrous crystalline product, 33.4 g., was obtained which melted at 94.5–95°; yield 70%.

TABLE III

SULFANILAMIDE DERIVATIVES

-N¹-Sulfanilamide	M. p., °C.	Yield, %	Acetyl derivative, m. p., °C.
γ-Diethylaminopropyl-	109–110	20	[a]
γ-Dipropylaminopropyl-	98–98.5	57	[a]
γ-Dibutylaminopropyl- (as hydrochloride)	110–115	53.5	[a]
γ-Piperidinopropyl-	105.5–106	63.5	109–111
γ-Morpholinopropyl-	94.5–95	79	97–98
Di-(γ-diethylaminopropyl)- (as hydrochloride)	195–197	66.5	83–85
Di-(γ-piperidinopropyl)-	74–76	71	[a]

[a] The acetyl derivatives were obtained only as thick viscous sirups which would not crystallize and were so hydrolyzed without purification.

Summary

The reaction of acrylonitrile with ammonia, primary amines, secondary amines, and amino alcohols and the reduction of the resultant beta-substituted propionitriles to the very useful γ-aminopropylamines has been studied. Twenty of these compounds are described.

γ-Aminobutyronitriles have been prepared from γ-chlorobutyronitrile and reduced to the corresponding δ-aminobutylamines.

The reduction of these basically substituted nitriles not only gives the primary amines but also basically substituted secondary amines in yields of 5 to 30%. Eleven new compounds of this type were isolated.

The procedures described offer a convenient and general method for the synthesis of γ- and δ-basically substituted alkylamines in good yields.

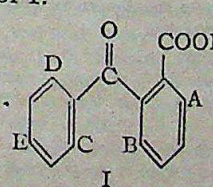
STATE COLLEGE, PA. RECEIVED OCTOBER 18, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

Normal and Pseudo Esters of 2-Benzoylbenzoic Acid Types. II

BY MELVIN S. NEWMAN AND BRADLEY T. LORD[1]

A study of the acid catalyzed esterification of substituted 2-benzoylbenzoic acids was undertaken in order to find out more about the structural features which determine whether normal or pseudo esters will form. In a previous publication[2] we outlined a program for the preparation of all of the substituted 2-benzoylbenzoic acids having one or more methyl groups at positions A, B, C, and D of I.



I

We have modified our program to include methyl groups at E because the compounds containing groups at C and/or D are easier to make if they also have a group at E. The presence of a group at E would not be expected to affect any results greatly.

Furthermore, by having groups at E, the preparation of the required compounds becomes more instructive because it is possible to compare the behavior of substituted phthalic anhydrides in the Friedel–Crafts and Grignard condensations. For example, it is possible to compare the behavior of 3-methylphthalic anhydride with benzene in the Friedel–Crafts reaction and with phenylmagnesium bromide since a mixture of the same keto-acids is obtained in each case.[3] It is not possible to compare these reactions using toluene and *o*-tolylmagnesium bromide because toluene

(1) The material in this paper was taken from the Thesis of B. T. L., presented to the Ohio State University in partial fulfillment of the requirements for the Ph.D. degree, August, 1943.

(2) Newman and McCleary, THIS JOURNAL, 63, 1537 (1941).

(3) Newman and McCleary, *ibid.*, 63, 1542 (1941).

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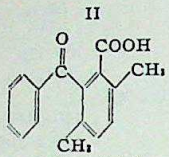
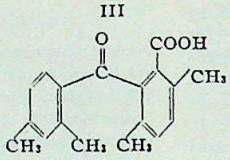
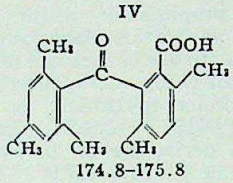
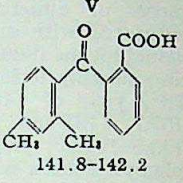
TABLE I

PROPERTIES AND YIELDS OF METHYL ESTERS

Compound	II	III	IV	V
Formula				
M. p., °C. (cor.)	182.6–183.2	165.2–165.8	174.8–175.8	141.8–142.2
A (Fischer) % yield	85	34	78	90
A (Fischer) m. p., °C.	112.0–113.8	61.0–63.0	110.0–111.0	64.0–65.5
B (Normal) % yield	87	83	92	95
B (Normal) m. p., °C.	50.4–51.6	62.6–63.6	110.8–111.8	64.6–65.6
C (Pseudo) % yield	79	75	60	71
C (Pseudo) m. p., °C.	113.6–114.4	86.8–87.2	110.0–111.0	62.2–63.2

In all cases the per cent. yield means the yield of crystalline product with the indicated melting point. The total yield of ester in each case was well over 90%. Compound IV: all esters identical. Compound V: ester C different from ester A and B, the mixed melting point being 41–52°.

orients para. With *m*-xylene and 2,4-dimethylphenylmagnesium bromide, however, the same products are formed and comparison is possible. The same is true with mesitylene and 2,4-6-trimethylphenylmagnesium bromide.

In this paper we report on the esterification of 3,6-dimethyl-2-benzoylbenzoic acid, II, 3,6-dimethyl-2-(2,4-dimethylbenzoyl)-benzoic acid, III, 3,6 - dimethyl - 2 - (2,4,6 - trimethylbenzoyl) - benzoic acid, IV, and 2-(2,4-dimethylbenzoyl)-benzoic acid, V. Of these acids, II, III, and V could be converted into two different methyl esters. As in the previous cases[2] the esters formed with diazomethane were assumed to be normal esters whereas those formed by treatment of the acid chlorides with methanol and pyridine were assigned the cyclic structure. We have confirmed this assignement of structure by ultraviolet absorption spectra studies.[4] Acid IV gave only the normal ester under all conditions of esterification tried, as was the case previously with 2 - (2,4,6 - trimethylbenzoyl) - benzoic acid.[2] The behavior of the acids II, III, IV, and V on Fischer–Speier esterification and the properties of the various esters are indicated in Table I.

The preparation of acids II, III, and IV is described in the following publication.[5]

Experimental

2-(2,4-Dimethylbenzoyl)-benzoic Acid, V.—This acid was prepared by the condensation of phthalic anhydride with *m*-xylene[6] in sulfur-free benzene. The yield of crude acid, m. p. 139–141°, was 95%. On recrystallization from benzene, the pure acid V, m. p. 141.8–142.2° cor., was obtained.

Preparation of Methyl Esters.—The esters in columns A, B, and C of Table I were made by (A) refluxing the acid in absolute methanol containing dry hydrogen chloride, (B) treatment of the acid with ethereal diazomethane, and (C) treatment of the acid chloride with methanol and pyridine. The esters were isolated as described in detail in previous work.[2] The analyses of the new esters formed are given in Table II.

TABLE II

ANALYSIS OF METHYL ESTERS

Compound	Calcd. C	Calcd. H	Found C	Found H
Methyl 2-(2,4-dimethylbenzoyl)-benzoate	76.1	6.0	76.0	6.4[n]
	$C_{17}H_{16}O_3$		76.1	6.1[n]
			76.2	6.3[p]
			76.0	6.2[p]
Methyl 2-benzoyl-3,6-dimethylbenzoate	76.1	6.0	76.1	5.8[n]
			75.9	5.7[n]
	$C_{17}H_{16}O_3$		76.3	6.1[p]
			76.1	6.1[p]
Methyl 2-(2,4-dimethylbenzoyl)-3,6-dimethylbenzoate	77.0	6.8	77.1	6.7[n]
			77.0	6.5[n]
	$C_{19}H_{20}O_3$		77.2	6.8[p]
			77.0	6.8[p]
Methyl 2-(2,4,6-trimethylbenzoyl)-3,6-dimethylbenzoate	77.4	7.1	77.3	6.9[n]
	$C_{20}H_{22}O_3$		77.1	7.2[n]

n analyses marked [n] are for normal esters. *p* analyses marked [p] are for pseudo esters. Microanalyses by J. E. Varner and Jean Anderson.

(4) Brode, Newman and Lord, to be reported.

(5) Newman and Lord, THIS JOURNAL, 66, 733 (1944).

(6) The authors are indebted to Professor C. E. Boord for a gift of purified *m*-xylene from the American Petroleum Institute Project at the Ohio State University.

COLUMBUS, OHIO RECEIVED JANUARY 10, 1944

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

The Behavior of 3,6-Dimethylphthalic Anhydride in Friedel–Crafts and Grignard Condensations

BY MELVIN S. NEWMAN AND BRADLEY T. LORD[1]

While preparing certain compounds required in another investigation[2] we obtained some results which were not at all what we expected. Because of their bearing on the mechanisms of the Grignard and Friedel–Crafts reactions, we are reporting these results separately.

The Grignard Reaction.—Many believe that the first step in the reaction of Grignard reagents with esters or acid halides consists in addition to the carbonyl group.[3] An alternate mechanism supposes a metathetical reaction involving the carbon–oxygen single bond in esters and the carbon–halogen bond in acid halides.[4]

As an outgrowth of many studies of the reactions of Grignard reagents with substituted phthalic anhydride types, we have become interested in this same choice of mechanisms as applied to anhydrides. In previous work it was found that when Grignard reagents reacted with unsymmetrical phthalic anhydride types, substituents ortho to one of the carboxyl functions cut down reaction at this group.[5] A more careful study of the reaction of phenylmagnesium bromide on 3-methylphthalic anhydride[6] showed that the ratio of products of reaction at the carboxyl in the unhindered position (position 1) to products of reaction at the hindered carboxyl (position 2) was about 3. This ratio is lower than one would expect on the assumption that condensation takes place exclusively by addition to the carbonyl groups.

Because of the hindrance to both carbonyl groups in 3,6-dimethylphthalic anhydride it was expected that reaction with the Grignard reagent would take place with difficulty if at all. However, this anhydride reacted smoothly with phenylmagnesium bromide to give the expected 3,6-dimethyl-2-benzoylbenzoic acid in 81% yield. Successful condensations also took place with 2,4-dimethyl- and 2,4,6-trimethylphenylmagnesium bromides (see Table I). These condensations provide evidence that Grignard reagents may react with anhydrides by a metathetical mechanism involving the carbon–oxygen single bond. The successful competition of the metathetical reaction with the addition reaction is probably responsible for the above-mentioned low ratio in the case of 3-methylphthalic anhydride and similar anhydrides.

The Friedel–Crafts Reaction.—Little or nothing is known about the effect of steric hindrance on the ease of reaction of acylating agents in the Friedel–Crafts reaction. Several 3-substituted phthalic anhydrides have been condensed with aromatic derivatives but in most cases the separation and identification of the isomeric keto-acids were not carried out carefully enough for valid conclusions to be drawn.[7] Frequently a preference for condensation at the 2-position was noted.

In previous work with benzene and 3-methylphthalic anhydride, we determined that condensation at the 1- and 2-positions took place to almost the same extent.[6] Consequently we expected that 3,6-dimethylphthalic anhydride would condense readily with benzene. However, after refluxing for five hours, 78% of the anhydride was recovered with the production of only 12% of keto acid. Heating in *sym*-tetrachloroethane solution at 100° for eight hours was required for complete disappearance of anhydride yet only 57% of keto-acid was obtained. No obvious explanation of the contrasting behaviors of 3-methyl- and 3,6-dimethylphthalic anhydrides is apparent. However, with the more reactive *m*-xylene 3,6-dimethylphthalic anhydride condensed readily. The condensations of 3,6-dimethylphthalic anhydride with benzene, *m*-xylene, and mesitylene are summarized in Table I.

The keto-acids resulting from condensations with benzene and *m*-xylene were reasonably pure as first isolated. The acid fractions from reaction with mesitylene, however, had wide melting ranges. Although this suggested that rearrangement of the methyl groups might have taken place, the mesitylene recovered was pure. In order to establish the structure of 3,6-dimethyl-2-(2,4,6-trimethylbenzoyl)-benzoic acid, it was decarboxylated to 2,4,6,2′,5′-pentamethylbenzophenone. This new ketone, synthesized by condensing 2,5-dimethylbenzoyl chloride with mesitylene, proved identical with the decarboxylation product.

(1) Part of the material in this paper is contained in the Ph.D. thesis of B. T. L., The Ohio State University, August, 1943.

(2) Newman and Lord, THIS JOURNAL, **66**, 731 (1944).

(3) Part of the evidence supporting this view is well summarized in Gilman, "Organic Chemistry," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1943, p. 501 ff.

(4) Evidence for the metathetical mechanism is provided by the reaction of hindered acid chlorides with Grignard reagents; see Ruson, *et al.*, THIS JOURNAL, **59**, 1508 (1937); **60**, 2063, 2269 (1938).

(5) For examples see Newman, *et al.*, *ibid.*, **58**, 2376 (1936); **59**, 1003 (1937); **60**, 586, 1368 (1938); **61**, 244 (1939); and **63**, 2109 (1941).

(6) Newman and McCleary, *ibid.*, **63**, 1542 (1941).

(7) Lawrance, *ibid.*, **42**, 1874 (1920); Stephens, *ibid.*, **43**, 1950 (1921); Knesebeck and Ullmann, *Ber.*, **55**, 306 (1922); Simonsen and Rau, *J. Chem. Soc.*, **119**, 1339 (1921); Bistrzycki and de Schepper, *Ber.*, **31**, 2790 (1898); Graebe and Leonhardt, *Ann.*, 290, 217 (1896); Eder and Widmer, *Helv. Chim. Acta*, **6**, 419 (1923); Mitter, *et al.*, *J. Ind. Chem. Soc.*, **7**, 619 (1930); **8**, 685 (1931); Graves and Adams, THIS JOURNAL, **45**, 2439 (1923); Waldmann, *J. prakt. Chem.*, [2] **127**, 195 (1930); **131**, 71 (1931); Mayer and Stark, *Ber.*, **64**, 2003 (1931); and Hayashi, *et al.*, *Bull. Chem. Soc., Japan*, **11**, 184 (1936).

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TABLE I

REACTIONS OF 3,6-DIMETHYLPHTHALIC ANHYDRIDE

Reactants	Conditions	% rec. anhyd.	Acid yield, %	M. p. (uncor.), °C.
C_6H_5MgBr	Reflux 1 hr. in C_6H_6	..	81	180–182
m-$(CH_3)_2C_6H_3MgBr$	Reflux 1 hr. in C_6H_6	31	56	162–165
2,4,6-$(CH_3)_3C_6H_2MgBr$	Reflux 2 hr. in ether	33	27	174–175
2,4,6-$(CH_3)_3C_6H_2MgBr$	Reflux 1 hr. in C_6H_6	22	44	174–176
Benzene–$AlCl_3$	Reflux 5 hr. in C_6H_6	78	5	182–183
Benzene–$AlCl_3$	Stir 2 days, reflux 5 hr. in C_6H_6	63	28	179–182
Benzene–$AlCl_3$	Stir 2 days, reflux 11 hr. in C_6H_6	43	34	178–183
Benzene–$AlCl_3$	8 hr. at 100° in *sym*-$C_2H_2Cl_4$	..	57	180–183
m-Xylene–$AlCl_3$	Reflux 3.5 hours in C_6H_6	8	72	150–155
m-Xylene–$AlCl_3$	Reflux 12 hours in C_6H_6	..	80	146–156
m-Xylene–$AlCl_3$	Heated to 48° in *m*-xylene during 11 hr.	..	96	161–165
Mesitylene–$AlCl_3$	Heated to 60° during 15 hr. in mesitylene	34	34	125–150
	Heated to 68° during 11 hours in mesitylene	24	23	143–157

The 3,6-dimethylphthalic anhydride used was prepared by the dehydration in 90% sulfuric acid of the adduct of dimethylfuran and maleic anhydride.[8]

Experimental[9]

3,6-Dimethylphthalic Anhydride.—To a well-stirred suspension of 49 g. (0.5 mole) of freshly distilled maleic anhydride in 50 cc. of dry ether was added slowly 48 g. (0.5 mole) of 2,5-dimethylfuran.[10] After stirring for four and one-half hours at room temperature, during which the maleic anhydride dissolved and crystals of adduct began to separate, the mixture was cooled in an ice–salt-bath for one hour. The liquid was drawn off through a filter stick using cheesecloth and the air-dried pinkish crystals, m. p. 59–63°, weighed 82.7 g. (85%).[8] The neutral equivalent of this crude product was 96.6 (calcd. 97.1). Dehydration was best accomplished by slowly adding 81.6 g. (0.42 mole) of the above powdered adduct to 800 cc. of 90% sulfuric acid at −6 to 0°. The solution was agitated for one-half hour at 0° and the temperature then allowed to rise to 10°. After pouring on 2 kg. of ice the light brown precipitate was collected, washed with ice water, and dissolved in 600 cc. of water containing 30 g. of sodium hydroxide. Upon addition of 50 cc. of glacial acetic acid 5.3 g., m. p. 132–134°, of crude 2,5-dimethylbenzoic acid was obtained. From the filtrate 38.4 g. (52%) of crude 3,6-dimethylphthalic anhydride, m.p. 139–142°, was obtained by strongly acidifying with hydrochloric acid. On crystallization from benzene 21.8 g. (29%) of pure anhydride, m. p. 142–143°, and 12.0 g. (16%) of anhydride, m. p. 140–142°, were obtained. Some reagents found unsuitable for dehydration included dry hydrogen chloride and phosphorus pentoxide in benzene, sodium sulfate, acetyl chloride, and acetic anhydride. Although it is reported that[11] the addition of hydrochloric acid to a solution of the sodium salt of 3,6-dimethylphthalic acid precipitated the free acid, we were unable to confirm this fact. In our hands, such treatment precipitated white plates which melted without any evidence of dehydration at 142–143° and showed no depression when mixed with authentic anhydride, m. p. 142–143°. Samples of supposed acid, precipitated at 0° and dried over calcium chloride at room temperature or recrystallized from ether by cooling with dry-ice showed the correct neutralization equivalent (88) and carbon–hydrogen values[b] (C, 67.9, 67.8; H, 4.3, 4.5) for the anhydride.

Grignard Reactions.—One molar equivalent of the appropriate Grignard reagent in ether was added to a stirred benzene solution of the anhydride. The mixture was heated until the ether was removed and then refluxed for the indicated time (see Table I). An ether–benzene solution of the hydrolyzed reaction products was shaken with carbonate. The keto-acid was liberated with acetic acid and crystallized once from a suitable solvent. The unreacted anhydride was recovered after strong acidification with mineral acid. The original ether–benzene extract contained varying amounts of phthalide-like material not further examined.

Friedel–Crafts Reactions.—A slight excess of anhydrous aluminum chloride (Calco Standard) was added to a suspension of the anhydride in the reacting hydrocarbon, with or without added solvent. The reaction mixture was stirred for varying times before warming produced moderate or copious evolution of hydrogen chloride. Heating and stirring were then increased as dictated by gas evolution. When this slowed considerably the mixture was poured on ice and the products isolated as described under Grignard reactions.

2-Benzoyl-3,6-dimethylbenzoic Acid.—This acid was recrystallized from benzene and finally from alcohol for analysis to a constant melting point of 182.6–183.2° cor. It formed dense colorless plates.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.5; H, 5.6. Found[a]: C, 75.9, 75.6; H, 5.7, 5.7.

2-(2,4-Dimethylbenzoyl)-3,6-dimethylbenzoic Acid.—This acid, m. p. 165.2–165.8° cor., was crystallized from benzene for analysis.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4. Found[b]: C, 76.5, 76.4; H, 6.7, 6.5.

2-(2,4,6-Trimethylbenzoyl)-3,6-dimethylbenzoic Acid.—This acid separated from benzene as transparent prisms which became opaque on drying to constant weight, evidently losing benzene of crystallization. The pure crystals melted at 174.8–175.6° cor.

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.0; H, 6.8. Found[b]: C, 76.9, 76.9; H, 6.9, 6.9.

2,2′,4,5′,6-Pentamethylbenzophenone (by Decarboxylation).—A mixture of 0.78 g. of the above acid and 0.66 g. of its copper salt was heated at 192–195° for one hour. On vacuum distillation and crystallization from ether by cooling in dry-ice 0.28 g. of white needles, m. p. 74–78°, was obtained. Recrystallization from alcohol yielded the pure ketone, m. p. 77.0–78.0° cor.

By Friedel–Crafts Reaction.—To a cold solution of 8.6 g. of pure mesitylene and 6.5 g. of pure 2,5-dimethylbenzoyl chloride in 50 cc. of carbon bisulfide was added in portions 5.7 g. of aluminum chloride. Immediate gas evolution was followed by the appearance of a bright orange complex. After stirring at room temperature for twenty-five minutes

(8) Diels and Alder, *Ber.*, **62**, 554 (1929).

(9) All melting points, except those corrected, were taken with the same thermometer which was calibrated within one degree of a standard thermometer. All benzene used in condensations was sulfur-free. Analyses marked *a* by J. E. Varner and *b* by Jean Anderson.

(10) The authors thank Professor C. E. Boord for gifts of purified dimethylfuran and *m*-xylene by the American Petroleum Institute Project at the Ohio State University.

(11) Freund and Fleischer, *Ann.*, **411**, 14 (1916).

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and refluxing for one hour, the reaction mixture was poured on ice. Vacuum distillation yielded 9.0 g. (90%) of a pale green liquid, b. p. 147–148° at 3 mm., m. p. 76–78°. A sample recrystallized from alcohol for analysis melted at 77.0–78.0° cor. A mixed melting point with the decarboxylation product was not depressed.

Anal. Calcd. for $C_{18}H_{20}O$: C, 85.7; H, 8.0. Found[b]: C, 85.7, 85.6; H, 7.9, 8.0.

Summary

Evidence is provided that when Grignard reagents react with phthalic anhydride types, the mechanism involves reaction both by addition to the carbonyl group and metathetical reaction by cleavage of the carbon–oxygen single bond. A series of reactions of 3,6-dimethylphthalic anhydride with Grignard reagents and with aromatic hydrocarbons is described.

COLUMBUS, OHIO RECEIVED JANUARY 10, 1944

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, NATIONAL INSTITUTE OF HEALTH, U. S. PUBLIC HEALTH SERVICE]

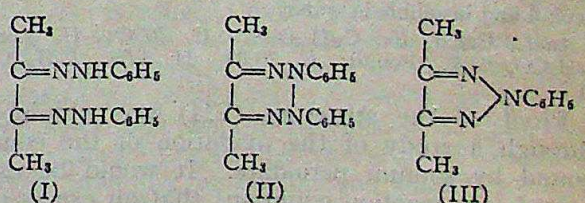
The Action of Copper Sulfate on Phenylosazones of the Sugars. Phenyl-D-glucosotriazole

BY RAYMOND M. HANN AND C. S. HUDSON

In a previous communication[1] it was shown that the phenylhydrazides of the aldonic acids of the sugar group are readily decomposed in hot aqueous copper sulfate solution with the production of nitrogen, benzene and the free sugar acid; the reaction appears to proceed quantitatively, as is evident from the fact that upon removal of the inorganic materials and concentration of the solution, a nearly theoretical yield of lactone of the acid is obtained. It seemed of interest to test the action of copper sulfate solutions on the phenylosazones of the sugars. They are known to reduce Fehling solution but no record has been found of a test with copper sulfate under acid conditions.

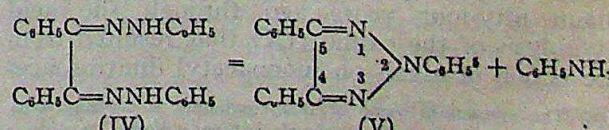
In the initial experiments a suspension of pulverized phenyl-D-glucosazone (5.0 g.) in 600 cc. of an aqueous solution containing two molecular equivalents (7.0 g.) of copper sulfate pentahydrate was boiled under reflux,[2] most of the osazone dissolved in one hour and as the reaction progressed the precipitation of a small amount of copper or cuprous oxide was noted and the color of the solution changed from blue to green. At the end of a second hour only traces of undissolved osazone remained; the mixture was filtered hot and from the filtrate, while still warm, glistening needle crystals separated. They were filtered from the cooled solution and a second crop was obtained by concentration of the mother liquor to 100 cc.; the total yield of product, which proved to be nearly pure though its color was tan from adsorbed dye, was 2–3 g. It was obtained as colorless pure asbestos-like crystals by recrystallizing once or twice from one hundred parts of boiling water and filtering through a bed of decolorizing carbon in a steam-heated Buchner funnel. The substance melts sharply at 195–196° without decomposition and the cooled melt crystallizes; the compound is very stable. It is not sufficiently soluble in water at ordinary temperatures to permit observation of its rotation, but in pyridine its specific rotation $[\alpha]^{20}D$ was −81.6° (*c*, 0.8). The crystals are anhydrous and their analysis showed 54.44% carbon, 5.71% hydrogen and 15.78% nitrogen (Dumas), values which lead to the formula $C_{12}H_{15}O_4N_3$.

It will be observed that the empirical formula of the substance differs from that of phenyl-D-glucosazone by the elements of aniline, as though the reaction might be $C_{18}H_{22}O_4N_4 = C_{12}H_{15}O_4N_3 + C_6H_5NH_2$. Aniline was indeed detected in the mother liquor by removing the copper as sulfide, making the solution alkaline, extracting it with ether and converting the oily residue from the evaporation of the ether extract to acetanilide (yield, 20%). The evidence led to the possibility that the substance might belong to the class of osotriazoles of v. Pechmann,[3] which are very stable substances. In the case of diacetyl diphenylhydrazone (I), he showed that it was converted by oxidation with potassium dichromate in dilute acetic acid to an osotetrazone (II), which with stronger acidity (HCl) gave a 20% yield of the osotriazole (III). The latter reaction is evidently complex; much tar was produced and aniline was detected.



(I) (II) (III)

A direct conversion of an osazone type of compound to the corresponding osotriazole was reported by Auwers and Victor Meyer,[4] who heated benzil diphenylhydrazone (IV) in alcohol solution at 200° and obtained 2,4,5-triphenylosotriazole (V) and aniline.



(IV) (V)

(1) Hann and Hudson, THIS JOURNAL, 56, 957 (1934).

(2) The osazone is difficult to wet and foaming during the first half hour was troublesome; in later experiments this was much reduced by the addition of a few cc. of *n*-butyl alcohol. It was also found that the reaction proceeds equally well but somewhat slower on the steam-bath; the best solvent that has been found so far is acidified 40% isopropyl alcohol at its boiling point, as is described further on.

(3) v. Pechmann, *Ber.*, **21**, 2751 (1888); *Ann.*, **262**, 265 (1891).

(4) Auwers and Victor Meyer, *Ber.*, **21**, 2806 (1888).

(5) The numbering is that of formula No. 77 of Patterson and Capell's "The Ring Index," Reinhold Publishing Corporation, New York, N. Y., 1940. The name osotriazole, introduced by v. Pechmann, implies the 2,1,3-triazole that is related to osazones.

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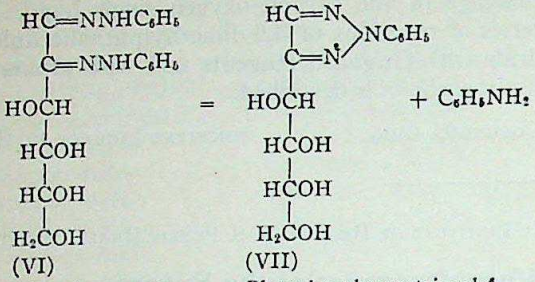
An analogous course for the phenyl-D-glucosazone reaction would be expressed by formulas (VI) and (VII).



(VI) Phenyl-D-glucosazone

(VII) Phenyl-D-glucosotriazole[6]

As previously mentioned, the analysis of the derivative agrees well with this postulated osotriazole structure; it was also found that the substance yields a crystalline tetraacetate and tetrabenzoate, as would be expected if it possesses this structure.

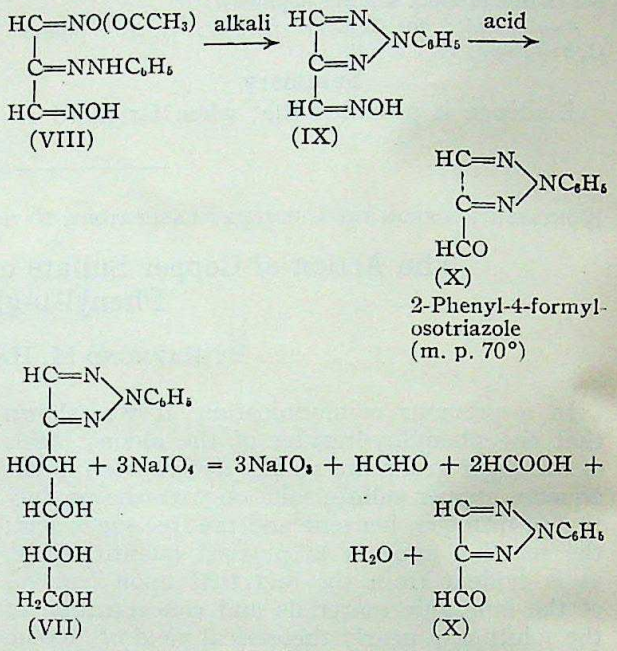
Phenyl-D-glucosotriazole Tetraacetate.—A solution of 1.0 g. of the osotriazole in a mixture of 15 cc. of pyridine and 15 cc. of acetic anhydride was kept at 25° for eighteen hours and then poured upon crushed ice; the product, which was obtained in nearly quantitative yield, was recrystallized from 5 parts of methyl alcohol. The pure substance melts at 81–82°, shows $[\alpha]^{20}D$ −25.6° in chloroform (*c*, 0.92), and its minute needle crystals are easily soluble in acetone and ethyl acetate and insoluble in water.

Anal. Calcd. for $C_{20}H_{23}O_8N_3$: C, 55.42; H, 5.35; CH_3CO, 39.7. Found: C, 55.53; H, 5.49; CH_3CO, 39.7.

Phenyl-D-glucosotriazole Tetrabenzoate.—Benzoyl chloride (4.0 cc.) was mixed with an ice-cold solution of 1.1 g. of the osotriazole in 15 cc. of pyridine and the mixture kept at room temperature for eighteen hours. On pouring it into water the gummy benzoate precipitated; this mass was repeatedly triturated with fresh water and after several days it crystallized in nearly quantitative yield, and was recrystallized from 15 parts of alcohol. The fine needles show m. p. 112–113° and $[\alpha]^{20}D$ +3.0° in chloroform (*c*, 0.92); they are soluble in acetone, ether and hot alcohol and insoluble in water.

Anal. Calcd. for $C_{40}H_{31}O_8N_3$: C, 70.47; H, 4.58; C_6H_5CO, 61.7. Found: C, 70.34; H, 4.63; C_6H_5CO, 61.7.

Proof of the structure (VII) was obtained through a study of the oxidation of the compound by sodium periodate. It would be expected (see reaction equation) that an excess of the oxidant would generate in quantitative manner one mole of formaldehyde, two moles of formic acid and one mole of the aldehyde (X), and that three moles of the oxidant would be reduced. Luckily, the substance having structure (X) is known; it was produced by v. Pechmann fifty-four years ago through the acid hydrolysis of the oxime (IX) that resulted from the action of alkali on monoacetyl dinitrosoacetone phenylhydrazone (VIII). The quantitative measurements confirmed these expectations, and v. Pechmann's aldehyde (X) was obtained from this oxidation in a high yield.



(VIII) (IX) (X)

2-Phenyl-4-formyl-osotriazole (m. p. 70°)

Sodium Periodate Oxidation of Phenyl-D-glucosotriazole.—A suspension of 0.5078 g. of phenyl-D-glucosotriazole in a mixture of 50 cc. of water and 15 cc. of 0.428 *M* aqueous sodium periodate solution (3.35 molecular equivalents) was agitated at 25° for twenty-four hours; the appearance of the suspended crystals changed from that of long fine needles to shorter and more thickened ones; the crystals were removed by filtration and washed well with cold water, the filtrate and washings being finally adjusted to a volume of 100 cc. and analyzed as described in the following paragraph. The crystals melted at 68–69° and this value was not changed by recrystallization, which was accomplished by dissolving them in sixteen parts of alcohol and adding thirty-two parts of water. The substance possesses a faint sweetish odor, as was noted by v. Pechmann, who records the m. p. as 70°. Warming the crystals in the closed palm of the hand accentuates the odor, which we would describe as being suggestive of that from geraniol. The crystals weighed 0.28 g., which corresponds to 0.84 mole per mole of phenyl-D-glucosotriazole. The method makes this rare and interesting aldehyde, 2-phenyl-4-formyl-osotriazole, easily available from common phenylglucosazone through the easily prepared phenylglucosotriazole.

(VII) (X)

Anal. Calcd. for $C_9H_7ON_3$: C, 62.41; H, 4.07. Found: C, 62.46; H, 4.07.

The filtrate from the crystals of the aldehyde was analyzed for other oxidation products as follows: one 20-cc. aliquot was titrated for excess periodate by the usual iodine–arsenite procedure and it was found that 3.03 molecular equivalents of oxidant had been reduced; a second 20-cc. aliquot was titrated with 0.1 *N* sodium hydroxide, using methyl red as indicator, and the observed 7.38 cc. of alkali indicated the production of 1.93 molecular equivalents of formic acid; a third 20-cc. aliquot was added to 100 cc. of 0.4% dimethone solution and the 0.1130 g. of formaldimethone which crystallized corresponded to the formation of 1.01 molecular equivalents of formaldehyde.

The transformation of phenyl-D-glucosazone to phenyl-D-glucosotriazole (m. p. 195–196°, yield 67%) by copper sulfate is apparently a general reaction with all the sugar phenylosazones.

(6) The systematic name of this compound is 2-phenyl-4-[D-*arabino*-tetrahydroxybutyl]-osotriazole, which indicates in only a veiled way the genetic relationship of the substance to phenyl-D-glucosazone. We give it an alternative common name **phenyl-D-glucosotriazole.** An additional reason for such a designation is the fact that the systematic names in the disaccharide group are so very complicated that common names (phenyllactosotriazole, etc.) seem necessary in those cases and advisable consequently in the monose series.

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Crystalline phenylosotriazoles, the sharp melting points and yields of which are indicated, have been prepared by this reaction from the phenylosazones of the following additional sugars; L-sorbose (158–159°, 50%), D-galactose (110–111°, 47%), D-altrose (134–135°, 62%), D-xylose (88–90°, 40%), cellobiose (164–165°, 62%), lactose (180–181°, 62%), and turanose (193–194°, 70%). These will be described at length in a later article. All of them are much more soluble in water than the glucose derivative. The exceptionally low solubility of phenyl-D-glucosotriazole, its ease of spontaneous crystallization, stability and sharply characteristic m. p., rotation and crystalline appearance, lead us to recommend this substance for use in confirming the identity of phenylglucosazone, especially in the case of small samples.

Confirmatory Test for Phenyl-D-glucosazone.—A suspension of 0.2 g. of powdered osazone in a solution composed of 18 cc. water, one cc. 0.5 *N* sulfuric acid, 0.6 g. of copper sulfate pentahydrate and 12 cc. of isopropyl alcohol, is refluxed for one hour, using a piece of porous plate to ensure even boiling. The osazone dissolves within fifteen minutes and the solution shows a deep red color. During the next half hour the red fades to orange and finally to yellowish green. The solution is concentrated on the steam-bath by an air current to about 5 cc.; crystallization of the osotriazole occurs during this operation and is increased by keeping the mixture three hours in the refrigerator. The tan colored precipitate is removed by filtration, washed with water, boiled with 30 cc. water and 0.1 g. decolorizing carbon, and the solution filtered hot. On keeping the colorless filtrate cold overnight the long needle crystals of pure osotriazole separate; wt. 20–40 mg., m. p. 195–196°; 18.3 mg. in 25 cc. pyridine solution rotated α_D −0.23° in a 4-dm. tube, the calculated value being −0.24°. Methyl alcohol may be substituted for isopropyl alcohol in these directions if the refluxing time is increased to two hours; yield, 56 mg., m. p. 195–196°, observed rotation for 50 mg. in 25 cc. of pyridine solution, 4-dm. tube, −0.64°, calculated −0.65°. Obviously, the test would be applicable likewise to a small sample of phenyl-L-glucosazone, and dextro-rotation would be observed for its osotriazole; any aid to the positive detection in nature of the L-forms of glucose, mannose or fructose seems worth mentioning because of the biological interest that is involved.[7]

Phenyllactosotriazole is hydrolyzed by acids at nearly as fast a rate as lactose; on cooling the hydrolysis solution, phenyl-D-glucosotriazole crystallizes rapidly and the filtrate from this substance yields crystalline D-galactose readily after removal of the mineral acid.

Curiosity naturally arises concerning the mode of action of copper sulfate in bringing about so easily this splitting of the phenylosazone molecule to phenylosotriazole and aniline. The gross equation of the reaction does not show any role of the copper salt. Some reduction of the latter is always noticed but this may be the result of side reactions, the occurrence of which is indicated by the fact that the yields of osotriazole are always much below quantitative. The great stability of the osotriazole ring may be the factor underlying the reaction; apparently the presence of the copper salt opens a path by which the reaction can proceed at good speed. Independent of speculations, it is demonstrable that the main reaction takes place in two successive stages, which are visually apparent if conditions are favorable for fairly rapid solution of an osazone. Phenylturanosazone (8.6 g.) was readily soluble in 170 cc. water at 90° to form an ordinary yellow osazone solution; a hot solution of 13 g. of copper sulfate pentahydrate in 90 cc. water was prepared separately; on mixing the two solutions an intense red color appeared instantly, indicating that the formation of the osazone–copper ion complex is instantaneous when the components are in solution; on the steam-bath the solution lightened in color to become orange and finally green, all within ten minutes, which gives an approximate measurement of the speed of the second stage of the reaction in the case of this osazone. The complex is red colored, the osotriazole is colorless and the green color is that of residual copper sulfate in the presence of aniline and products from the side reactions. The following experiment shows the formation of the complex at room temperature: when a mixture of 2 g. of phenyllactosazone and 1 g. of copper sulfate crystals was shaken with 200 cc. of 85% methyl alcohol the osazone and some copper sulfate dissolved in one hour to yield a clear brownish-red solution, which did not change in twenty-four hours. Decanting this solution and removing the copper from it as sulfide, left a light yellow filtrate from which crystalline phenyllactosazone was recovered in good yield by concentration *in vacuo* to 50 cc. When phenylglucosazone is refluxed with aqueous copper sulfate solution no red color is noticed; evidently the rate of solution is so slow that the complex is never present in sufficient quantity to affect the blue or green color of the copper salt. However, in the confirmatory test for phenylglucosazone the rate of solution is rapid and the gradual change of color from red to orange and finally green, is observed. The rate of the second stage of the reaction is doubtless a characteristic of each osazone as it appears to be more rapid for phenylturanosazone than for phenylglucosazone; mild mineral acidity appears to increase the rate of this second stage. The various experiments lead us to believe that the role of the copper sulfate in the osazone–osotriazole reaction is that of a promoter which forms an unstable complex with the osazone and thereby opens a path for a speedy formation of the highly stable osotriazole ring by the splitting out of aniline from the osazone.

Thanks are expressed to Dr. W. T. Haskins for assistance in the experimental work and to Dr. A. T. Ness for carrying out the microchemical analyses.

(7) Although L-glucose has been reported to occur in *Grindelia robusta* [Power and Tutin, *Pub. Wellcome Chem. Research Lab.*, **57**, 1 (1905)], in capsularin, a glycoside from jute (*Corchorus capsularis*) [Saha and Choudhury, *J. Chem. Soc.*, **121**, 1044 (1922)], and collagen [Beek, THIS JOURNAL, **63**, 1483 (1941); *J. Research Natl. Bur. Standards*, **27**, 507 (1941)], the evidence is not conclusive in any case.

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Summary

The preparation of a new type of sugar derivative is described. The heating of a suspension of phenyl-D-glucosazone with an aqueous solution of copper sulfate causes the production of aniline and a very stable substance which proves to be a substituted osotriazole, now named phenyl-D-glucosotriazole. Proof of the structure of the substance has been obtained through the oxidation by sodium periodate to yield v. Pechmann's 2-phenyl-4-formyl-osotriazole. The role played by the copper sulfate apparently concerns an osazone–copper ion complex, of deep red color, the formation of which is readily observable in the case of easily soluble osazones. Phenyllactosotriazole is hydrolyzed by mineral acids at nearly as fast a rate as lactose and yields phenyl-D-glucosotriazole and D-galactose. The phenylosotriazoles from several other sugars are mentioned, in advance of later full publication; the reaction is a general one for sugar phenylosazones and the yields are good. Owing to the very low solubility of phenyl-D-glucosotriazole and its high tendency to crystallize, its production from phenyl-D-glucosazone is a useful confirmatory test for the latter substance, especially for small quantities of it.

BETHESDA, MARYLAND RECEIVED FEBRUARY 16, 1944

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Hydrolysis of Trimethylethylene Bromide. Mechanism of Ketone Formation

BY C. M. SUTER[1a] AND HARRY D. ZOOK[1b]

It has long been known that the hydrolysis of certain olefin bromides results in the formation of carbonyl compounds. Eltekoff[2] obtained acetaldehyde and ethylene glycol from ethylene bromide or chloride, acetone and propionaldehyde from the propylene halides, isobutyraldehyde from isobutylene bromide and methyl isopropyl ketone from trimethylethylene bromide. His procedure consisted in heating the halide with lead oxide and water to 140–150°. The formation of methyl isopropyl ketone also has been studied by Ipatieff[3a] and more recently by Whitmore and Evers,[3b] who found the use of lead oxide or a high temperature unnecessary. This reaction is now the most convenient source of the ketone.[4] Some other olefin bromides give aldehydes or ketones on hydrolysis but the yields are not large.[5]

Little consideration has been given to the mechanism by which the olefin halides are converted to the carbonyl compounds. Eltekoff[2] found that the longer a halide was heated with water and lead oxide the larger the yield of aldehyde or ketone and the smaller the amount of glycol. He concluded, therefore, that the dehydration of the glycol in the slightly acidic solution was the source of the carbonyl compound. He further found that trimethylethylene glycol was converted to the ketone when its aqueous solution was heated to 220°. Ayres[6] has shown that tetramethylethylene bromohydrin when heated to 100° in the dry state or when shaken with aqueous silver nitrate or oxide yields pinacolone directly without intervention of the glycol. Some time ago Whitmore[7] suggested that ketone formation from a dibromide occurred without involving either a bromohydrin or glycol as an intermediate.

$$(CH_3)_2CBrCHBrCH_3 \xrightarrow{H_2O} [(CH_3)_2C^+CHBrCH_3] \longrightarrow$$
$$[(CH_3)_2CHC^+BrCH_3] \xrightarrow{H_2O} (CH_3)_2CHCOCH_3$$

However, behavior of indene bromide where the halogen adjacent to the benzene ring shows about the same activity as that of a tertiary alkyl halide, is not in accord with this mechanism.[8] Here indene bromohydrin is the primary hydrolysis product and this may be converted to 1-indanone or through the glycol to 2-indanone. If the bromohydrin were an intermediate in the hydrolysis of trimethylethylene bromide, ketone formation could occur either directly with the shift of a methyl group or indirectly by way of the glycol, but in the case of isobutylene bromide, the bromohydrin should give methyl ethyl ketone, whereas only isobutyraldehyde has been observed. Here, at least, it seemed clear that if the bromohydrin is an intermediate, so also is the glycol. In the present investigation a detailed study has been made of the hydrolysis of trimethylethylene and isobutylene bromides, mostly in dioxane–water mixtures.

As was pointed out recently by Vaughan and Rust,[9] pure trimethylethylene bromide has not been described. The action of bromine upon *t*-amyl alcohol gives a product from which a mix-

(1) (a) Present address, Winthrop Chemical Company, Rensselaer, N. Y. (b) Present address, Pennsylvania State College, State College, Pa.

(2) Eltekoff, *J. Russ. Phys.-Chem. Soc.*, **10**, 215 (1878); *Ber.*, **11**, 989 (1878).

(3) (a) Ipatieff, *J. prakt. Chem.*, (2) **53**, 266 (1896); (b) Whitmore and Evers, THIS JOURNAL, **55**, 812 (1933).

(4) Whitmore, Evers and Rothrock, "Organic Syntheses," **13**, 68 (1933); Calonge, *Bull. soc. chim.*, [5] **3**, 501 (1936).

(5) Froebe and Hochstetter, *Monatsh.*, **23**, 1082 (1902); Evers, Rothrock, Woodburn, Stahly and Whitmore, THIS JOURNAL, **55**, 1136 (1933).

(6) Ayres, *ibid.*, **60**, 2956 (1938).

(7) Whitmore, *ibid.*, **54**, 3274 (1932).

(8) Porter and Suter, *ibid.*, **57**, 2022 (1935).

(9) Vaughan and Rust, *ibid.*, **61**, 215 (1939); Conn, Kistiakowsky and Smith, *ibid.*, **61**, 216 (1939).

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ture of isomeric dibromides may be separated by distillation but these resist further purification by this means. The bromination of trimethylethylene gives a mixture of substitution and addition products from which by fractional distillation and crystallization the dibromide has now been isolated in a state of satisfactory purity. To get an equally pure product from the isomeric dibromides obtained directly from *t*-amyl alcohol required some thirty crystallizations and gave a low yield.

In a preliminary experiment involving 0.058 *M* trimethylethylene bromide in 50% by volume aqueous dioxane at 80°, it was found that over 90% of the theoretical amount of hydrobromic acid was formed in twenty-five minutes but that no appreciable amount of ketone had appeared. After ten hours ketone formation still amounted to less than 20% of the theoretical amount. This at once indicated that the hydrolysis of the bromides was in no way directly related to the formation of methyl isopropyl ketone. That the ketone arises from trimethylethylene glycol through the catalytic action of the hydrogen ions in the solution was confirmed by preparing the pure glycol and measuring the rate at which it was converted to the ketone under various conditions. In dilute (0.11 *M*) sodium carbonate solution at reflux temperature no detectable amount of ketone resulted in thirteen hours. In distilled water the odor of ketone became noticeable within an hour and at the end of six hours, the ketone present corresponded to 1.2% of the theoretical amount. The solution had, however, become slightly acidic due to some side reaction and it appears that some decomposition with formation of a trace of acid preceded ketone formation. Measurements in sulfuric and hydrobromic acid solutions showed that the reaction rate was dependent upon the hydrogen ion activity. The rate of ketone formation in a solution made by dissolving trimethylethylene bromide in water by stirring for some time at 80° was in agreement with that in a solution obtained by adding the glycol to hydrobromic acid. The value of K, the first order constant, showed some decrease as the reaction progressed, probably due to side reactions among which was the formation of the unidentified acidic substance already mentioned. At 80° the initial value of K was 0.20 hours^{-1} decreasing to 0.18 hours^{-1} at half reaction where

$$K = \frac{2.3}{t\gamma[H^+]} \log \frac{a}{a - x}$$

Several methods of estimating methyl isopropyl ketone were investigated in some detail.[10] It was found that precipitation with 2,4-dinitrophenylhydrazine was unsatisfactory since ketone solutions less than 0.01 *M* in 3:2 dioxane–water mixtures gave negative tests. Messinger's iodoform method[11] which works well for acetone gave somewhat variable results. The amount of iodine consumed in 3:2 dioxane–water solutions for ketone concentrations ranging from 0.01 *M* to 0.1 *M* corresponded to 50 ± 5% of the theoretical amount based upon the equation

$$C_6H_{10}O + 4I_2 + 5NaOH \longrightarrow (CH_3)_2CICOONa + CHI_3 + 4H_2O + 4NaI$$

The analytical method finally adopted was based upon that of Marasco[12] for acetone. The reaction of the ketone with hydroxylamine hydrochloride was found to be 66 ± 3% complete for ketone solutions of concentrations ranging from 0.01 *M* to 0.1 *M* made up in 3:2 dioxane–water solution. In distilled water the reaction was 58 ± 2% complete. In both cases the percentage decreased rapidly for lower concentrations being 51% for 0.005 *M* ketone in water.

The formation of hydrogen bromide from trimethylethylene bromide occurred at a convenient rate at 45° and most of the hydrolysis measurements were made at this temperature. It was first found that acid formation occurred by a first order reaction since changing the initial concentration did not change k_1. This is a characteristic of the halogen in simple tertiary alkyl halides.[13] Under some circumstances olefin formation is known[14] to accompany hydrolysis but this was unimportant for the dibromide.[15] However, when the value of k_1 for the hydrolysis of the dibromide to the bromohydrin was determined for various time intervals on the assumption that no other reaction was taking place, the value increased regularly with time. This is what would be expected if the bromohydrin were undergoing conversion to the glycol at a rate comparable to that of the first reaction. A satisfactory value was obtained for k_1 by plotting its apparent value against time and extrapolating to zero time.

$$(CH_3)_2CBrCHBrCH_3 \xrightarrow[H_2O]{k_1} (CH_3)_2COHCHBrCH_3 \xrightarrow[H_2O]{k_2} (CH_3)_2COHCHOHCH_3$$

With k_1 known, the quantity of hydrobromic acid formed at a given time from the first hy-

(10) It is interesting to note that although methyl isopropyl ketone is the only carbonyl compound that has been isolated from this hydrolysis, 2,3-dihydroxybutane gives some dimethylacetaldehyde along with methyl ethyl ketone when heated with aqueous sulfuric acid. The former compound is formed by a methyl rearrangement of the pinacol–pinacolone type. Akabori, *J. Chem. Soc. Japan*, **59**, 1132 (1938); *Chem. Abs.*, **33**, 2106 (1939). NOTE ADDED IN PROOF: Cook, Krimmel and Whitmore have just reported (A. C. S. meeting at Cleveland) that up to 1% of trimethylacetaldehyde is formed in the hydrolysis of trimethylethylene bromide.

(11) Scott, "Standard Methods of Chemical Analysis," D. Van Nostrand Co., New York, N. Y., 1927, p. 1759.

(12) Marasco, *Ind. Eng. Chem.*, **18**, 701 (1926).

(13) Cooper and Hughes, *J. Chem. Soc.*, 1183 (1937); Bateman, Hughes and Ingold, THIS JOURNAL, **60**, 3080 (1938); Olson and Halford, *ibid.*, **59**, 2644 (1937). These references mention earlier work.

(14) Bateman, Hughes and Ingold, *J. Chem. Soc.*, 881 (1938); French, McShaw and Johler, THIS JOURNAL, **56**, 1346 (1934); Woodburn and Whitmore, *ibid.*, **56**, 1394 (1934).

(15) This was evident since heating trimethylethylene bromide with water gave only water soluble products and gave also the theoretical amount of hydrobromic acid. 2-Methyl-3-bromo-2-butene would be water insoluble and inert to further hydrolysis. Ipatieff[2] has shown that alcoholic potassium hydroxide acts with the dibromide to produce this unsaturated compound.

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drolysis was calculated and subtracted from the quantity found by titration. The excess was a measure of the extent to which the bromohydrin had hydrolyzed and the difference between the concentration of acid from the first reaction and that of the second gave the concentration of bromohydrin. The value of k_2 was then obtained by a graphical method[16] from the equation for two consecutive first order reactions

$$y = a + \frac{ak_1}{k_1 - k_2}e^{-k_1t} - \frac{ak_1}{k_1 - k_2}e^{-k_2t}$$

Here y is the concentration of hydrobromic acid from the second reaction at time t and a is the initial dibromide concentration. The calculation of k_2 for various time intervals showed a decrease with time but the initial value corresponded approximately to that of k_1.

The decrease of k_2 with time led us to consider another mechanism for the formation of glycol from dibromide. If it is assumed that the second bromine hydrolyzes at the same time as the first or that the second reaction occurs with great rapidity compared with the first, the hydrolysis data could be expressed by $k^*t = 2.3 \log a/(a - 0.5\ z)$, where a is the initial concentration of dibromide and z is the concentration of hydrobromic acid. As may be seen in Table I this hypothesis fits the experimental results with considerable accuracy.

TABLE I

Time, min.	$k_1 \times 10^4$ (apparent value)[a]	$k_2 \times 10^4$	$k^* \times 10^4$
60	23	..	11.0
120	25	..	11.6
170	27	..	12.1
290	30	..	11.9
470	42	..	12.0
680	..	16	12.0
890	..	15	11.9
1220	..	14	11.7
1490	..	13	11.7

[a] Extrapolation to zero time in this and other experiments gave $k_1 = 0.0021$ at 45°.

Trimethylethylene bromohydrin was then prepared and its hydrolysis studied. In brief, its hydrolysis rate was in agreement with that deduced from the experiments on dibromide hydrolysis, the rate exhibiting the same decrease with time. It was therefore necessary to decide experimentally between the two mechanisms. If k_1 and k_2 were approximately equal, the concentration of bromohydrin in the solution would reach an appreciable value whereas if the glycol were formed directly, the bromohydrin's concentration would be negligible. A method for determining the bromohydrin was therefore devised. In separate experiments it was found (1) that a bromohydrin could be titrated with standard alkali in hot solution using phenolphthalein as the indicator and (2) the distribution ratio of the bromohydrin between the two phases of a system containing water, dioxane and carbon tetrachloride was convenient for analysis of the aqueous layer. It was necessary to add the carbon tetrachloride to remove any unreacted dibromide, as this also reacts with hot dilute alkali. The distribution ratio of trimethylethylene bromohydrin was determined by shaking the carbon tetrachloride layer after the first separation again with a dioxane–water mixture and titrating a second time for bromohydrin. From these data both the total amount of bromohydrin present and the distribution ratio were readily calculated. The ratio for the isobutylene bromohydrin mentioned later was obtained by starting with a known quantity of pure compound. Application of this procedure to a sample of a hydrolysis mixture of trimethylethylene bromide showed that the bromohydrin was actually present and the quantity was in fair agreement with that calculated from the value of k_1. The approximate equality of k_1 and k_2 was therefore a coincidence. As a further check on this, the hydrolysis rates of isobutylene bromide and isobutylene bromohydrin were investigated. These compounds reacted at a much lower rate than the trimethylethylene homologs, k_1 being 12×10^{-5} compared with 21×10^{-4} and k_2 3×10^{-5} as compared with 16×10^{-4}. It is to be noted that here the bromohydrin hydrolyzes much more slowly than the dibromide. The rate of aldehyde formation from isobutylene glycol was not investigated.

Since the hydrolysis rate of a tertiary alkyl halide is not modified by either hydrogen or hydroxyl ions, it was of interest to determine the behavior of the trimethylethylene bromide in this respect. While the values of k_1 and k_2 both remained unchanged in acid solution, in alkaline solution the dibromide hydrolyzed at a much more rapid rate. This was not investigated in detail. The rapid action of alkali with the bromohydrin has already been mentioned.

The first rate determinations made on the hydrolysis of the bromohydrins were later found to be seriously in error. This was caused by the fact that when 0.1 N sodium hydroxide is added to a solution containing hydrogen ions and a bromohydrin, the latter reacts to a marked extent before neutralization of the alkali has taken place. This was not at all obvious in carrying out the titration since with methyl red–methylene blue indicator a sharp end-point was obtained. However, when 0.01 N or 0.001 N alkali was employed and the titration conducted at 0° a quite different curve resulted. The values obtained with 0.1 N alkali fell on a smooth curve so long as a standard titration procedure was used. Variation in the rate of adding the alkali or in stirring the solution gave erratic results. Titration of the hydrolysis mixtures from the dibromides gave less trouble

(16) Hitchcock and Robinson, "Differential Equations in Applied Chemistry," John Wiley and Sons, New York, N. Y., 1923, p. 56.

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as here the bromohydrin concentration was apparently low enough to reduce the alkali reaction to a minor factor.

Experimental

Preparation of Olefin Bromides.—The isobutylene bromide was prepared by fractionation of the product obtained by bromination of *t*-butyl alcohol. The sample used for rate determinations distilled constantly at 61° (40 mm.) and had $n^{25}D$ 1.5070.

Bromination of 435 ml. (4 moles) of *t*-amyl alcohol[4] and fractionation of the product through a 150 cm. column packed with glass helices gave 192 ml. of product distilling at 55° (17 mm.) and having a m. p. of −3 to +5° along with lower and higher boiling fractions that could not be solidified at −12°. Fractional crystallization involving thirty crystallizations gave 30 ml. of dibromide, m. p. 9–12°.

To 165 g. (2.36 moles) of trimethylethylene (obtained by fractionation of the olefins resulting from the dehydration of *t*-amyl alcohol with oxalic acid[17]) dissolved in 200 ml. of carbon tetrachloride was added slowly with stirring at 10–20° during two hours 124 ml. (2.3 moles) of bromine dissolved in 150 ml. of carbon tetrachloride. Fractionation gave 195 g. (125 ml.) of product distilling at 59.5–61° (19 mm.) and melting at 3–7°. Refractionation through a 60 cm. packed column gave 14 ml., m. p. 9–12° and other fractions with lower melting points. Systematic fractional crystallization of these gave 23 ml., m. p. 12–13°, $n^{25}D$ 1.5078, d^{25}_4 1.663 and 32 ml., m. p. 9–12°. The fraction melting at 12–13° was used for rate studies. The highest melting point previously reported[18] is 7°. Recently, a very pure product has been obtained directly by more careful fractionation of both the trimethylethylene and the dibromide. Twenty-three fractions boiled constant at 63°, $n^{20}D$ 1.5090, m. p. 14–16°.

Preparation of Olefin Bromohydrins.—Trimethylethylene bromohydrin has been prepared previously[19] in an impure state but isobutylene bromohydrin has not been described.

To a vigorously stirred mixture of 232 g. of trimethylethylene in 7 liters of water was added 200 ml. of bromine dissolved in 8 liters of water containing 600 g. of potassium bromide. The water layer was removed from 100 ml. of heavy oil (found later to be 76% dibromide) and subjected to a continuous ether extraction for eight hours. When the oily layer containing dibromide was not separated, it was found impossible to get pure bromohydrin, probably due to the formation of a constant boiling mixture. Distillation of the residue remaining after evaporation of the ether gave eight fractions of material all distilling at 48° (14 mm.) but ranging in refractive index from $n^{25}D$ 1.4680 to 1.4710. The last two fractions, $n^{25}D$ 1.4710, amounting to 46 ml. were combined and analyzed.

Anal. Calcd. for $C_5H_{11}OBr$: Br, 47.87. Found: Br, 47.70.

The pure bromohydrin proved to be unstable, a brown color developing within a few days and after thirty days a dark green mixture remained which upon distillation gave fractions apparently containing methyl isopropyl ketone, bromohydrin and dibromide. There remained a dark green water-insoluble residue. Redistillation of the bromohydrin before the green color developed regained the pure compound. It was necessary to keep the temperature below 60° during distillation or decomposition became appreciable. When heated at 100°, the characteristic odor of methyl isopropyl ketone became evident.

In the preparation of isobutylene bromohydrin, isobutylene from 600 ml. of *t*-butyl alcohol was passed through a flask containing 1500 ml. of water. A solution of 150 ml. of bromine and 400 g. of potassium bromide in 8 liters of water was added as fast as reaction took place as was indicated by the disappearance of the bromine color. The contents of the flask were stirred vigorously during the reaction. The aqueous solution of bromohydrin was decanted from an oily layer of 95 ml. and extracted three times with ether using 1 liter each time. The ether solution was dried over anhydrous magnesium sulfate and fractionated. Obtained were: fractions 2–4, 62 g., b. p. 48–49.5° (17 mm.), $n^{25}D$ 1.4680–1.4705; fractions 5–8, 164 g., b. p. 49.5° (16 mm.), $n^{25}D$ 1.4710, d^{25}_4 1.437. In contrast to trimethylethlene and tetramethylethylene[6] bromohydrins this material was stable almost indefinitely.

Trimethylethylene Glycol.—The following procedure was based upon the patented method of Schering.[20] Trimethylethylene bromide (62 ml., m. p. 9–12°) was stirred for three days at 50° with 1.5 liters of water containing 45 g. of sodium hydroxide. The water layer was separated from 5 ml. of a heavy oil and saturated with potassium carbonate (approximately 1 kg.). The glycol layer was taken up in ether and the salt solution continuously extracted with ether for five hours. From the combined ether solutions was obtained after distillation 21.5 g. (57%) of glycol, b. p. 75–76° (14 mm.), $n^{25}D$ 1.4375.

Purification of Dioxane.—The dioxane purified by the method of Eigenberger[21] after careful fractionation distilled at 100.3° (750 mm.) but still had appreciable iodine consumption.[11] This was reduced by fractional crystallization. It was noted that the crystals were white and translucent until the iodine consumption fell to zero when they became transparent.

Estimation of Methyl Isopropyl Ketone.—Solutions containing known concentrations of methyl isopropyl ketone in water and in water–dioxane mixtures were prepared. The acid liberated when 25-ml. samples of each of these solutions reacted with 400 ml. of neutralized hydroxylamine hydrochloride solution[12] was then determined by titration and the per cent. reaction plotted against concentration of ketone. The acid liberated amounted to 66 ± 3% for ketone solutions ranging from 0.01 to 0.1 *M* in 3:2 dioxane–water mixtures, decreasing to 54% for a 0.005 *M* solution. For ketone solutions in water the percentages were 58 ± 2% and 51%. The dioxane employed in making up the solutions had no iodine consumption and gave no test for carbonyl compounds with dinitrophenylhydrazine reagent. Making use of these data the extent of ketone formation in various reaction mixtures was determined.[10]

Ketone Formation from Trimethylethylene Bromide and Glycol.—A preliminary hydrolysis of the dibromide in dioxane–water solution at 79.8° showed practically quantitative formation of hydrobromic acid in one hour while ketone formation amounted to 10.3%. In a second experiment 2 ml. of the dibromide was added to 248 ml. of water at 79.8° and stirred until solution was complete. Then 25 ml. (24.4 ml. at 25°) samples were analyzed at various time intervals for ketone. In Table II $K = \frac{2.303}{t\gamma[H^+]} \log \frac{a}{a-x}$ where $\gamma = 0.812$[22] and $[H^+] = 0.113$. In a similar experiment in sulfuric acid solution in which 1.91 g. (2 ml.) of trimethylethylene glycol was added to 248 ml. of 0.119 *N* acid the average value of *K* to 50% reaction time (ninety-five hours) was 0.21 hours^{-1}. Here $\gamma = 0.341$.[23] In a solution made in the same way from 0.117 *N* hydro-

TABLE II

Time, hours	24	52.5	73	92	
x (ketone concn.)	0.0202	0.0322	0.0393	0.0413	0.0565
K, hours^{-1}	0.20	0.18	0.18	0.16	

(17) Sherrill and Walter, THIS JOURNAL, **58**, 742 (1936); Thompson and Sherrill, *ibid.*, **58**, 745 (1936).
(18) Blaise and Courtot, *Bull. soc. chim.*, [3] **35**, 583 (1906).
(19) Read and Reid, *J. Chem. Soc.*, 1487 (1928).
(20) Schering, German Patent 246,572, *Frdl.*, **10**, 1010; *Chem. Zentr.*, **83**, I, 1874 (1912).
(21) Eigenberger, *J. prakt. Chem.*, **130**, 75 (1931).
(22) Livingston, THIS JOURNAL, **48**, 46 (1926).
(23) Randall and Scott, *ibid.*, **49**, 654 (1927).

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bromic acid the value of K decreased markedly with time from 0.20 to 0.14 hour^{-1} at 36% ketone formation.

A solution containing 4.78 g. (5 ml.) of glycol in 100 ml. of water was refluxed for 5.75 hours. The characteristic odor of methyl isopropyl ketone became evident within one hour. A 25-ml. sample of the solution required 0.45 ml. of 0.141 N sodium hydroxide to neutralize the acid produced. Analysis for ketone indicated a yield of 1.2%. In another experiment where 1.2 g. of sodium carbonate was added at first, no ketone was formed.

Refluxing and stirring 16.63 g. (10 ml.) of trimethylethylene bromide with 200 ml. of water and 10 g. of sodium carbonate for six hours gave no detectable amount of ketone. The dibromide phase, however, disappeared in two hours.

Summary

The mechanism by which trimethylethylene bromide is converted into methyl isopropyl ketone has been studied. The reaction proceeds in steps through trimethylethylene bromohydrin and trimethylethylene glycol as evidenced by rate measurements on the hydrolysis of the bromide and bromohydrin and on the conversion of glycol to ketone.

Preliminary experiments with isobutylene bromide indicate that a similar mechanism holds for the hydrolysis of this compound.

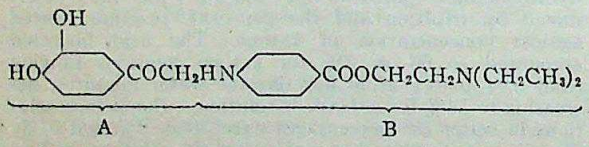
EVANSTON, ILLINOIS RECEIVED DECEMBER 22, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

Amines Related to Epinephrine. I. Some Amines of the "Eprocaine" Type[1]

BY RALPH HILL[1] AND GARFIELD POWELL

Among local anesthetics which have pressor action, a compound appears[2] under the name of "Eprocaine." It is a particularly simple combination of a well-known pressor residue (A) and an anesthetic residue (B), and is reported to have pressor and anesthetic activity.[2]



We have sought, in the work described below, a confirmation of the preparation and properties of "eprocaine" itself, and the synthesis of other compounds in which the residue A is unchanged and the residue B is varied to include other anesthetic residues which have been subjected to some physiological testing. "Eprocaine" itself has been studied, and also the di-*n*-propyl, di-isopropyl, di-*n*-butyl homologs on the aliphatic amino group. We have also prepared, for comparison, the compounds in which B is the "benzocaine" residue (ethyl *p*-aminobenzoate) and the homologs of this having *n*-propyl and *n*-butyl ester groups, together with derivatives. The ethyl ester[3] has previously been described (with a much lower melting point) but no mention has been made of derivatives or physiological testing.

"Eprocaine" was found to give a definite rise in blood pressure when injected intravenously into a pithed decerebrate cat anesthetized with nembutal. A 1% solution gave definite anesthesia, administered intracutaneously to the guinea pig, with evidence the next day of severe tissue damage at the point of injection.[4] On the second group of amines (with B as benzocaine and related residues), anesthetic testing was limited (because of the low solubility of the salts in water) to dusting on the exposed sciatic nerve of the frog. With benzocaine as control, absence of activity was indicated.[5]

Experimental

β-Diethylaminoethyl *p*-(3,4-Dihydroxyphenacylamino)-benzoate Hydrochloride, "Eprocaine."—Fifteen grams of procaine was dissolved in 75 cc. of boiling water and 11.8 g. of chloroacetylcatechol added. The mixture was refluxed for two hours and then concentrated *in vacuo* nearly to dryness. On addition of 75 cc. of alcohol the residue crystallized. Recrystallized from 85% alcohol it melted at about 205° with darkening; yield 73% from procaine.

Anal.[6] Calcd. for $C_{21}H_{27}O_5N_2Cl$: C, 59.9; H, 6.5; N, 6.6; Cl, 8.4. Found: C, 59.8; H, 6.4; N, 6.9; Cl, 8.7.

"Eprocaine" is only slightly soluble in hot alcohol, but quite soluble in water. With ferric chloride solution it gives an emerald green color, turning violet on careful addition of sodium carbonate solution. All compounds described in this paper derived from 3,4-dihydroxyphenacyl halides responded to this test, with addition of alcohol when needed for solubility purposes. The free base is precipitated by sodium hydroxide and is dissolved in excess. The base is soluble in alcohol, acetone, and hot water, insoluble in cold water and benzene.

Table I shows the results obtained in the preparation of homologs by the following general procedure, in each case using a corresponding amount of the proper ester. Four grams of ethyl *p*-aminobenzoate was dissolved in about 500 cc. of boiling water and 4.5 g. of chloroacetylcatechol added. The clear solution was boiled for four hours, keeping the volume constant by the addition of water. During this process the product separated out as white flocculent crystals. The crystals were filtered hot, washed with hot water, and recrystallized from alcohol.

Dibenzoate of β-Diethylaminoethyl *p*-(3,4-Dihydroxyphenacylamino)-benzoate.—A solution of 0.5 cc. of benzoyl chloride in 3 cc. of benzene was added to 0.5 g. of "eprocaine" dissolved in 20 cc. of water. One-half gram of sodium carbonate was added in portions with shaking and cooling. The product separated as a gummy mass which

(1) From a dissertation submitted by Ralph Hill in partial fulfillment of the requirements for the Ph.D. degree at Columbia University. Original manuscript received January 15, 1943.

(2) Osborne, *Science*, **85**, 105 (1935).

(3) Ishiwara, *Ber.*, **57**, 1126 (1924).

(4) Private report of M. G. Mulinos, Columbia University.

(5) Private report of Edwin J. Fellows, Temple University.

(6) For analyses reported in this paper we are indebted to Mr. Saul Gottlieb.

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TABLE I

Compound formed	Ester reacting	M. p., °C.	Yield, % of theoret.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
I	Ia	220–221[a] with darkening		$C_{17}H_{17}O_5N$	68.5	5.4	68.6	5.2
II	IIa	210–211	60	$C_{18}H_{19}O_5N_2$	65.8	5.5	66.0	5.8
III	IIIa	196–196.5	58	$C_{19}H_{21}O_5N$	66.5	6.1	66.7	6.2
IV	IVa	Abt. 225 with darkening	69	$C_{23}H_{31}O_5N_2Cl$	61.3	6.9	61.5	7.1
V[b]	Va	223–224	66	$C_{23}H_{31}O_5N_2Cl$	61.3	6.9	61.3	7.1
VI[b]	VIa	227–230	55	$C_{25}H_{35}O_5N_2Cl$	62.7	7.3	62.6	7.5

I is ethyl *p*-(3,4-dihydroxyphenacylamino)-benzoate from Ia: ethyl *p*-aminobenzoate
II is propyl *p*-(3,4-dihydroxyphenacylamino)-benzoate from IIa: propyl *p*-aminobenzoate
III is butyl *p*-(3,4-dihydroxyphenacylamino)-benzoate from IIIa: butyl *p*-aminobenzoate
IV is β-diisopropylaminoethyl *p*-(3,4-dihydroxyphenacylamino)-benzoate hydrochloride from IVa: β-diisopropylaminoethyl *p*-aminobenzoate
V is β-di-*n*-propylaminoethyl *p*-(3,4-dihydroxyphenacylamino)-benzoate hydrochloride from Va: β-di-*n*-propylaminoethyl *p*-aminobenzoate
VI is β-di-*n*-butylaminoethyl *p*-(3,4-dihydroxyphenacylamino)-benzoate hydrochloride from VIa: β-di-*n*-butylaminoethyl *p*-aminobenzoate hydrochloride.

[a] Literature m. p. 201°; see ref. 3. [b] Recrystallized from dilute acetic acid containing a little hydrochloric acid.

solidified after an hour of shaking. The solid was filtered off, washed with benzene, air dried, and recrystallized from alcohol. The melting point was 150–150.5°.

Anal. Calcd. for $C_{35}H_{34}N_2O_7$: C, 70.7; H, 5.7. Found: C, 70.7; H, 5.6.

The corresponding acetyl derivative appears to be unstable to water.

Dibenzoate of β-Di-*n*-propylaminoethyl *p*-(3,4-Dihydroxyphenacylamino)-benzoate.—This was prepared in the same manner as the above and recrystallized from alcohol; m. p. 154–154.5°.

Anal. Calcd. for $C_{37}H_{38}N_2O_7$: C, 71.3; H, 6.2. Found: C, 71.6; H, 6.4.

Diacetate of Ethyl *p*-(3,4-Dihydroxyphenacylamino)-benzoate.—Three grams of ethyl *p*-(3,4-dihydroxyphenacylamino)-benzoate was suspended in 200 cc. of water to which ice had been added, and solution was effected by addition of 4.1 cc. of 20% sodium hydroxide solution (slight excess of three equivalents), and 2.8 cc. of acetic anhydride was added rapidly with stirring. A gelatinous precipitate formed. Sufficient acetic acid was added to give a clear solution on boiling. On cooling the product separated in crystalline form. The crystals were filtered, washed with 50% acetic acid followed by water, and recrystallized from alcohol; m. p. 179–181°.

Anal. Calcd. for $C_{21}H_{21}O_7N$: C, 63.1; H, 5.3. Found: C, 63.1; H, 5.5.

The Triacetates of Ethyl, Propyl, and Butyl *p*-(3,4-Dihydroxyphenacylamino)-benzoates.—These all were prepared by a procedure similar to the following, given for the ethyl ester, with results shown in Table II. One-half gram of ethyl *p*-(3,4-dihydroxyphenacylamino)-benzoate was suspended in 20 cc. of acetic anhydride, and two drops of concentrated sulfuric acid added. The mixture was warmed slightly and the suspended solid gradually dissolved. The solution was allowed to stand for an hour, and was then poured into about 125 cc. of water. As the excess acetic anhydride hydrolyzed, the product separated out as a white solid. It was recrystallized from dilute acetic acid.

Hydrolysis of β-Di-*n*-propylaminoethyl *p*-(3,4-Dihydroxyphenacylamino)-benzoate.—A quantity of this compound was dissolved in an excess of 0.1 *N* sodium hydroxide solution and allowed to stand at room temperature for several hours. On acidification with dilute hydrochloric acid, crude *p*-(3,4-dihydroxyphenacylamino)-benzoic acid separated as a white amorphous solid. This was washed free from chloride with water, by centrifuging and decanting the washings. The product was recrystallized first from dilute acetic acid and then from alcohol. It decomposed at 241° when placed in a melting point tube at 230° and heated at the rate of 3° per minute. The product was soluble in sodium bicarbonate with evolution of carbon dioxide. It gave an emerald green color with ferric chloride solution.

TABLE II

Compound	M. p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Ethyl ester	143–144	$C_{23}H_{23}O_8N$	62.6	5.2	62.7	5.5
Propyl ester	129–131	$C_{24}H_{25}O_8N$	63.3	5.5	63.3	5.7
Butyl ester	120	$C_{25}H_{27}O_8N$	64.0	5.8	64.2	5.9

Anal. Calcd. for $C_{15}H_{13}NO_5$: C, 62.7; H, 4.5. Found: C, 62.5; H, 4.6.

Hydrolysis of the ester linkage thus proceeds normally without affecting the phenacylamino group.

Summary

Diethylaminoethyl *p*-(3,4-dihydroxyphenacylamino)-benzoate, "eprocaine," and related esters in which the alcohol group is ethyl, propyl, butyl, β-diisopropylaminoethyl, β-di-*n*-propylaminoethyl, and β-di-*n*-butylaminoethyl were prepared by interaction of the suitable *p*-aminobenzoic ester with chloracetylcatechol. Dibenzoyl derivatives of the β-diethylaminoethyl and β-di-*n*-propylaminoethyl *p*-(3,4-dihydroxyphenacylamino)-benzoates were prepared, and also the di- and tri-acetates of ethyl *p*-(3,4-dihydroxyphenacylamino)-benzoate, as well as the triacetates of the propyl and butyl esters.

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[CONTRIBUTION FROM THE PHILADELPHIA INSTITUTE FOR MEDICAL RESEARCH IN THE PHILADELPHIA GENERAL HOSPITAL]

Some 4-(ω-Carboxyalkyl)-2-aminothiazoles and their Reaction with Acetylsulfanilyl Chloride

BY WILLIAM M. ZIEGLER

In a previous paper[1] it was shown that acetylsulfanilyl chloride would not react with 4-(α-carbethoxyalkyl)-2-aminothiazoles nor in one instance with the free acid itself. However, the 4-alkyl substituted aminothiazoles, obtained by the decarboxylation of these acids reacted readily with the chloride even though the side chain was seven carbons long. From this it was assumed that the carboxy or carbethoxy group exerted an inhibitory effect upon the amino group insofar as its reactivity with the sulfonyl chloride was concerned. Therefore, it was thought of interest to prepare several 4-(ω-carboxyalkyl)-2-aminothiazoles and to investigate their behavior toward acetylsulfanilyl chloride.

The aminothiazoles were prepared from the esters of acetodibasic acids by a method similar to the one previously reported[1] for the preparation of 4-alkyl-2-aminothiazoles. The preparation of 4-(β-carbethoxyethyl)-2-aminothiazole given herewith is typical.

To 86.5 g. (0.4 mole) of ethyl α-acetosuccinate[2] dissolved in two volumes of carbon disulfide and cooled in an ice–water mixture, 21 ml. (0.4 mole; 63 g.) of bromine was added. The flask was stoppered and allowed to stand for 18–24 hours. The solution was washed twice with water and the carbon disulfide removed under diminished pressure, holding the bath temperature at 35–40°. To this product was added 70 ml. of water, 30 g. of ice and 33 g. (0.43 mole) of thiourea, and the mixture shaken for one hour. Slightly more than the calculated quantity of ammonia water (30 ml.) was added and the mixture chilled. The crystalline product was removed by filtration, dissolved while moist in a minimum quantity of methyl alcohol and again chilled. The product thus obtained was recrystallized from 70% methyl alcohol.

Forty and eight-tenths grams (0.15 mole) of the above ester was refluxed with 30 ml. of 95% alcohol, 50 ml. of water, and 20 ml. of concentrated hydrochloric acid until the evolution of carbon dioxide had ceased (three to five hours). To the hot solution some decolorizing carbon was added, the material filtered, and a further quantity of 20 ml. of concentrated hydrochloric acid added. The solution was then evaporated at 60° until crystals separated. It was then chilled, the product removed by filtration and recrystallized from water. The mother liquors were evaporated to a small volume and worked up in the same manner. The hydrochloride of the aminothiazole was thus obtained. The free base was liberated by dissolving the hydrochloride in hot water and adding the calculated amount of sodium hydroxide solution.

In a similar manner 4-(γ-carboxypropyl)-2-aminothiazole, 4-(δ-carboxybutyl)-2-aminothiazole, and 4-(λ-carboxyundecanyl)-2-aminothiazole, were prepared from ethyl α-acetoglutarate,[3] ethyl α-acetoadipate,[4] and α-aceto-α,λ-dicarbethoxyundecane.[5] Pertinent data concerning all the compounds may be found in the table.

TABLE I

R = 4-R-2-aminothiazole	Yield, %	M. p.,[a] °C.	N Analyses, % Calcd.	Found	
α,β-Dicarbethoxyethyl-	45	118–119[b]	10.3	10.1	10.3
α,γ-Dicarbethoxypropyl-	64	87– 88[b]	9.76	9.72	9.78
α,δ-Dicarbethoxybutyl-	51	83– 84[c]	9.37	9.62	9.63
α,λ-Dicarbethoxyundecanyl-	34	79– 80[d]	7.03	6.85	6.87
β-Carboxyethyl hydrochloride	75	243–245	13.4	13.3	13.3
free base	..	213–214	16.3	16.5	16.5
γ-Carboxypropyl hydrochloride	70	207–209	12.6	12.5	12.5
free base	..	125–127[e]	15.0	14.7	14.8
δ-Carboxybutyl hydrochloride	70	235–237	11.9	12.1	12.3
free base	..	202–203.5	14.0	14.2	14.3
λ-Carboxyundecanyl hydrochloride	64	178–179.5	8.36	7.99	8.00
free base	..	105–107	9.11	8.91	8.95
4-(β-Carboxyethyl)-2-sulfanilamidothiazole hydrochloride	33	277–279[f]	11.5	11.5	11.5
free base	..	143–145	12.8	12.6	12.8
4-(γ-Carboxypropyl)-2-sulfanilamidothiazole hydrochloride	11	204–206[f]	11.1	11.0	11.2
4-(λ-Carboxyundecanyl)-2-acetylsulfanilamidothiazole	40	98–100[b]	8.48	8.36	8.37

[a] All products were recrystallized from water unless otherwise stated, and all melting points are corrected. [b] Recrystallized from 70% methanol. [c] Recrystallized from 70% ethanol. [d] Recrystallized from 95% ethanol. [e] After drying at 120°. The monohydrate melts at 99–101°. [f] With partial decomposition.

Some difficulty was experienced in the isolation of products from the reaction of the amines with acetylsulfanilyl chloride. Finally the following method was used.

Nineteen grams (0.11 mole) of 4-(β-carboxyethyl)-2-aminothiazole was dissolved in 70 ml. of pyridine and 28 g. (0.12 mole) of acetylsulfanilyl chloride was added. The solution was warmed for one hour on a steam-bath and then poured into 600 ml. of 2 *N* hydrochloric acid. There was no precipitate, so the mixture was refluxed for forty minutes. The product was decolorized with Norite and

(1) Ziegler, THIS JOURNAL, **63**, 2946 (1941).

(2) Conrad, *Ann.*, **188**, 218 (1877).

(3) Emery, *Ber.*, **24**, 285 (1891).

(4) Fichter and Gully, *ibid.*, **30**, 2047 (1897).

(5) The ester used was prepared from ethyl acetoacetate and ethyl ω-bromoundecylate in the usual manner. After the removal of the unreacted ethyl acetoacetate, an aliquot of the product, which would not distill at 8 mm., was titrated with bromine to estimate the concentration of the desired dibasic ester. Using this ester to prepare 4-(α,λ-dicarbethoxyundecanyl)-2-aminothiazole, it was necessary to allow the mixture to stand for one week in the refrigerator after neutralization to obtain a solid.

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filtered. It was then brought to a *p*H of 4.5–5.0 and evaporated at 60° to 300 ml., chilled and filtered. The residue was mainly sulfanilic acid. The filtrate was evaporated on a steam-bath until sodium chloride crystals appeared, and then chilled and filtered. The product obtained was recrystallized from water. The free base was obtained by treating a warm solution of the hydrochloride with the calculated amount of sodium hydroxide in a little water.

In this manner fair yields of product were obtained from 4-(β-carboxyethyl)-2-aminothiazole, and poor yields were obtained from 4-(γ-carboxypropyl)-2-aminothiazole. The mother liquors from the latter reaction were combined and evaporated to dryness. The product obtained was recrystallized from a small quantity of water. This proved to be identical with 4-(γ-carboxypropyl)-2-aminothiazole sulfanilate, which was also produced by heating the free base with sulfanilic acid in a small quantity of water and allowing it to crystallize. The product was obtained in over 50% yields in all batches. With 4-(δ-carboxybutyl)-2-aminothiazole, 75% of the amine was recovered, indicating a lack of or very little reaction. 4-(λ-Carboxyundecanyl)-2-acetylsulfanilamidothiazole was isolated from the pyridine reaction mixture of the corresponding amine and acetylsulfanilyl chloride. This product was incompletely hydrolyzed by 2 *N* hydrochloric acid, while refluxing with 2 *N* sodium hydroxide destroys it.

That the sluggishness of reaction is a characteristic of the amine rather of the other reactants or some possible conditions is supported by the following facts. The sulfonyl chloride used was of a good grade and gave excellent yields of sulfanilamide and sulfanilanilide. Further, the 4-(δ-carboxybutyl)-2-aminothiazole did not react with *p*-toluenesulfonyl chloride in the refluxing pyridine; 70% of the amine was recovered unchanged. That the acetylsulfanilamide may have been formed and hydrolyzed[6,7] does not seem probable since no hydrolysis was run in the reaction with the *p*-toluenesulfonyl chloride just mentioned; nor did a sample of 4-(γ-carboxypropyl)-2-sulfanilamidothiazole change when refluxed for two hours with 2 *N* hydrochloric acid.

(6) Winterbottom, THIS JOURNAL, **62**, 160 (1940).

(7) Lur'e, Starobogatov, and Nikitskaya, *J. Gen. Chem.* (U. S. S. R.), **11**, 545 (1941); *C. A.*, **35**, 6938 (1941).

Thus, since 2-amino-4-propylthiazole and 2-amino-4-amylthiazole react well with acetylsulfanilyl chloride, it seems that the conversion of the end carbon in the chain to the carboxy group had a decided inhibitory effect upon the reaction. Also, this effect varies greatly with the position of the carboxy group in the chain. Very striking is the fact that, except for the acetic acids, the interference increases as the carboxy group is moved outward from the ring, to a maximum at five or possibly six carbons and then probably decreases, since the carboxyundecanyl derivative gave yields comparable to the carboxyethyl compound.

The 4-(β-carboxyethyl)-2-sulfanilamidothiazole was found ineffective against experimental streptococcus and pneumococcus infections in mice.

The author wishes to thank Dr. G. H. A. Clowes of Eli Lilly and Company for having the pharmacological work done and the American Philosophical Society for financial support of the work.

Summary

1. Several 4-(ω-carboxyalkyl)-2-aminothiazoles were prepared from the ethyl esters of α-acetodibasic acids.

2. The yields of sulfonamides from these aminothiazoles decreased as the alkyl group increased, to a certain point, from two to four carbons, increasing again when it contained eleven carbons.

3. It is concluded that the conversion of the end carbon of a 2-amino-4-alkylthiazole to a carboxy group has a decided inhibitory effect upon the reaction of that amine with acetysulfanilyl chloride and the interference increases as the chain increases to five or possibly six carbons, then decreases.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF INDIANA UNIVERSITY]

Antispasmodics and Anticonvulsants. III.[1] Miscellaneous Amides and Esters

BY JOHN H. BILLMAN AND JOHN L. RENDALL[2,3,4]

A large portion of the work that has been done in the field of antispasmodics and anticonvulsants has been concerned with the preparation and testing of amides and esters. As we were interested in a study of compounds having the above physiological activity, we decided to prepare a number of miscellaneous esters and amides in an attempt to find some compounds not previously reported as having antispasmodic or anticonvulsant activity. Since benzyl alcohol and 2-diethylaminoethanol have been used frequently in making active esters, we treated these alcohols with a number of different substituted acids.

(1) II, John H. Billman and John L. Rendall, THIS JOURNAL, **66**, 540 (1944).

(2) Submitted to the Faculty of the Graduate School in partial fulfillment of the requirements for the degree, Doctor of Philosophy, in the Department of Chemistry, Indiana University.

(3) Eli Lilly Fellow for the years 1941–3.

(4) Present address: B. F. Goodrich and Co., Akron, Ohio.

At the same time we decided to prepare *p*-dibenzylacetaminoacetophenone and *p*-dibenzylacetaminobenzophenone. It was felt that these amides might be active inasmuch as they are derivatives of acetophenone or benzophenone, which are both active by themselves. Two benzyl substituted ureas were prepared and submitted for testing.

The compounds which have been prepared are listed in Table I.

Acknowledgment.—The authors wish to thank Eli Lilly and Company for the generous grant which made this work possible.

Experimental

General Procedure for Esters.—The esters with the exception of benzyl dibenzylacetate were prepared by refluxing a xylene solution of the acid and alcohol and measuring the water evolved in a calibrated water trap to ascertain the extent of completion of the reaction. Benzyl di-

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TABLE I

AMIDES AND ESTERS

Compound	I[a]	II[b]	M. p., °C., uncor.	B. p., °C.	Pressure, mm.	Yield, %	Analyses, % Calcd.	Found
Benzyl dibenzylacetate[5]	+	0	81.5			53.0		
Benzyl α,β-diphenylpropionate[6]	0	0		197–201	1	73.2		
Benzyl levulinate[7]	−	+		148–150	3	85.0		
Benzyl 2-pyrrolidone-5-carboxylate	0	+		202–204	2	68.5	N, 6.39	6.06
β-Diethylaminoethyl γ-diethylamino-α-phenylbutyrate	0	0		170–173	1	62.5	N, 8.38	8.47
β-Diethylaminoethyl acetoacetate	−	−		113	2	51.8[c] 59.0[d]	N, 6.97	6.95
β-Diethylaminoethyl 2-pyrrolidone-5-carboxylate	0	0		183–184	3	26.1	N, 12.28	12.44
β-Diethylaminoethyl nicotinate[8]	0	0		130–132	2	50.0		
Benzyl urea[9]	−	+	147.5			100.00		
N-Triphenylmethyl-N′-benzylurea	+	0	228			18.0	C, 82.65	82.97
							H, 6.17	6.66
p-Dibenzylacetaminobenzophenone	0	0	60			15.0	N, 3.34	3.38
p-Dibenzylacetaminoacetophenone	+	0	135–6			50.0	C, 80.67	81.30
							H, 6.49	6.66

[a] Anticonvulsant activity: 0, inactive; +, poor; ++, moderate; +++, good; −, no test reported to date. [b] Antispasmodic activity: same symbols. [c] Prepared from diketene and β-diethylaminoethanol. [d] Prepared from acetoacetic ester and β-diethylaminoethanol by *trans*-esterification.

benzylacetate was prepared by the action of dibenzylacetyl chloride on benzyl alcohol in pyridine.

General Procedure for Amides.—The amides were prepared by the reaction of the acid chloride with the amine in pyridine.

2-Pyrrolidone-5-carboxylic Acid.—2-Pyrrolidone-5-carboxylic acid was prepared by heating glutamic acid at 170° for two hours similar to the procedure described by Haitinger.[10]

Benzyl 2-Pyrrolidone-5-carboxylate.—A mixture of 14.7 g. (0.10 mole) of 2-pyrrolidone-5-carboxylic acid and 72.0 g. (0.655 mole) of benzyl alcohol in 100 ml. of xylene was refluxed for eight hours, the water evolved being caught in a water trap. Distillation *in vacuo* yielded 15.0 g. (68.5% of theoretical) of the ester boiling at 202–204° (2 mm.).

p-Dibenzylacetaminoacetophenone.—Fourteen grams (0.058 mole) of dibenzylacetic acid and 16.9 g. (0.14 mole) of thionyl chloride were mixed and allowed to stand ten hours. The mixture was heated for two hours in a water-bath maintained at 50°. The excess thionyl chloride was removed *in vacuo*. A solution of 10.0 g. (0.074 mole) of p-aminoacetophenone in 10 g. of pyridine was added slowly to the acid chloride (cooled in ice.). The reaction mixture was heated in a water-bath at 40–5° for three hours and then added to a mixture of ice and water. The semisolid which formed was crystallized twice from alcohol yielding 8.5 g. (50.0% of theoretical) of the amide melting at 35–36°.

Benzyl Urea.—Benzyl urea was prepared in a quantitative yield by heating an aqueous solution of benzylamine hydrochloride with potassium cyanate.

N-Triphenylmethyl-N′-benzylurea.—A solution of 18.0 g. (0.0644 mole) of triphenylchloromethane and 9.68 g. (0.0644 mole) of benzyl urea in 75 ml. of pyridine was refluxed for five hours and then added to a mixture of ice and water. The solid which formed was recrystallized from absolute alcohol twice to give 4.9 g. (18.0% of theoretical) of product melting at 228°.

(5) Delépine, *Compt. rend.*, **190**, 878 (1930).
(6) Ramart and Haller, *ibid.*, **178**, 1583 (1924).
(7) Sah, Lei and Fang, THIS JOURNAL, **55**, 4727 (1933).
(8) Ingersoll and Robbins, *ibid.*, **48**, 2449 (1926).
(9) Schiff, *Ber.*, **9**, 81 (1876).
(10) Haitinger, *Monatsh.*, **3**, 228 (1882).

Summary

Twelve miscellaneous esters and amides have been prepared and tested for antispasmodic and anticonvulsant activity.

BLOOMINGTON, IND. RECEIVED DECEMBER 17, 1943

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[Contribution from the Research Laboratories of Winthrop Chemical Company, Inc.]

The Preparation of 1-(3,4-Dihydroxyphenyl)-2-amino-1-butanol[1]

By C. M. Suter and A. Wayne Ruddy

In the prolonged search that has been made for sympathomimetic amines, which possess pharmacological actions similar to but more desirable than epinephrine, 1-(3,4-dihydroxyphenyl)-2-amino-1-butanol has aroused considerable interest. Under the names ethylnorsuprarenin and ethylnoradrenalin it has been tested in several laboratories and a number of papers have been published on the pharmacology of this compound by Tainter and co-workers,[2] Raymond-Hamet,[3] and Bacq.[4] Unpublished work by Tainter, Cameron, and Whitsell indicates that it is equally as effective as epinephrine in the relief of acute asthmatic attacks in doses one-half larger, and this relief is accompanied by fewer side effects; that it is approximately one one-hundredth as toxic as epinephrine; that it neither excites the central nervous system nor raises systolic blood pressure, but instead lowers diastolic pressure and increases the pulse rate, thus improving circulation without a proportionate rise in cardiac work.

There is little doubt that the compound tested pharmacologically was 1-(3,4-dihydroxyphenyl)-2-amino-1-butanol, but a thorough search of the literature has thus far failed to reveal any description of its synthesis or physical constants. Consequently its synthesis was attempted in these laboratories, and successfully completed. A new process was used which may have a general application.

In a search for a suitable means of obtaining this amine the usual methods of introducing a primary amino group proved unsatisfactory. Although Hartung[5] has described α-isonitroso-3,4-dihydroxybutyrophenone, our attempts to nitrosate both 3,4-dihydroxybutyrophenone and 3,4-dibenzyloxybutyrophenone were unsuccessful. Treatment of α-bromo-3,4-dibenzyloxybutyrophenone with ammonia was unsatisfactory as a synthetic method. The reaction of the bromoketone with hexamethylenetetramine was too slow to be practical.

In the present investigation the possibility of forming a primary amine by hydrogenolysis of a secondary amine has been studied. Since the catalytic hydrogenolysis of a tertiary benzylmethylamino compound has been generally used for producing a methylamino compound, it was believed that a high molecular weight secondary amine might behave similarly to produce a primary amine. It was found that a benzhydryl group could be removed readily by hydrogenation in the presence of a palladium catalyst. Benzhydrylamine was allowed to react with a bromoketone and the benzhydrylamino compound successfully reduced to the desired primary amine.

3,4-Dihydroxybutyrophenone has been prepared by the Fries isomerization of catechol dibutyrate and guaiacol butyrate in nitrobenzene or carbon disulfide.[6,7,8] The methods either gave low yields or required a high reaction temperature and tedious manipulation. Catechol was treated with *n*-butyryl chloride and aluminum chloride in chlorobenzene to give a 68% yield of 3,4-dihydroxybutyrophenone with no difficulties encountered. The product was benzylated readily with benzyl chloride and the 3,4-dibenzyloxybutyrophenone obtained in excellent yield. α-Bromo-3,4-dibenzyloxybutyrophenone has been previously prepared,[9] but has not been characterized. The dibenzyloxyketone was brominated without difficulty and its identity was established. The bromoketone was treated with benzhydrylamine and the resulting α-benzhydrylamino-3,4-dibenzyloxybutyrophenone hydrochloride was hydrogenated to yield 1-(3,4-dihydroxyphenyl)-2-amino-1-butanol.

Experimental

3,4-Dihydroxybutyrophenone.—To 165 g. (1.5 moles) of catechol in 660 ml. of dry chlorobenzene was added 200 g. (1.87 moles) of *n*-butyryl chloride and the mixture heated at 50° for thirty minutes. It was then cooled and 426 g. (3.2 moles) of anhydrous aluminum chloride added in small portions. Then the temperature of the mixture was gradually raised to 110° and held there for three hours. The mixture was hydrolyzed in ice and hydrochloric acid, and the chlorobenzene removed by steam distillation. While still warm, 75 ml. of concentrated hydrochloric acid and 125 ml. of toluene were added. After thorough cooling, the product was filtered and washed well with water and toluene. When recrystallized from water it melted at 146–146.5°. It is reported to melt at 146–147°.[6] The yield of 3,4-dihydroxybutyrophenone was 68% of the theoretical. A small amount of 4-chlorobutyrophenone, m. p. 34–35°, was isolated from the toluene washings.

3,4-Dibenzyloxybutyrophenone.—A mixture of 184.5 g. (1.023 moles) of 3,4-dihydroxybutyrophenone, 278.5 g. (2.2 moles) of benzyl chloride, 187 g. (1.35 moles) of anhydrous potassium carbonate, 13.5 g. (0.09 mole) of sodium iodide in 500 ml. of alcohol and 8 ml. of water was refluxed and stirred five hours, when all effervescence had ceased. The alcohol was distilled and any unreacted benzyl chloride removed by steam distillation. The warm mixture was poured into dilute sodium hydroxide, cooled, filtered, and

(1) Presented before the Division of Medicinal Chemistry, A. C. S., Cleveland, Ohio, April, 1944.

(2) Tainter, *et al.*, *Arch. intern. pharmacodynam.*, **46**, 192 (1933); *J. Pharmacol.*, **51**, 371 (1934); **55**, 242 (1935); **57**, 152 (1936); **62**, 318 (1938); **63**, 340 (1938); **66**, 146 (1939); **67**, 56 (1939); **71**, 62 (1941); *Am. J. Med. Sci.*, **197**, 796 (1939); *J. Physiol.*, **98**, 263 (1940).

(3) Raymond-Hamet, *Bull. sci. pharmacol.*, **41**, (36) 481–489 (1934); *Compt. rend.*, **202**, 690 (1936); *Compt. rend. soc. biol.*, **128**, 827 (1938).

(4) Bacq, *Arch. intern. pharmacodynam.*, **55**, 190 (1937); Heirman and Bacq, *Arch. intern. physiol.*, **50**, 100 (1940).

(5) Hartung, U. S. Patent 1,995,710.

(6) Rosenmund and Lohfert, *Ber.*, **61B**, 2601 (1928).

(7) Coulthard, Marshall and Pyman, *J. Chem. Soc.*, 280 (1930).

(8) Miller, Hartung, Rock and Crossley, This Journal, **60**, 7 (1938).

(9) Bockmühl, Ehrhart & Stein, U. S. Patent 2,083,001.

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washed with water until neutral to litmus. Recrystallization from alcohol gave a 90% yield of 3,4-dibenzyloxybutyrophenone, m. p. 86–87°. It is reported to melt at 88°.[10]

α-Bromo-3,4-dibenzyloxybutyrophenone.—This bromoketone was prepared by the procedure of Bockmühl, Ehrhart and Stein,[9] who prepared and used the compound without isolating and characterizing it. To 335.5 g. (0.93 mole) of 3,4-dibenzyloxybutyrophenone dissolved in 1500 ml. of methylene chloride was added 110 g. (1.1 moles) of powdered calcium carbonate and then 149 g. (0.93 mole) of bromine in 400 ml. of methylene chloride. The excess calcium carbonate was dissolved with dilute hydrochloric acid, the methylene chloride layer separated, washed with water, and dried over sodium sulfate. After removing the solvent under reduced pressure the residue was recrystallized from alcohol. A 70% yield of cream-colored crystals, m. p. 100–101° was obtained.

Anal. Calcd. for $C_{24}H_{23}O_3Br$: C, 65.61; H, 5.28. Found: C, 65.48; H, 5.14.

α-Benzhydrylamino-3,4-dibenzyloxybutyrophenone Hydrochloride.—To 57.1 g. (0.13 mole) of α-bromo-3,4-dibenzyloxybutyrophenone in 175 ml. of absolute alcohol was added 47.7 g. (0.26 mole) of benzhydrylamine and the mixture refluxed three hours. The alcohol was completely removed under reduced pressure and 400 ml. of dry ether added. The precipitated benzhydrylamine hydrobromide was filtered and washed with dry ether. The ether solutions were combined and thoroughly shaken with 10% hydrochloric acid. An oil separated which slowly crystallized. It was filtered off, washed with water and with ether to remove traces of color. A 75% yield of cream-colored needles, m. p. 175–176° dec., was obtained.

(10) I. G. Farbenind. A. G., British Patent 457,824.

Anal. Calcd. for $C_{37}H_{36}O_3NCl$: N, 2.42; Cl, 6.13. Found: N, 2.38; Cl, 6.09.

1-(3,4-Dihydroxyphenyl)-2-amino-1-butanol Hydrochloride.—To 28.9 g. (0.1 mole) of α-benzhydrylamino-3,4-dibenzyloxybutyrophenone hydrochloride, dissolved in 150 ml. of absolute alcohol, was added 0.5 g. of palladium sponge catalyst.[11] It was shaken at 55–70° under fifty pounds pressure until three equivalents of hydrogen had been used. After the alcohol was removed the residue was dissolved in water and the toluene and diphenylmethane removed by extracting with ether. The aqueous solution was boneblacked and further hydrogenated until the fourth equivalent of hydrogen had been used. The catalyst was removed and the solution taken to dryness under reduced pressure. The residue was boneblacked in absolute alcohol, an equal volume of acetone added and then dry ether until precipitation was complete. A 60% yield of colorless material was obtained. When completely dry it melted with decomposition at 199–200° (uncor.).

Anal. Calcd. for $C_{10}H_{16}O_3NCl$: N, 5.99; Cl, 15.17. Found: N, 6.17; Cl, 15.08.

Summary

1. The synthesis and characterization of 1-(3,4-dihydroxyphenyl)-2-amino-1-butanol has been described.

2. It has been shown that the intermediate benzhydrylaminoketone readily undergoes hydrogenolysis to the desired primary amine.

(11) Willstätter and Waldschmidt-Leitz, *Ber.*, **54**, 123 (1921).

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[CONTRIBUTION FROM ALLERGEN INVESTIGATIONS, BUREAU OF AGRICULTURAL AND INDUSTRIAL CHEMISTRY, AGRICULTURAL RESEARCH ADMINISTRATION, U. S. DEPARTMENT OF AGRICULTURE, AND THE ALLERGY CLINIC OF PROVIDENCE HOSPITAL]

The Chemistry of Allergens. IX. Isolation and Properties of an Active, Carbohydrate-Free Protein from Castor Beans[1]

BY JOSEPH R. SPIES, E. J. COULSON, DORRIS C. CHAMBERS, HARRY S. BERNTON AND HENRY STEVENS

The method of isolation, amino acid content and chemical and immunological properties of a non-toxic, allergenic, protein-polysaccharidic fraction, CB-1A, from castor beans were recorded in a previous publication.[1b]

The importance of the role of carbohydrate in the immunological specificity of pneumococcus organisms[2] and recognition of a possible analogous relationship in allergenic specificity[3] led to the isolation and chemical characterization of an essentially carbohydrate-free protein (CS-60C) from cottonseed.[4]

To determine similarly the significance of the polysaccharidic portion of the castor bean allergen, an attempt was made to isolate a carbohydrate-free protein from CB-1A, by electrophoresis, analogously to the previously described fractionation of CS-1A from cottonseed.[4,5] However, the final cathodic fraction, CB-60C, so obtained, contained 0.47% carbohydrate. Therefore, CB-1A was subjected to a varied and prolonged series of procedures involving chromatographic adsorption of the picrate, electrophoretic recovery of the protein from the picrate, electrophoresis of the protein, and solvent fractionation. The final active fraction, CB-65A, contained only a trace of carbohydrate as shown by chemical tests. The present paper describes the isolation of CB-60C and CB-65A and compares their chemical and immunological properties with those of CS-60C from cottonseed.

Experimental

Apparatus.—The high voltage electrophoresis apparatus described and illustrated in papers IV[5] (Fig. 1) and VI[4] of this series was used except that 250, 125, 50 or 25 ml. cells

(1) (a) Not copyrighted. (b) For Article VIII of this series see Spies and Coulson, THIS JOURNAL, **65**, 1720 (1943).

(2) First demonstrated by Heidelberger and Avery, *J. Exptl. Med.*, **38**, 73 (1923).

(3) The possible non-protein nature of allergens is discussed by Coca, Walzer and Thommen, "Asthma and Hay Fever in Theory and Practice," Charles C. Thomas, Baltimore, 1931, pp. 734 *et seq*; also Vaughn, "Practice of Allergy," C. V. Mosby Co., St. Louis, Mo., 1939, p. 607.

(4) Spies and Umberger, THIS JOURNAL, **64**, 1889 (1942).

(5) Spies, Bernton and Stevens, *ibid.*, **63**, 2163 (1941).

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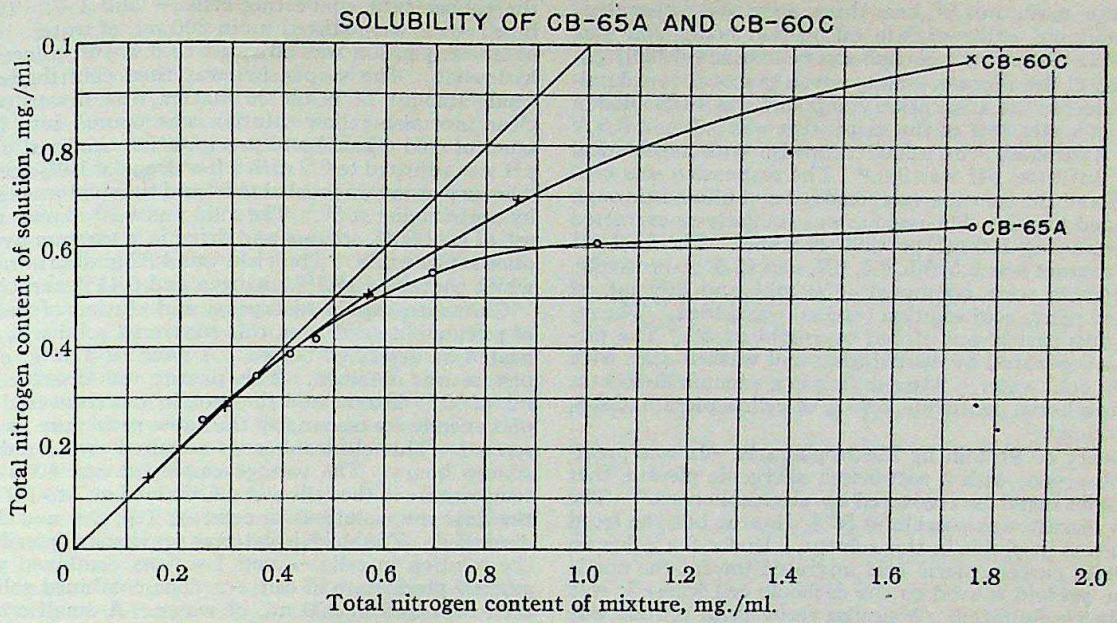

Fig. 1.—Solubility curves of CB-60C and CB-65A: weighed quantities of the protein fractions were placed in glass stoppered tubes. Samples of CB-60C were dissolved in 1.5 ml. of 0.05 *M* acid potassium phthalate buffered at *p*H 5.0. One ml. of absolute ethanol was added to each solution. Samples of CB-65A were dissolved in 0.75 ml. of the same buffered solution and 0.75 ml. of absolute ethanol was added to each. The tubes were fastened in a larger stoppered tube and the suspensions were equilibrated by slowly rotating the tubes in a water-bath at 5 ± 0.1° for at least twenty hours. The excess solid collected on the walls of the tubes during equilibration, leaving a clear supernatant solution, which was decanted and analyzed for total nitrogen content.

were employed, depending on the quantity of material fractionated. Cylindrical (10 × 25 mm.) platinum gauze electrodes were used in terminal cells.

Preparation of CB-60C.—CB-60C was obtained from CB-1A[6] by an electrophoretic fractionation similar to that used to obtain CS-60C [4] from the cottonseed allergen, CS-1A. That portion of CB-1A which migrated toward the cathode was used as starting material in five successive fractionations. The principle of the procedure has been discussed before[4,5] and, therefore, will not be given in detail here. However, pertinent data are assembled in Table I. In the initial fractionation a solution of 15.3 g. of CB-1A dissolved in 200 ml. of water was used. In each fractionation the starting solution was placed in cell 2— of a 6-cell apparatus and an equal volume of distilled water was placed in each of the other cells. The volumes of the cells used were 250, 125, 50, 50 and 25 ml. for fractionations numbered one to five, respectively. Direct current at voltages ranging from 2500 to 7500 was employed. Temperature within the cells was maintained at 15 to 25°. Anodic and cathodic fractions were precipitated by pouring the respective solutions into five volumes of ethanol followed by adjustment of the *p*H to 6.0–6.5 with dilute acetic acid or sodium hydroxide. Fractions, separated by centrifuging, were dried in a vacuum over phosphorus pentoxide. The dried fractions were ground to pass a 100-mesh sieve and were equilibrated with air before analysis.

TABLE I

DATA CONCERNING THE ISOLATION OF CB-60C BY ELECTROPHORETIC FRACTIONATION OF 15.3 G. OF CB-1A

Fractionation No.	*p*H Range[a] Anodic[b]	Cathodic[c]	Yield, g. Anodic	Cathodic	Carbohydrate content,[e] % Anodic	Cathodic
1	2.80–5.40	6.02–11.3	5.92	8.13	4.15	1.61
2	4.39–5.64	6.31– 9.57	3.11	3.27	1.94	0.97
3	4.98–5.68	6.51–10.1	0.86	1.89	1.09	.73
4	4.68–6.70	7.39–10.5	0.80	0.78	0.80	.55
5	4.90–7.43	8.12–10.0	0.26	0.34[d]	0.51	.47

[a] The *p*H of solutions was determined with a Beckman *p*H meter. [b] The anodic *p*H range is for solutions taken from cells +, 1+ and sometimes 2+. In each case the anodic fraction was isolated from the combined contents of these cells. [c] The cathodic *p*H range is for solutions taken from cells —, 1—, 2— and sometimes 2+. In each case the cathodic fraction was isolated from the combined contents of these cells. [d] This fraction was designated CB-60C. [e] Percentages are on an ash and water free basis.

Picrate Formation.—A 10-g. composite sample, consisting of 3.6 g. of CB-1A and 6.4 g. of anodic fractions of CB-1A (obtained in preparing CB-60C), was dissolved in 200 ml. of water. To the solution was added 300 ml. of a saturated water solution (25°) of picric acid. The resulting suspension was stored overnight at 5° and the picrate was separated by centrifuging at 5°. The yellow picrate was washed once by stirring it up with 75 ml. of cold water followed by centrifuging. The solid (CB-3) was dried in a vacuum over phosphorus pentoxide. The yield of CB-3 was 12.43 g.

Chromatographic Adsorption.—CB-3 (12.43 g.) was dissolved in 1500 ml. of 50% ethanol (volume concentration) by warming and stirring. The slightly turbid solution, obtained by filtering, was passed slowly through a 44 × 135 mm. column of activated aluminum oxide (Brockmann).[7] The column was washed with 100 ml. of 50% ethanol. The picrate was adsorbed in a well-defined 30 mm. layer at the top of the column. Two smaller 2-mm. layers formed

Preparation of CB-65A.—CB-65A was obtained from CB-1A by a prolonged series of procedures involving chromatographic adsorption of the picrate, electrophoretic recovery of protein from its picrate, electrophoresis of the protein and solvent fractionation.

(6) Isolation and properties of CB-1A from castor beans have been described.[1b] CB-1A contained 18.4% nitrogen, 2.33% sulfur and 3.12% polysaccharidic carbohydrate.

(7) Obtained from Merck and Co., Rahway, N. J.

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under the main one,[8,9] but these were not separated. The aluminum oxide–picrate adsorption compound was removed and dried over phosphorus pentoxide (yield 67 g.).

Elution of the Picrate.—Sixty-seven grams of the aluminum oxide–picrate adsorption compound was suspended in 150 ml. of water (*p*H of the suspension was 5.0) and 0.5 *N* sodium hydroxide was added dropwise with mechanical stirring until the *p*H was 9.0.[10] The suspension was centrifuged and the solution was removed and filtered through a hardened paper. The residue was similarly re-extracted five times using 100 ml. portions of water. The final *p*H of each extract was 9.5, 9.5, 9.5, 9.7, and 10.0, respectively. The extracts were combined (650 ml.) and 300 ml. of saturated picric acid solution (excess) was added. The resulting suspension was stored overnight at 5°. The picrate was separated by centrifuging and washed once with 50 ml. of cold water. After drying in a vacuum desiccator over phosphorus pentoxide, 6.99 g. of yellow picrate, CB-5, was obtained.[11]

Recovery of Protein by Electrophoresis.—It was previously observed, with a cottonseed allergenic picrate, that the protein could be recovered by electrophoresis.[12] The protein picrate was soluble in 50% dioxane but the freed protein was insoluble in this solvent. Under the influence of a direct current picric acid migrated toward the anode and the protein moved to the cathodic cell where it was partially precipitated. A similar recovery of protein was carried out on CB-5 as follows:[13]

A solution of 6.80 g. of CB-5 in 200 ml. of 50% aqueous dioxane was placed in cell 2− (250 ml. volume) of a 6-cell apparatus. An equal volume of 50% dioxane was placed in each of the other cells. Direct current at 4000 to 5000 volts was applied at the electrodes for twenty-seven hours. The current, initially at 5.1 ma., increased to a maximum of 18.5 ma. The temperature in the cells was kept at 14 to 21°. After the electrophoresis, the orange solution in anodic cell + was removed and replaced with 200 ml. of fresh solvent. Electrophoresis was continued at 4000 volts for twenty-six hours. The orange solution in cell + was again replaced with fresh solvent and electrophoresis continued for twenty-two hours. Solution in cells + and 1+ was then replaced with fresh solvent. Electrophoresis was continued at 5000 volts. At twenty-six, twenty-two and twenty-six hour intervals solvent in cells +, 1+ and 2+ was replaced with fresh solvent. After a final seventy-two hour period at 6000 volts, during which the current was 4.0 to 4.1 ma., the electrophoresis was stopped. Solutions in cells +, 1+, 2+ and 2− were discarded. Solutions in cells − and 1− were decanted and poured into 600 ml. of cold ethanol. Precipitation occurred when the *p*H was adjusted to 6.0–6.5 with dilute sodium hydroxide. The suspension was cooled to 10° and the solid was separated by centrifuging. This solid was combined with the gummy substance which had precipitated in cell − and in the rubber tube connecting cells − and 1−. The combined solids were stirred up in 200 ml. of water. The *p*H of the suspension was adjusted to 6.4 with dilute sodium hydroxide. The suspension was then centrifuged and a small amount of insoluble matter was discarded. The clear brownish-yellow solution was poured into five volumes of cold ethanol and precipitation occurred when the *p*H was adjusted to 6.2 with a few drops of 10% acetic acid. The suspension was cooled to 5° and the solid was separated by centrifuging at 5°. The solid was washed once with 150 ml. of cold 80% ethanol and dried in a vacuum over phosphorus pentoxide. The yield was 4.82 g. of brownish solid which contained 18.7% nitrogen and 0.41% carbohydrate.

Chromatographic adsorption and elution of the 5.77 g. of picrate obtained from this recovered solid was then repeated as described before. A yield of 3.97 g. of eluted picrate was obtained. This picrate was dissolved in 200 ml. of 50% dioxane and the protein was recovered electrophoretically by essentially the same procedure as just described. This electrophoresis required two hundred and sixteen hours. The voltage employed was 4000 and the temperature in the cells was maintained at 7 to 12°. After the final run, solutions in cells +, 1+, 2+ and 2− were discarded. The solid, isolated as previously described from the solution in cells − and 1−, was combined with the gummy precipitate in cell −. The combined solids were then dissolved in 200 ml. of water. A small amount of insoluble matter, separated by centrifuging, was discarded. Solid was isolated from the solution by ethanol precipitation and centrifugation. A yield of 3.01 g. of brownish colored substance containing 18.9% nitrogen and 0.31% carbohydrate was obtained.

Electrophoresis of the Protein.—A solution containing 2.91 g. of solid, recovered from the picrate and containing 0.31% carbohydrate, in 50 ml. of water (*p*H of the solution was 5.65) was placed in cell 2− (50 ml. volume) of a 6-cell apparatus. Fifty ml. of water was placed in each of the other cells and direct current at 3500 volts was applied to the system for twenty-three hours. The temperature was kept at 15 to 19°. A small amount of dark-colored precipitate separated in all of the cells. After the electrophoresis the *p*H of solutions in the cells was: +, 4.94; 1+, 5.30; 2+, 5.44; 2−, 5.93; 1−, 6.33; −, 7.00. The solutions in cells + and − were replaced with 50 ml. of water and electrophoresis was continued at 6000 volts for forty-eight hours at a temperature of 16 to 17°. The *p*H of solution in the cells was then: +, 4.63; 1+, 5.17; 2+, 5.39; 2−, 5.73; 1−, 6.25; −, 7.19.

The solution removed from cell −, after the first run, and the solution from cells −, 1−, 2− and 2+ of the second run were combined (*p*H 5.92). The combined solution, after boiling for fifteen minutes with 1 g. of activated charcoal, was cooled and centrifuged. Then it was filtered through a hardened paper and solid was isolated from the filtrate by ethanol precipitation. A yield of 1.45 g. of solid containing some colloidal carbon was obtained.

Solvent Fractionation and Reprecipitations.—The solid obtained by electrophoresis (1.45 g.) was dissolved in 50 ml. of water and boiled with 300 mg. of carbon. The carbon, removed by centrifuging, was washed with 10 ml. of water. The wash solution was combined with the main solution which was filtered through a Seitz sterilizing pad.[14] Solid was separated from the clear slightly yellow solution by precipitation with five volumes of ethanol. A yield of 1.27 g. was obtained. This solid was dissolved in 50 ml. of water and decolorized with carbon. This combined solution and washings (75 ml.) was passed through a Seitz sterilizing pad and 25 ml. of ethanol was added to the filtrate. This solution was kept at −6° overnight. The white suspension which formed on standing was decanted from a small amount of gummy solid that had collected on the bottom of the container. This residual solid, which contained most of the color, was discarded. The decanted suspension was poured into 350 ml. of cold ethanol. The

(8) A similar layering was observed in a previous study of CS-5, the analogous picrate of the cottonseed allergen, Spies, Coulson, Bernton and Stevens, THIS JOURNAL, 62, 1420 (1940). No difference was demonstrable in clinical activity of the three layers from CS-5. Therefore, in this study the layers were not separated.

(9) The filtrate from the adsorption was evaporated to dryness and 845 mg. of yellow powder (CB-10) was obtained. Clinical tests on castor bean sensitive subjects, using solid obtained from previous similar adsorptions, showed that CB-10 was completely inactive. The solid (CS-10) similarly obtained from cottonseed also showed no clinical activity, and was not antigenic.

(10) A commercially available *p*H meter employing a glass electrode with mechanical stirrer was used.

(11) CB-5 from another similar adsorption contained 18.9% total nitrogen and 31.6% picric acid. See Spies, Bernton and Stevens, THIS JOURNAL, 62, 2793 (1940), for the method used for determining picric acid.

(12) Spies, *ibid.*, 63, 1166 (1941).

(13) The rapid method of recovering the allergenic protein from its picrate by ethanol precipitation at the isoelectric point, reference 8, was not used, in this case, because protein recovered from CB-5 by this method contained 0.93% carbohydrate whereas that recovered by electrophoresis contained 0.41%.

(14) Seitz pads were washed before use by filtering through them 100 ml. of boiling water and 130 ml. of cold water to remove traces of soluble carbohydrate.

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resulting suspension was cooled to 4° and centrifuged. The solid was washed once with cold 80% ethanol and dried as usual. A yield of 601 mg. of almost colorless material was obtained. This solid was dissolved in 35 ml. of water and stirred at room temperature with 200 mg. of carbon. The carbon was removed and the solid was isolated as usual. A yield of 503 mg. of solid containing 19.0% nitrogen and 0.22% carbohydrate was obtained.

Four hundred and twenty-two mg. of this solid was dissolved in 25 ml. of water. The practically clear, colorless solution was filtered through a washed hardened filter paper into a 250 ml. conical centrifuge cup. To this solution was added 8.3 ml. of ethanol. The solution, which remained clear at room temperature, was cooled at −7° for three hours. The resulting suspension was centrifuged at −7°. The supernatant solution was discarded. The solid was washed once with 25 ml. of cold 80% ethanol and dried in a vacuum over phosphorus pentoxide. A yield of 314 mg. of white solid (CB-65A) was obtained. This solid was ground to pass through a 100-mesh sieve and equilibrated with air before analysis.

CB-65A was completely soluble in water. Results of color tests on a 1% solution of CB-65A were: pinkish biuret, deep purple ninhydrin, positive Millon, and Benedict test for reducing sugars, negative.

Determination of Carbohydrate.—Carbohydrate was determined on protein fractions by the orcinol method of M. Sørensen and Haugaard[15] as modified by Heidelberger and Kendall.[16] Galactose, $[\alpha]^{20}D$ +79.7; *C*, 3.00 g./100 ml., was used as a standard and color comparison was made with a Duboscq colorimeter. Test showed that no color (blank) developed on heating protein fractions in the acid solution without orcinol.

Carbohydrate in CB-65A was determined by the orcinol method, using a photoelectric colorimeter for measuring the color developed. Twenty-eight mg. of CB-65A was placed in a 125-ml. Erlenmeyer flask with 1.0 ml. of water, 2.0 ml. of a 2% orcinol solution in 25% sulfuric acid, and 15.0 ml. of 60% sulfuric acid. The solution was heated in a water-bath, in the dark, at 80° for twenty-five minutes. After cooling at −7° the solution was warmed to room temperature and the intensity of the color was read on an Evelyn photoelectric colorimeter using filter No. 520. The reagent (blank) contained 1.0 ml. of water, 2.0 ml. of the orcinol reagent and 15.0 ml. of 60% sulfuric acid. Negligible color developed when a blank was run on a solution containing 27.8 mg. of protein,[17] 1.0 ml. of water, 2.0 ml. of 25% sulfuric acid and 15.0 ml. of 60% sulfuric acid. The carbohydrate content of CB-65A, calculated from color readings in comparison with the curve obtained with solutions containing 0.01, 0.05, and 0.10 mg. of galactose was 0.11%.

A Molisch test on a 1% solution of CB-65A, while difficult to read, was considered doubtfully positive.

Comparison of Antigenic Potency of CB-1A and CB-65A, Using Guinea Pigs.—Comparison of CB-1A and CB-65A with regard to the median sensitizing dose (SD-50) and the median lethal dose (LD-50) in previously sensitized guinea pigs, was made from dosage-response curves according to the method of computation of Bliss.[18] The Bliss method, originally developed for the evaluation of toxicological studies, has been adapted to the quantitative comparison of antigenic potency of cottonseed allergenic fractions.[19]

The SD 50's of CB-1A and CB-65A were 63.6 ± 13γ and 746 ± 240γ (on ash and water free basis), respectively. From the complete dosage response curve the LD 50 of CB-1A was found to be 2.38 ± 0.36γ. Owing to the limited quantity of CB-65A available the mortality ratio was determined at only the critical level. Each of 10 guinea pigs (previously sensitized with 1.0 mg. of CB-1A) was injected intravenously with 2.7γ of CB-65A. The mortality ratio was six fatal to four non-fatal anaphylactic reactions. This mortality ratio was identical with that previously observed when similarly sensitized animals were injected with 2.7γ of CB-1A. The shocking capacity of CB-65A is, therefore, very close to that of CB-1A.

(15) M. Sørensen and Haugaard, *Comp. rend. trav. lab. Carlsberg*, **19**, no. 12 (1933).
(16) Heidelberger and Kendall, *J. Immunol.*, **30**, 267 (1936).
(17) This sample was an intermediate fraction obtained from CB-1A.
(18) Bliss, *Ann. Appl. Biol.*, **22**, 134 (1935); **22**, 307 (1935).
(19) Coulson and Spies, *J. Immunol.*, **46**, 367 (1943).

Discussion

Results of elementary analyses and some properties of CB-65A and CB-60C are compared, in Table I, with those of the analogous protein fraction CS-60C, from cottonseed. The nitrogen content of CS-60C was higher than that of CB-60C or CB-65A, probably because of the higher proportion of arginine in the cottonseed allergen.[1b] Carbon and hydrogen contents of the three fractions were of the order of magnitude usually found in proteins. Like CS-60C, both CB-60C and CB-65A were levorotatory. There was, however, no marked difference between the rotatory power of CB-60C and CB-65A. This indicated that changes which might have occurred in CB-65A as a result of the more drastic fractionation had not taken place in that part of the molecule which determines optical rotation. The solubility curves of CB-60C and CB-65A, Fig. 1, indicated that neither was chemically homogeneous. CB-65A, however, was more nearly homogeneous, by this criterion, than was CB-60C.

Eighty-seven per cent. of the nitrogen of CS-60C was precipitable by trichloroacetic acid (TCA) in contrast with only 27% for CB-60 and none for CB-65A. No radical change in constitution or composition of CB-60C appeared to have occurred as a result of fractionation because 22.5% of the nitrogen of precursor fraction CB-1A was precipitable by TCA. However, some change appeared to have occurred in CB-65A either by molecular rearrangement as a result of the drastic fractionation or by the

TABLE II

COMPARISON OF CHEMICAL COMPOSITION AND PROPERTIES OF CB-65A AND CB-60C WITH CS-60C[a]

Determination[b]	Fraction CB-65A	CB-60C	CS-60C
Nitrogen	19.0	19.1	20.4
Nitrogen pptd. by 5% trichloroacetic acid at 20 ± 0.1°[c]	0.0	26.7	86.6
Carbon	47.6	50.1	48.2
Hydrogen	6.95	6.36	6.58
Sulfur[d]	2.57	2.53	2.35
$[\alpha]^{20}D$ 1% water solution	−49.5	−45.0[e]	−140

[a] The carbohydrate-free allergenic fraction, CS-60C, obtained from cottonseed has been previously described (ref. 4). [b] All analyses are expressed on an ash- and water-free percentage basis. CB-65A and CB-60C contained 1.0 and 0.13% ash and 7.30 and 7.09% water, respectively. Analyses were made by micro methods. [c] See Paper IV of this series, Table I, for the method used. [d] In precursor fractions cystine sulfur accounted for 90% of the total sulfur. [e] Optical rotation of CB-60C was determined with a 2% water solution.

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TABLE III

COMPARISON OF THE THRESHOLD QUANTITY OF CB-65A AND CB-1A REQUIRED TO PRODUCE POSITIVE PASSIVE TRANSFER REACTIONS USING SERUM FROM A CASTOR BEAN SENSITIVE SUBJECT[a]

Quantity of fraction injected.[b] Millimicrogram, mγ[c]	Recipients[d] (wheal diameter in mm.) F. F. CB-1A	F. F. CB-65A	M. P. CB-1A	M. P. CB-65A	E. H. CB-1A	E. H. CB-65A
10	12 × 13	13 × 13	16 × 22	16 × 21	16 × 16	16 × 17
1	11 × 12	12 × 12	10 × 12	12 × 18	11 × 12	13 × 15
0.1	10 × 10	10 × 11	9 × 8	9 × 13	10 × 11	11 × 12
0.01	±[e]	±	±	0	±	±

[a] This serum (A. M.) gave positive passive transfer reactions to test with castor bean allergen when diluted $1:10^2$ but not when diluted $1:10^3$; *cf.* Coca and Grove, *J. Immunol.*, **10**, 445 (1925). [b] Quantity of fraction (contained in 0.025 ml. of sterile physiologic salt solution) injected into each sensitized site. [c] *Chemical and Engineering News*, **18**, 491 (1940). [d] Subjects who reacted negatively to cutaneous test with powdered de-fatted castor bean meal and also negatively to intracutaneous test with 0.1 γ of CB-1A were used as recipients. Recipients were uniformly sensitized with 0.05 ml. of serum in each of four sites on the upper arms. All tests of a series were conducted simultaneously. The size of the wheals which formed in fifteen to thirty minutes are in mm. A negative control test was made on the unsensitized skin of the recipient at the time of the passive transfer tests. [e] See Paper VIII, footnote *e* of Table V for comments on the ± reaction.

removal of constituents precipitable by TCA. Whichever possibility occurred CB-65A suffered no demonstrable loss in capacity to produce positive passive transfer reactions as compared with precursor fraction CB-1A. Results of this clinical comparison, Table III, show that 1×10^{-10} g. of both CB-1A and CB-65A produced positive passive transfer reactions of equal size. However, alteration in the antigenic potency of CB-65A was demonstrable, using guinea pigs as test animals. The median lethal dose of CB-65A was the same as that of CB-1A but the median sensitizing dose of CB-65A was more than eleven times as great as that of CB-1A.

An interpretation analogous to the conclusions drawn from more exhaustive studies of cottonseed allergenic fractions may explain these observations. From chemical evidence previously presented,[5] it was suggested that the cottonseed allergenic fraction, CS-1A, was a mixture containing principally a specifically active protein and compounds of this same protein chemically combined with varying proportions of polysaccharidic carbohydrate. Later the active, essentially carbohydrate-free protein, CS-60C, was isolated.[4] Antigenic studies on excised uterine muscle from sensitized guinea pigs substantiated the view that carbohydrate did not determine antigenic specificity.[20] Carbohydrate, however, had a marked influence on antigenic potency[21] of fractions separated from CS-1A which, as in the cases of CB-1A and CB-65A, was manifested only in the sensitizing capacity.[19] Thus the median lethal doses of CS-51R[5] and CS-56R,[5] which contained 0.9 and 35.2% carbohydrate, respectively, was 5.61 ± 0.39 γ of nitrogen and 6.75 ± 0.77 γ of nitrogen, respectively. The median sensitizing dose of CS-51R was 91.7 ± 15.7 γ of nitrogen or more than eight times as high as that of CS-56R which was 11.0 ± 2.0 γ of nitrogen. Fraction CB-65A retained the same antigenic specificity as characterized CB-1A. Therefore the decreased sensitizing capacity of CB-65A may be owing to the removal of protein-polysaccharidic compounds from CB-1A having relatively high molecular weight and being, therefore, more effective in sensitizing power.

An alternate explanation of the decreased sensitizing power of CB-65A is that sensitization and shock may be produced by different functional groupings in the antigenic molecule. One grouping might therefore be altered without causing change in the other.

It is noteworthy that analogous manifestations of antigenicity in humans (capacity to incite positive passive transfer reactions) and in animals (shocking power) were unaffected by the fractionation required to obtain CB-65A. No comparison of the sensitizing capacity of this fraction for human subjects and animals was attempted because of the hazard of establishing in human subjects a permanent hypersensitivity to castor bean allergen.

Final decision as to whether protein or carbohydrate is responsible for the allergenic specificity of such highly purified substances as CS-60C and CB-65A cannot be made on the basis of chemical tests for carbohydrate. Even if tests for carbohydrate were unequivocally negative the possibility would still remain that sufficient carbohydrate was present to produce clinical reactions. As shown in Table III, solutions of CB-65A containing 4.0×10^{-9} g./ml. were clearly detectable by passive transfer technique. This is beyond the sensitivity of chemical tests on solutions of pure sugars. If the activity of CB-65A were owing to the 0.1% carbohydrate indicated by the orcinol method, then the concentration of active substance in CB-65A detectable by passive transfer would be 4.0×10^{-12} g./ml. At present there is no basis for accepting either 4.0×10^{-9} or 4.0×10^{-12} g./ml. as the approximate sensitivity of a castor bean allergenic preparation by the passive transfer technique. More decisive than chemical tests is the fact that CB-1A, which contained at least thirty times as much carbohydrate as did CB-65A, was not

(20) Coulson, Spies and Stevens, *J. Immunol.*, **46**, 347 (1943).

(21) Antigenic activity of a compound consists of two measurable manifestations, capacity to sensitize and capacity to shock.

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demonstrably more effective in producing passive transfer reactions, or in shocking sensitized guinea pigs.

The obvious fact that biological tests on castor bean allergenic preparations are more sensitive than chemical tests for a given constituent provides justification for having employed the involved procedures used to isolate CB-65A. That CB-65A was obtained by such prolonged, varied, and drastic fractionation must be regarded as substantiating evidence that its activity is inherent and not owing to the presence of a difficultly removable contaminant. Osborne, Mendel and Harris[22] used similar reasoning in deciding that the powerful toxic action of ricin, from castor beans, was inherent in the albumin fraction exhibiting maximum toxicity and not owing to a difficultly removable contaminant.

Summary

An essentially carbohydrate-free allergenic protein, CB-65A, has been isolated from fraction CB-1A from castor beans by a prolonged series of procedures involving chromatographic adsorption of the picrate, electrophoretic recovery of the protein from its picrate, electrophoresis of the protein, and solvent fractionation. Elementary analyses and properties of CB-65A are compared with those of an analogous fraction CS-60C from cottonseed.

Positive passive transfer reactions were produced by 1×10^{-10} g. of CB-65A. Fraction CB-65A was antigenic as shown by tests using guinea pigs. CB-65A was as potent as precursor fraction CB-1A in producing passive transfer reactions and in shocking guinea pigs, but its sensitizing capacity was approximately one-eleventh that of CB-1A. Available evidence indicates that the principal allergenic and anaphylactogenic specificities of both CB-1A from castor beans and CS-1A from cottonseed are inherent in the essentially carbohydrate-free protein fractions CB-65A and CS-60C obtained from them.

(22) Osborne, Mendel and Harris, *Am. J. Physiol.*, **14**, 259 (1905).

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[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

The Action of Ultraviolet Light upon Cellulose. I. Irradiation Effects. II. Post-Irradiation Effects[1]

BY ROBERT A. STILLINGS[2a,b] AND ROBERT J. VAN NOSTRAND[2a,3]

Irradiation Effects[2a,b]

Although a number of studies of the effect of ultraviolet light on cellulose have been reported, the results are in many ways contradictory and incomplete, especially with respect to the role of oxygen and the mechanism of the reaction. The objectives of this investigation were to clear up existing discrepancies and to gain information as to the reaction mechanism.

Apparatus, Materials and Methods

Irradiation Apparatus.—The apparatus used in this investigation (Fig. 1) consisted of a gas purification train, an exposure chamber with a magnetic stirrer and capable of being evacuated, a mercury vapor lamp, and a gas analysis train with provision for the quantitative estimation of water, carbon dioxide, formaldehyde, hydrogen, carbon monoxide and organic combustibles.

The gas used as the atmosphere surrounding the cellulose sample during the experiment was passed first through a calibrated flowmeter of the orifice type. The gas line leading from the flowmeter had a side connection leading to a bubbler, in which the water level was maintained about two inches above the gas outlet. This side tube served as a safety valve, never permitting the gas pressure in the exposure chamber to rise above two inches of water. From the flowmeter, the gas passed through a calcium chloride tower to remove water vapor, a copper gauze furnace to remove oxygen, an Ascarite–Anhydrone bottle to remove carbon dioxide and the last traces of water vapor and, finally, through a three-way stopcock into the exposure chamber. The copper gauze furnace was of the type described by Savage and Ordal[4]; it consisted of 40-mesh copper wire gauze wound on a Calrod heating element (General Electric Company), the assembly being encased in a tight-fitting Pyrex tube. When oxygen was used as the gaseous atmosphere, the furnace was turned off; otherwise, the gas received the same purification treatment.

The outer shell of the exposure chamber consisted of an open-top brass cylinder 2.25 inches high by 10.25 inches in diameter (inside dimensions). Inside of this was a concentric, rotatable, open-top brass cylinder 1.5 × 10 inches (outside dimensions) supported on ball bearings. Two pieces of soft iron were fastened to the bottom of the inner cylinder, so that it might be turned by a motor-driven electromagnet rotating in a horizontal plane below the outer shell. Direct current was fed to the coils of the magnet by means of slip rings, about 50 watts being required for satisfactory operation of the agitator. The cellulose was placed in the inner cylinder. When the latter rotated, the material was mixed by stationary plows attached to the upper rim of the outer shell. The plow holder was removable, allowing the inner cylinder to be taken out. A mercury-in-glass thermometer, shielded from direct radiation, was attached to the plow holder. To keep the temperature down during irradiation, a fan blew air over the exposure chamber.

The cover consisted of four pieces (each 5.625 inches square) of Vycor high-silica ultraviolet-transmitting glass (Corning Glass Works), sealed in place with beeswax–

(1) Original manuscript received December 14, 1942.

(2) (a) A portion of a thesis submitted in partial fulfillment of the requirements of The Institute of Paper Chemistry for the degree of Doctor of Philosophy from Lawrence College, Appleton, Wis. This work was carried out under the direction of Emil Heuser. Presented before the Division of Cellulose Chemistry at the 106th Meeting of the American Chemical Society, Pittsburgh, Pa., Sept., 1943.

(2) (b) Present address, Kimberly-Clark Corporation, Neenah, Wis.

(3) Present address, Brown Co., Berlin, N. H.

(4) Savage and Ordal, *Science*, **91**, 222 (1940).

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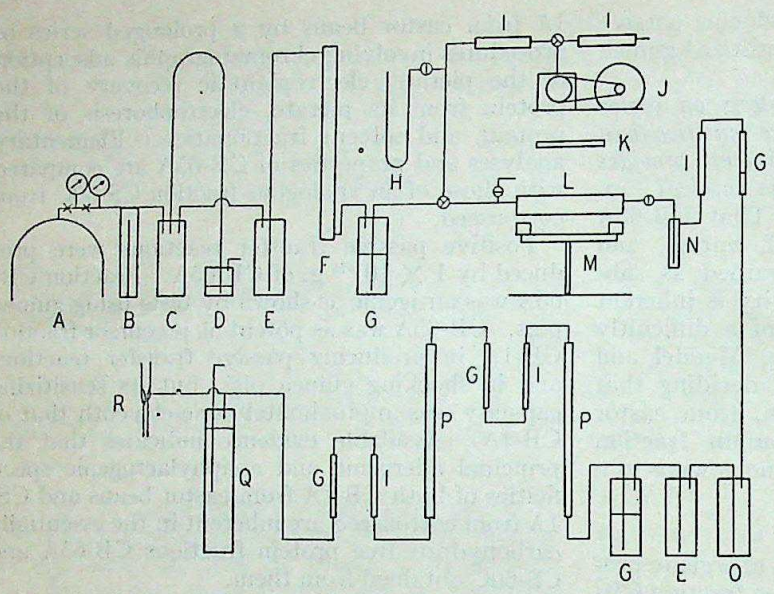

Fig. 1.—Schematic diagram of irradiation apparatus: A, nitrogen tank; B, flowmeter; C, trap; D, bubbler; E, $CaCl_2$ tube; F, copper gauze furnace; G, ascarite–anhydrone tube; H, manometer; I, anhydrone tube; J, Cenco pump; K, Uviarc lamp; L, exposure chamber; M, electromagnet; N, trap; O, NaOI tube; P, combustion tube; Q, pressure regulator (H_2O); R, aspirator.

rosin mixture at the start of each experiment. An auxiliary cover (consisting of a vacuum desiccator lid) was placed on top of the Vycor glass during evacuation, which was carried out with a Cenco Hyvac pump; the pressure was indicated by a closed-tube mercury manometer opening into the evacuation line, which also contained an Anhydrone tube to absorb water vapor.

A General Electric Portable Uviarc outfit, consisting of a UA-26A2 quartz tubular, A. C. Uviarc in a mat aluminum reflector, was used as the source of radiation. Technical data for this 360-watt discharge tube have been given by Johnson and Webster.[5] In all the experiments the distance from the discharge tube to the glass cover of the chamber was eight inches.

The gas emerging from the exposure chanber was passed through a glass-wool trap to remove any entrained particles of cellulose, through an Anhydrone tube for the estimation of water, an Ascarite–Anhydrone tube for the estimation of carbon dioxide, and an alkaline solution of standard iodine for the estimation of formaldehyde or other easily oxidizable substances. The mixture of gases then passed through a calcium chloride bottle to remove water, an Ascarite–Anhydrone bottle to remove any carbon dioxide and the last traces of water, and into the first cupric oxide-filled combustion tube. This tube was maintained at 260–270° for the combustion of carbon monoxide to carbon dioxide and hydrogen to water, which were estimated by absorption in Anhydrone and Ascarite–Anhydrone tubes. The gas was then passed into the second cupric oxide-filled tube, which was maintained at about 800° for the combustion of organic matter to carbon dioxide and water (estimated as before). The pressure drop through the gas analysis train was compensated by a pressure regulator connected to the end of the train, thus maintaining the pressure in the exposure chamber at the desired value.

The procedure followed in making a run on cellulose was as follows: The sample, which had been dried at room temperature in a vacuum desiccator over Anhydrone, was introduced into the exposure chamber. The latter was closed and the system evacuated. The cellulose sample was dried either by means of a small electric hotplate beneath the exposure chamber (35–40°) or by radiation from a 250-watt General Electric infrared drying lamp in a gold-plated reflector (60°), while passing through the chamber a current of air or nitrogen dried over Anhydrone. The first method permitted drying of the cellulose to 0.2% and the latter to less than 0.02% moisture (as determined by oven drying at 105°).

When the exposure was to be made in the absence of oxygen, the drying period was followed by repeated evacuation to a pressure less than 0.1 mm. of mercury and admission of purified nitrogen to a pressure of about 200 mm. of mercury. Calculation showed that seven of these cycles were sufficient to eliminate all oxygen which can be removed by the procedure. The entire system, including the gas analysis train, was then swept out by passing purified nitrogen through it for about five hours at a rate of 50 ml. per minute. The infrared lamp was then replaced by the mercury arc and the gas flow was continued at 50 ml. per minute throughout the exposure, except when the absorption tubes were being weighed.

Materials.—Hercules cotton linters, cut to an average fiber length of 0.4 mm. by the Clairemont Waste Manufacturing Co., had the characteristics given in Table I. Purified β-*d*-glucose[6] and β-cellobiose gave specific rotations of $[\alpha]^{0}D$ 20.0° (water, $C = 5.02$) and $[\alpha]^{20}D$ 35.8° (water, $C = 3.82$), respectively.

Tank nitrogen, after passage through the copper gauze furnace, contained about 0.002% by volume of oxygen as determined by the starch-iodine complex.[7]

Analytical Methods.—Copper number (according to Schwalbe), α-cellulose, ash and furfural were determined according to generally accepted methods. The reducing power of the glucose and cellobiose was determined by the method of Auerbach and Bodländer.[8] Staudinger's viscosity method was used to determine the average chain length of the cellulose, employing the apparatus and procedure described by Heuser and Green.[9] In calculating the degree of polymerization, (D. P.), 5×10^{-4} was used as the value of Staudinger's m constant.

Blank Tests.—To ascertain any increase in weight of the gas analysis absorption tubes when nitrogen or oxygen was passed through the system, blank tests were run before and after each exposure to ultraviolet light, and the small increases observed were taken into consideration. In addition, a gas mixture of known composition (consisting of carbon dioxide, hydrogen, carbon monoxide and methane) was allowed to pass through the apparatus while the chamber was being exposed to ultraviolet light and was analyzed as described above. The accuracy was quite satisfactory, and there was no indication that any appreciable interaction of these gases took place under the action of the ultraviolet light.

Standardization.—In all experiments with cellulose, the weight of sample used was 38.87 g. (oven-dry basis). The temperature of the cellulose during exposure was 45 ± 5°. In all experiments except 8, the rate of gas flow through the apparatus was maintained at 50 ml. per minute. A positive pressure of about one inch of water was maintained in the sample chamber during exposure. The time of irradiation varied between 24 and 336 hours.

(5) Johnson and Webster, *Rev. Sci. Instruments*, **9**, 325 (1938).

(6) Hudson and Dale, THIS JOURNAL, **39**, 320 (1917).

(7) Snell and Snell, "Colorimetric Methods of Analysis," 2nd edition, Vol. I, p. 133, D. Van Nostrand Co., New York, N. Y., 1936.

(8) Auerbach and Bodländer, *Angew. Chem.*, **36**, 602 (1933).

(9) Heuser and Green, *Ind. Eng. Chem.*, **33**, 868 (1941).

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TABLE I

IRRADIATION IN NITROGEN AND EFFECT OF OXYGEN

Expt.	Atmosphere	Length of exp., hr.	Final H_2O, %	Copper no.	Time,[a] days	α-Cellulose, %	Time,[a] days	D. P.[b]	Time,[a] days	Gases evolved millimoles CO_2	Gases evolved millimoles CO
Unexposed			2.82	0.28		96.8		1400			
5	N_2	24	0.22	.42	4	95.1	4	1290	4	0.06	0.08
				.44	103			1070	93		
10	10% O_2	24	.00	.58	4–5	92.2	4–5	950	50	.18	.17
9	20% O_2	24	.02	.78	4–5	90.0	4–5	870	57	.22	.22
6	O_2	24	.24	1.49	4–5	82.9	4–5	740	85	.39	.37
Blank	O_2	22	.28	0.29	..	..	..	..	..	..	..
4	N_2	96	.00	.65	7	92.6	7	1040	16		
				.80	97	88.6	108	930	35	.24	.39
								870	84		
								860	113		
8	N_2	96	.30	.70	11	91.4	11	1050	12		
								840	63	.34	.44
								860	88		
2	N_2	48	.19	.50	8	93.8	8	1020	64	.12	.15
								970	146		
3	N_2	48	.38	.53	4	93.8	4	1000	71	.21	.22
				.66	131			960	106		
7	H_2O, N_2	48	4.34	.40	17	95.8	17	1260	11		
				.40	95			1210	17	.16	.11
								1230	86		
12	N_2	336	0.09	1.20	20	88.8	20	860	19		
								780	26	.33	.88
								700	39		

[a] The values in the column headed "Elapsed Time" indicate the number of days elapsed between the beginning of the exposure and the determination. The ash content of the unexposed material was 0.086%; the copper content of the ash amounted to not more than 0.4 p. p. m. and its iron content was not more than 16 p. p. m. Where the atmosphere was part oxygen, the rest was nitrogen. [b] D. P. is used to signify degree of polymerization.

Experimental Results

Experiments 4, 5, 6, 8–10, as well as the blank test, in Table I, summarize the results of a series designed to discover the effect of oxygen during the irradiation of cellulose. As will be discussed later in more detail, the specific viscosities as well as the copper numbers and the α-cellulose contents, continued to change for several months after the samples had been removed from the exposure chamber and while they were being stored in stoppered glass bottles. These changes were quite unexpected and were observed incidentally only toward the end of this investigation. Nevertheless, the values quoted in Table I would seem to be fairly comparable, either because the analyses (copper number and α-cellulose) were made after approximately the same elapsed time or the elapsed time was sufficiently long to insure approach to the ultimate values (D. P.).

The fact that the blank experiment in the presence of oxygen without irradiation caused no significant increase in the copper number of the cellulose, eliminated heating (43°) during drying and exposure and also the presence of oxygen in itself as the cause of the effects observed in the other experiments. These effects, measured by changes in degree of polymerization, copper number, α-cellulose, and by the evolution of gases must, therefore, have been photochemical, and experiments 4, 5 and 8 show them to be considerable, even in samples exposed in nitrogen with all possible precautions to exclude and remove oxygen. When oxygen-containing atmospheres were used (Experiments 10, 9 and 6), the rate of degradation of the cellulose increased over the whole range of oxygen concentration.

In spite of the precautions to remove and exclude oxygen during the exposures in nitrogen, significant amounts of oxygen could have been present in the nitrogen atmosphere or the cellulose. A comparison of experiments 4 and 8 eliminates the first possibility. The two experiments were identical, except that in experiment 4 nitrogen was passed continuously through the system, whereas in experiment 8 the nitrogen-filled chamber was sealed off. If the oxygen in the nitrogen were responsible for the degradation, the effect should have been greater in experiment 4, but this was not the case. In experiment 8, the calculated amount of oxygen introduced with the nitrogen (0.002% by volume of oxygen) was 0.024 millimole or 1.8×10^{-4}%, based on the cellulose. To prepare an oxycellulose of the same copper number as exposed sample 8 by other methods would require at least 0.05% oxygen, or 280 times the amount which was present in the nitrogen in experiment 8.

If oxygen retained by the cellulose had been

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the sole cause of the degradation, the rate of reaction would be expected to be maximum at the beginning and fall off to zero as the oxygen was consumed. This was not the case. During experiment 12, the rates of evolution of water, carbon dioxide, and carbon monoxide actually *increased* continuously during the course of the irradiation.

Kinetics and Mechanism of the Reaction in Nitrogen.—A study of the kinetics of the reaction was based upon experiments 2–8 and 12 of Table I.

Decrease in Chain Length.—For the early stages of a chain-splitting reaction, Sakurada and Okamura[10] developed the following equation relating the average number of scissions per molecule to the change in average degree of polymerization as determined by the viscosity method.

$$P^1/P = (2/S^2)(S - 1 + C^{-s})$$

where P = original D. P.
P^1 = D. P. after the reaction, and
S = average number of scissions per molecule.

Although the application of this equation to the present case would appear to be somewhat hampered by the instability in which the samples are left after irradiation, an attempt was made to calculate S by taking P^1 as the ultimate D. P.—*i. e.*, that reached after the post-irradiation effect had practically come to an end.

If the photolysis proceeded as a first order reaction, the rate of cleavage (rate of change of S) should have been essentially constant over the limited range studied. Figure 2 is a comparison of the actual rate of decrease of chain length with a theoretical, first-order rate chosen to make the curves intersect at the two-day mark. It is apparent that the reaction cannot be regarded as first-order, as the actual rate was too fast near the start and became too slow as the degradation progressed.

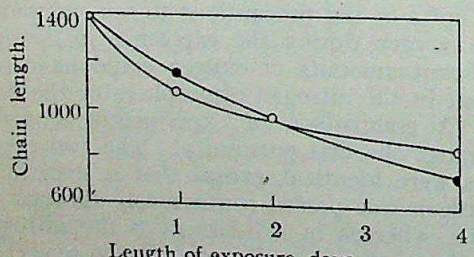

Fig. 2.—Actual (○) and theoretical (●) decrease in degree of polymerization during irradiation in nitrogen.

Possible explanations of this difference are the presence of oxygen in the system at the start of each exposure, and the formation of products of reaction having a higher absorption of ultraviolet light than the original material.

If some oxygen were present at the start of each experiment, the rate of cleavage would be higher at the start and would come to a constant rate only after all the oxygen was consumed. A correction for such an effect might be applied by subtracting a constant from the calculated S values. When 0.45 is used as the constant, the corrected curve is first-order for the first forty-eight hours, but the ninety-six-hour value is still significantly off. Thus, the deviation from the first-order rate cannot be completely explained by assuming the presence of oxygen, although oxygen as a contributing factor is not ruled out. With regard to the second possibility, the irradiated material did indeed show a decreased reflectance in the blue end of the visible spectrum, and indications were that the difference was even greater in the ultraviolet.

A third possibility is that the difference is the result of the presence in cellulose of cross linkages which, according to Steurer,[11] could have undergone cleavage at a faster rate than did the predominating 1,4-glycosidic linkages.

Increase in Copper Number.—The above considerations are equally applicable in explaining the fact that the increase in copper number (increase in reducing groups) proceeded at a decreasing rather than at a constant rate.

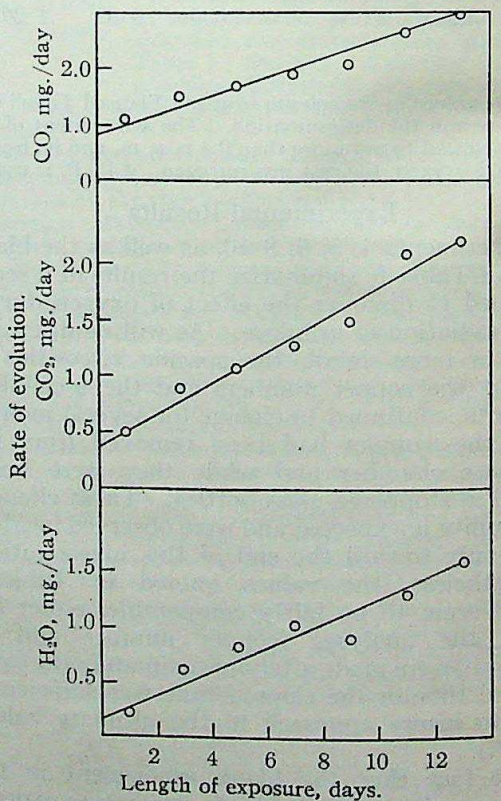

Fig. 3.—Ratio of evolution of gaseous products from cellulose during irradiation in nitrogen.

Formation of Gaseous Products.—Figure 3 shows that the rates of evolution of carbon monoxide, carbon dioxide, and water increased continuously during the course of the longest ex-

(10) Sakurada and Okamura, *Z. physik. Chem.*, **A178**, 289 (1940).

(11) Steurer, *ibid.*, **B47**, 127 (1940); Steurer and Mertens, *Ber.*, **74**, 790 (1941).

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posure made (experiment 12 of Table I). In the case of the first two, the increasing rate indicates that they were the products of secondary reactions or of both primary and secondary reactions. As the curves extrapolate to an appreciable rate at zero time, the latter alternative is more probable. The increasing rate of liberation of water may have been merely a result of the hygroscopic nature of the dried cellulose.

Control experiments were made in which glucose was irradiated for forty-eight hours and cellobiose for one hundred and eight hours. The rates of carbon monoxide and carbon dioxide evolution in millimoles per day were only 0.03 and 0.04 for glucose and 0.02 and 0.02 for cellobiose. As the rates for cellulose were 0.09 and 0.07, respectively (*i. e.*, roughly three times higher), it was concluded that these gases did not result from the photolysis of hemiacetal groups or glycosidic bonds in cellulose. The reducing power of both sugars remained constant to ± 0.2% during irradiation, but water solutions of both showed an increase in light absorption in the ultraviolet range.

Instability of Exposed Samples.—As mentioned above, degradation of the irradiated samples continued after the conclusion of the actual exposure—*i. e.*, during storage in air in screw-top glass bottles. No degradation occurred in the unexposed material stored under the same conditions during the investigation.

A portion of exposed sample 12 stored in nitrogen in the dark showed no decrease in chain of length during a two-week period, whereas the portion stored in air in the light of the laboratory underwent a drop in D. P. from 780 to 700. Two portions of another sample which had been irradiated 48 hours in the nitrogen atmosphere and had a D. P. of 1280 were stored in nitrogen and in air in the light of the laboratory. After six days of storage the sample in nitrogen showed a D. P. of 1310, whereas the sample in air had dropped to 1200. These results seem to suggest that the post-irradiation effects were due to oxidation by atmospheric oxygen. This conclusion is borne out further by the results of an experiment in which the viscosity of the last mentioned sample was determined as soon as possible after irradiation (about one hour's contact with air during the necessary manipulations). The D. P. thus determined was 1280 as compared with the original value of 1400 and with the ultimate D. P. after the post-irradiation effect of 960.

Reaction Mechanism.—If only the reducing end groups were involved in the primary reaction, no appreciable decrease in chain length would result unless the attack continued progressively along the chain, in which case the α-cellulose would show a decrease corresponding to the decrease in D. P. This was not the case. Another indication that the reducing end groups were not appreciably affected is the fact that irradiation of glucose and cellobiose resulted in no measurable change in reducing power.

Other investigators[12] have shown that, in the absence of oxygen, simple alcohols are stable to light of wave length above 200 mμ (lower wavelength limit in the present investigation was 230 mμ). This, together with the fact that no hydrogen was formed during irradiation of cellulose, indicates that photolysis of the alcohol groups did not occur, at least not in the usual manner.

If the decrease in chain length (measured immediately following exposure) was not caused by oxidation effects, it was, in all probability, the result of a photolysis of glycosidic linkages. The fact that the number 1 carbon atom is the only one linked to two oxygen atoms suggests this as the source of the carbon dioxide formed. Whether or not the photolysis of glycosidic linkages occurred as a primary reaction, there must have been some other primary reaction which did not break the chains but left them unstable to atmospheric oxygen, as evidenced by the post-irradiation decrease in chain length. The possibility that, under the action of ultra-violet light, the oxygen was converted into ozone (in which form it is known to degrade cellulose without the aid of ultraviolet light) is ruled out because no ozone could be detected inside the exposure chamber, although the surrounding atmosphere was pregnant with ozone while the lamp was operated.

The question arises whether the other measured changes in the cellulose were concerned in the reaction which led to chain splitting. Some indication may be obtained by comparing the *S* values calculated by the Sakurada equation with the formation of gases and reducing groups expressed as millimoles per millimole of cellulose (227 g. in this case). Table II is a tabulation of such a comparison. There is a fairly good correspondence between the *S* values and the carbon monoxide and dioxide values. This is a strong indication that the formation of these gases was involved in the reaction which led to chain cleavage, one molecule of each gas being produced per scission.

TABLE II

RELATIONSHIP OF ANALYTICAL RESULTS

Expt.	D. P.	*S*	Reducing power,[a] milliequiv.	CO,[a] millimoles	CO_2,[a] millimoles
5	1070	0.87	5.0	0.47	0.35
2	970	1.22	7.9	0.88	0.70
3	960	1.26	13.6	1.29	1.23
4	860	1.70	18.6	2.28	1.40
8	860	1.70	15.0	2.57	1.99
10	950	1.30	13.5	0.99	1.05
9	870	1.65	17.8	1.29	1.29
6	740	2.31	44.3	2.16	2.28
7	1230	0.40	4.3	0.64	0.94

[a] Based on one millimole or 227 g. of cellulose.

(12) Berthelot and Gaudechon, *Compt. rend.*, **156**, 68 (1913); Farkas and Hirschberg, THIS JOURNAL, **59**, 2450 (1937).

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However, the reducing power values (calculated from the increase in copper number) are about ten times the *S* values, corresponding to the production of five aldehyde or similar groups per chain split, which seems improbable. More likely, the reducing groups were formed, at least in part, from some other reaction not ultimately resulting in chain cleavage.

The fact that carbon dioxide and monoxide were formed, necessarily means that anhydroglucose units were decomposed. No change in pentosan content could be detected, but the possibility remains that desoxypentoses or carbohydrate units of fewer carbon atoms were formed.

Post-Irradiation Effect[2a,3]

To establish more firmly the conditions under which the post-irradiation effect occurred, portions of the exposed cellulose samples were analyzed immediately after exposure, whereas the remainder were stored in the desired atmosphere by transferring them—immediately after exposure—to round-bottom flasks which were evacuated, subsequently flushed, filled with purified nitrogen, air, or oxygen and finally sealed. The analysis of the samples was confined to the degree of polymerization, the copper number, and the α-cellulose content. The time of irradiation was, except in one case, ninety-six hours, whereas the storage time varied.

The equipment used in the first part of this investigation was improved in various respects. Particularly, the construction of the irradiation chamber was such that it withstood a considerably higher vacuum than previously employed to remove the air from the system as far as possible. The vacuum amounted to 25–30 microns as read from a Pirani gage.

Evacuation and flushing with nitrogen were repeated five times, after which only 4.38×10^{-17}% of the original atmosphere was present.

For the purification of the tank nitrogen, the copper gauze was replaced by colloidal copper deposited upon diatomaceous earth in accordance with the suggestion made by Meyer and Ronge.[13] In this way, the oxygen content of the tank nitrogen was reduced to as low a value as 3.4×10^{-4} (against 2×10^{-3} in the first part of the investigation).

Because the Uviarc lamp had lost a good deal of its efficiency in the previous experiments, the effect of irradiation was relatively small, as was the post-irradiation effect during storage of the irradiated sample in air at room temperature (Table III, run N2). However, the latter effect was considerably increased when the temperature during storage in air was raised to 70° (run N5) or when the air at room temperature was replaced by oxygen (run N4). Only a small part of the increased post-irradiation effect at 70° was due to the temperature alone, as may be seen from the extent to which an unirradiated sample was attacked when subjected to 70° in air for about the same length of time as was used for storing the irradiated sample (run N3).

(13) Meyer and Ronge, *Angew. Chem.*, **52**, 637 (1939).

TABLE III

CHANGE OF CHARACTERISTICS OF CELLULOSE ON IRRADIATION AND SUBSEQUENT STORAGE IN VARIOUS ATMOSPHERES

Experimental runs	Description	Degree of polymerization	Copper number	α-Cellulose content, %
	Original	1250	0.31	97.5
	Irradiated in nitrogen	1155	.62	94.9
N2	Stored in air for 25 days	1072	.67	..
	Stored in air for 60 days	1079	.61	94.4
	Irradiated in nitrogen	1100	.61	94.8
N5	Stored in air at 70° for 60 days	688	1.07	92.0
N3	Original cellulose, merely heated at 70° for 55 days	1060	0.37	..
	Irradiated in nitrogen	1130	.61	95.1
	Stored in nitrogen for 20 days	1155	.60	..
N4	Stored in nitrogen for 30 days, followed by 10 days in oxygen	904	.68	..
	Same as above, followed by 20 days in oxygen	854	.75	93.2

It is of interest that, even if the effect of temperature on the unirradiated cellulose sample is taken into account, the results show that irradiation in nitrogen had sensitized the cellulose to a far greater extent than could be derived from the drop in degree of polymerization from 1250 to 1155 or from that which occurred when the irradiated sample was stored in air at room temperature (from 1155 to 1072). It is seen also from Table III that the post-irradiation effect becomes practically constant if the oxygen is given sufficient time to act (N4, last two columns).

The irradiation effect from a new and stronger Uviarc lamp (600 as compared with 300-watt)

TABLE IV

CHANGE OF CHARACTERISTICS OF CELLULOSE ON IRRADIATION IN NITROGEN AND SUBSEQUENT STORAGE ALTERNATINGLY IN NITROGEN AND OXYGEN

Experimental Run N6

Description	Degree of Polymerization	Copper number	α-Cellulose Content, %
Irradiated	823	1.25	89.0
Stored, 10 days in nitrogen	787	1.36	89.0
Followed by 5 days in oxygen	665	..	87.3
Followed by 5 days in nitrogen	669	1.43	..
Followed by 23 days in oxygen	565	..	..
Followed by 7 days in oxygen	557	1.72	86.0

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was much greater as seen from the data in Table IV. In addition, it is shown and further illustrated in Fig. 4 that the post-exposure effect could be deferred or produced *ad libitum*, depending upon whether the sample was stored first in nitrogen and then in oxygen, then again in nitrogen, and finally again in oxygen. If sufficient time was allowed for this last phase, the post-exposure effect, as judged from the change in degree of polymerization, came to an end.

In the following series of experiments, irradiation was allowed to take place in oxygen instead of in nitrogen. As would be expected, the irradiation effect was much enhanced under these conditions. The degree of polymerization dropped from 1250 to a value as low as 450, the copper number increased from 0.31 to 5.92, and the α-cellulose content decreased from 97.5 to 56.8.

When the sample irradiated in oxygen was subsequently stored in oxygen for forty days, further drop in the degree of polymerization and increase in the copper number (6.45) occurred. However, when the storage in oxygen was lengthened by ten more days, the degree of polymerization remained practically constant, showing that the post-irradiation effect had come to an end. The data are shown in Table V.

TABLE V

CHANGE OF CHARACTERISTIC OF CELLULOSE IRRADIATED IN OXYGEN AND SUBSEQUENTLY STORED IN OXYGEN

	D.P.
Irradiated in oxygen for 4 days	450
Stored in oxygen for 40 days	320
Stored in oxygen for 10 additional days	333
Irradiated in oxygen for 10 days	272
Stored in oxygen for 10 days	240

This table contains also the data which were obtained when the cellulose was irradiated in oxygen for ten instead of four days (as in all previous experiments) and when the sample thus treated was subsequently stored in oxygen for ten days. The degree of polymerization decreased to 272 on irradiation in oxygen but remained practically unchanged on subsequent storage in oxygen.

The results reported above seem to confirm the previously advanced hypothesis—namely, that two reactions take place during the action upon cellulose of ultraviolet light in the absence of oxygen, one which results in the rupture of glycosidic linkages and another which does not rupture these linkages but leaves them in an unstable condition to oxygen. That these two reactions should take place simultaneously would imply that the glycosidic linkages are attacked to a different extent. This difference is possibly a result of the difference in their accessibility in the micellar system. Thus, the assumption may be made that those glycosidic linkages which belong to chains exposed on the surface are broken down completely, whereas those which belong to

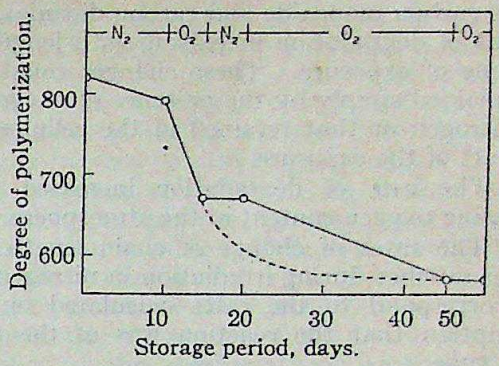

Fig. 4.—Change in degree of polymerization of cellulose previously irradiated in nitrogen and alternately stored in nitrogen and oxygen.

chains located in the interior of the micelles are only weakened. These weakened bonds are then completely ruptured by oxidation, either during irradiation in an oxygen atmosphere or during storage of the irradiated sample in oxygen. In other words, the activity of the oxygen may be eliminated from the irradiation stage and shifted to a subsequent and separate stage. Indeed, the two reactions—the action of oxygen during irradiation and the post-irradiation reaction—seem to be quite alike, the same changes being produced. Likewise, if a portion or all of the oxidation of weakened glycosidic linkages is allowed to take place during irradiation, only part or practically none of it occurs in the post-irradiation stage.

The mechanisms by which a portion of the glycosidic linkages is ruptured while another portion is left in an unstable condition and by which the weakened bonds are subsequently ruptured by oxidation are still obscure. Consideration also will have to be given to the possibility that the cleavage of glycosidic linkages is the result of hydrolysis caused by the small amount of water left in the cellulose and catalyzed by ultraviolet light energy.

Summary and Conclusions

An apparatus has been developed which is suitable for the ultraviolet irradiation of solids in powder form in various atmospheres and which provides for evacuation prior to exposure, continuous mixing and continuous analysis of gaseous products.

The influence of oxygen on the photolysis of cellulose has been studied, as have the kinetics of the reaction in nitrogen. In addition, samples of glucose and cellobiose have been irradiated in a nitrogen atmosphere under the same conditions.

The most important results obtained in the investigation may be summarized as follows.

1. Cellulose irradiated in nitrogen with all possible precautions to remove and exclude oxygen showed considerable degradation (chiefly, a drop in degree of polymerization and α-cellulose content, an increase in copper number and libera-

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tion of carbon monoxide and carbon dioxide), the amount of degradation increasing with lengthening time of exposure. These changes could not be explained simply by the presence of oxygen in the nitrogen or that retained in the cellulose at the start of the exposure.

2. The rate of degradation increased with increasing oxygen content in the atmosphere.

3. The rates of change of chain length and copper number during irradiation in nitrogen did not correspond to the rates calculated on the assumption that the reaction was of the first-order type.

4. Exposure of β-*d*-glucose and cellobiose likewise resulted in the production of carbon monoxide and carbon dioxide, but at a considerably slower rate than in the case of cellulose. No change could be detected in the reducing power of these sugars, but exposed samples showed an increased absorption of ultraviolet light.

5. Cellulose irradiated in the absence of oxygen was left in an unstable state at the conclusion of the exposure—*i. e.*, the changes which the cellulose underwent during irradiation continued to occur during storage when air was present, but ceased when air was absent.

6. The post-irradiation effect was increased by raising the temperature to 70° and by replacing the air in the storage bottles with oxygen. A small portion of the increased post-irradiation effect at 70° was due to the temperature alone.

7. The post-irradiation effect was deferred or produced *ad libitum* by alternating the atmospheres several times between nitrogen and oxygen. If the time of storage in oxygen was sufficiently long, the post-irradiation effect came to an end.

8. Cellulose which had been irradiated in the presence of oxygen still underwent the post-irradiation reaction. However, the effect was smaller and became almost negligible when the time during irradiation in oxygen was extended from four to ten days.

APPLETON, WISCONSIN RECEIVED FEBRUARY 12, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE ILLINOIS INSTITUTE OF TECHNOLOGY]

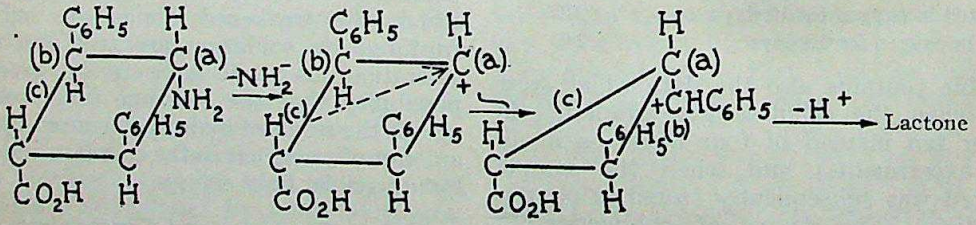
Studies in the Truxillic Acids. I. The Rearrangement of the Zeta-Truxinamic Acids and the General Theory of Molecular Rearrangements[1]

BY IRVING S. GOLDSTEIN[2] AND HERBERT I. BERNSTEIN

A general theory of molecular rearrangements was proposed by Whitmore[3] in 1932. The only essential modification since then has been that of the Walden inversion occurring on the carbon receiving the migrating group.[4]

Virtually all aliphatic rearrangements studied thus far fit into this theory. The evidence has been summarized briefly in a recent paper.[5]

It was further shown in that publication[5] that the amino acids of the truxillic and truxinic acid series lend themselves admirably for testing the stereochemical implications of the theory. Thus ε-truxillamic acid yielded the lactone of 1^c-carboxyl-2^c-benzoxyl-3^t-phenylcyclopropane upon treatment with nitrosyl bromide.[6] The theory would illustrate this as follows



The amino group is removed with its octet of electrons. Carbon a makes up for the resulting deficiency by taking a pair from the adjacent atom b, the pair constituting the bond c. The shifting electrons join carbon a opposite to the position held by the amino group. Thus carbon atom b, with only six electrons, is below the plane of the new cyclopropane ring. The missing electrons are supplied to b by a carboxyl oxygen and result from the loss of the carboxyl H, thus forming a lactone. The various steps need not be consecutive, but may all occur together, somewhat as in S_N2 substitution. Similar degradations of α-truxillaminic,[7] γ-truxillaminic,[8] β-truxinaminic,[9] and δ-truxinaminic acids[9] yielded isomeric cyclo-

(1) Presented before the Organic Division of the American Chemical Society, Detroit, Mich., April, 1943.

(2) Submitted by Irving S. Goldstein in partial fulfillment of the requirements for the degree of M.S. Now serving in the U. S. Navy.

(3) Whitmore, THIS JOURNAL, **54**, 3274 (1932).

(4) Bartlett and Pockel, *ibid.*, **59**, 820 (1937).

(5) Bernstein and Wallis, *J. Org. Chem.*, **7** 261 (1942).

(6) Stoermer, Neumarker and Schmidt, *Ber.*, **58**, 2707 (1925).

(7) Stoermer and Keller, *ibid.*, **64**, 2783 (1931). See also ref. 8.

(8) Stoermer, Schenck and Pansegrau, *ibid.*, **60**, 2575 (1927).

(9) Stoermer and Asbrand, *ibid.*, **64**, 2793 (1931).

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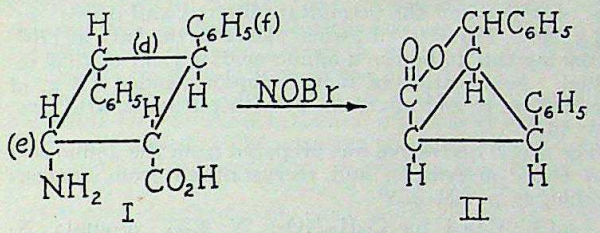
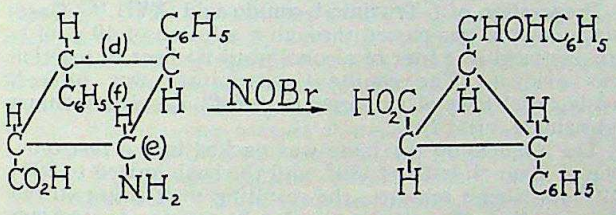
propane compounds whose configurations are explained readily by the general theory.

All of the possible stereoisomeric 1-carboxyl-2-benzoxyl-3-phenylcyclopropanes have been prepared and characterized by Schenck.[10] In this paper he also notes the fact that ζ-truxinic-a-amino acid (I) yielded a cyclopropane in which all three groups were *cis* (II), while the b-amino acid (III) gave an unknown bromo acid and a hydroxyl-acid having the phenyl group *trans* (IV).



I II

ζ-Truxinic-*b*-amino acid



III IV

ζ-Truxinic-*a*-amino acid

No experimental facts were given, and the only reference was to an unpublished Doctoral Dissertation.[11] These results can be explained by the theory illustrated above only by the additional assumption that the rearrangement is accompanied by an inversion of the ring-carbon bearing the phenyl group in the final cyclopropane compound. The pair of electrons making bond d (I) must shift onto carbon atom e. Therefore, regardless of whether retention or inversion of configuration occurred during the rearrangement, the a-amino acid should have yielded a cyclopropane with the phenyl f and carboxyl groups *trans* to each other, since neither of these groups is affected by the various changes. The b-amino acid (III) similarly should have yielded a three-membered ring with the phenyl and carboxyl groups *cis*. In other words, assuming inversion at e, we might have expected the a-amino acid (I) to yield IV, while the b-amino acid (III) should have given II.

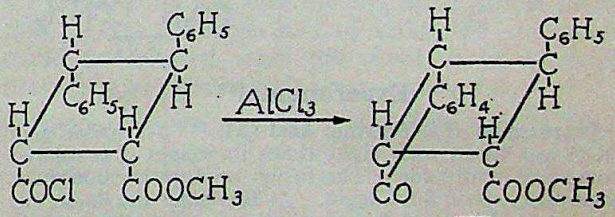
The amino acids (I and III) have been prepared and are newly described in the present paper. They were degraded with both nitrosyl bromide and nitrous acid. ζ-Truxinic-a-amino acid (I) gave principally the lactone (II) upon treatment with both nitrosyl bromide and nitrous acid. From nitrosyl bromide and the b-amino acid (III) a good yield of an unknown bromo-acid was obtained, but no acid IV. Only oils were obtained from nitrous acid and III. The degradation of the a-amino acid (I) to II checks the statement of Schenck,[10] and cannot be explained merely by the general theory of molecular rearrangements.

The above conclusions are dependent upon the correctness of the structures. All eight 1-carboxyl-2-benzoxyl-3-phenylcyclopropanes have been prepared and their configurations characterized[10]. Furthermore, if they were confused, then the degradation experiments previously run with other truxillic and truxinic acids[5] would no longer substantiate the general theory.

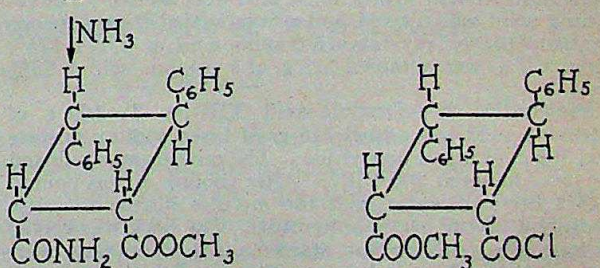
There also seems to be little doubt of the correctness of the configurations assigned to the amino acids. These are based on the reactions of the two isomeric ζ-truxinic-methyl ester-acid chlorides with aluminum chloride.[12] The compound which formed a truxonic (IX) ester was called ζ-truxinic-a-acid chloride-b-methyl ester (V). No ketonic compounds resulted from similar treatment of the isomer (VI). It is possible, but improbable, that the above authors[12] confused the a and b acids.

The configurations of the ζ-truxinamidic acids then were deduced from the conversion of both the a-amido acid (VII) and the ζ-truxinic-a-acid chloride-b-methyl ester (V) to the same a-amido acid-b-methyl ester (VIII).

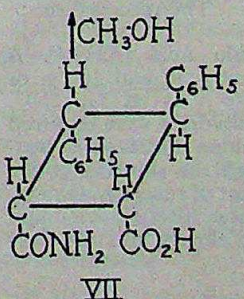
As was shown in a previous publication,[5] it may be safely assumed that the amino acids have the same configuration as the amido acids from which they were prepared by the Hofmann degradation.



V IX



VIII VI



VII

(10) Schenck, *J. Prakt. Chem.*, **134**, 215 (1932).

(11) Rasenack, Dissertation, Rostock, 1928.

(12) Stoermer and Klockmann, *Ber.*, **58**, 1164 (1925).

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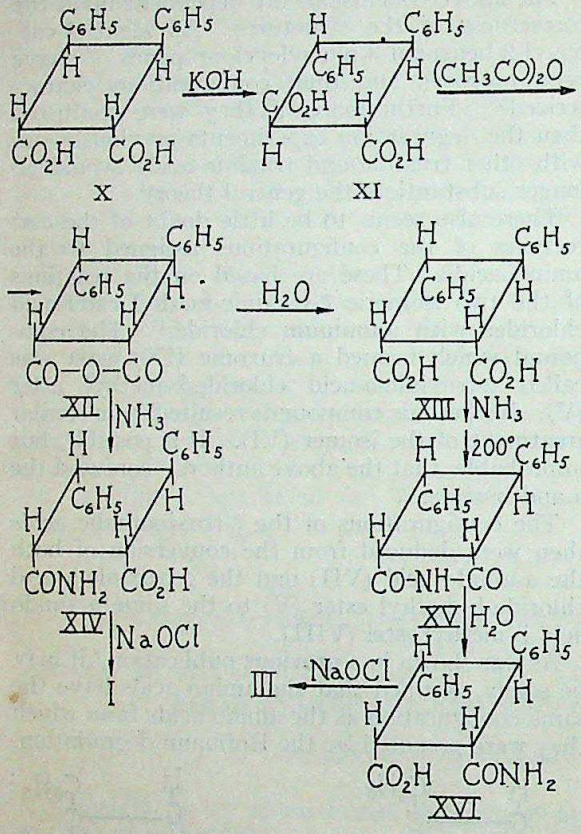
The flow sheet for the preparation of amino acids I and III from β-truxinic acid (X) is given below.



Experimental[13]

Preparation of δ-Truxinic Acid (XI).[14]—β-Truxinic acid (X)[15] was fused with eight times its weight of powdered potassium hydroxide. The fusion mixture became fluid, then pasty, then fluid again. At this point the flame was removed. The cooled fusion mixture was dissolved in water, and ice and hydrochloric acid were added. The resulting solid was filtered and recrystallized from aqueous methanol to yield crystals of δ-truxinic acid, m. p. 174–175°. From 127 g. was obtained 118 g. of δ-truxinic acid, a 93% yield.

Preparation of ζ-Truxinic Acid (XIII).[14]—To 169 g. of δ-truxinic acid was added 145 g. of fused sodium acetate and 365 g. of acetic anhydride. The mixture was refluxed for three hours at 200–210°. After cooling, it was poured into 2 liters of water, and the mixture heated to cause hydrolysis of the acetic anhydride. The flask was cooled as soon as a reaction had started. After standing overnight, the resultant solid was filtered off and dried, wt. 95.5 g. This was recrystallized from aqueous methanol to give crystals of m. p. 235–236° (d.). The recorded m. p. of ζ-truxinic acid is 239°.[12]

Preparation of ζ-Truxinic-a-amido Acid (XIV).[12]—A solution of 46.5 g. of crude ζ-truxinic acid and 140 g. of acetic anhydride was heated for two hours at 140–150°. The acetic acid formed and excess anhydride were removed by distillation *in vacuo*, and the residue dissolved in benzene. Ammonia was passed through the solution of the resulting anhydride until no more heat of reaction was evident. The voluminous precipitate was filtered, dried and dissolved in water. The resultant cloudy mixture was filtered until a clear yellow solution resulted. Acidification yielded a precipitate, which when filtered and dried weighed 30.5 g., m. p. 198–200°, yield 66%. Recrystallization from aqueous acetone raised the m. p. to 202–204°; literature,[12] m. p. 204°.

Preparation of ζ-Truxinic-a-amino Acid (I).—The method of Stoermer was used.[5] To 5.0 g. of ζ-truxinic-a-amido acid was added 70 cc. of 0.5 *N* sodium hypochlorite solution, and the resulting solution kept at 38–40° for two hours. It was then carefully neutralized, and made just basic with dilute sodium hydroxide. The small amount of insoluble precipitate was filtered off, and carbon dioxide passed into the clear filtrate. After an hour precipitation was complete and the precipitate filtered and dried; wt. 3.3 g., m. p. 178–180° (d.) when placed in the bath at 170°. Assuming this to be the a-amino acid, a yield of 73% resulted. Acidification of mother liquor yielded 1.2 g. of product, m. p. and mixed m. p. with ζ-truxinic acid 228–233° (d.).

The acetyl derivative was prepared from the amino acid and acetic anhydride, and recrystallized from aqueous alcohol, m. p. 224–225°.

Anal.[16] Calcd. for $C_{19}H_{19}NO_3$: N, 4.53. Found: N, 4.50.

Preparation of ζ-Truxinic-b-amido acid (XVI).[14]—Gaseous ammonia was passed through a solution of 49 g. of ζ-truxinic acid in 1 liter of alcohol until no heat of reaction was evident. The resultant precipitate was filtered, washed with alcohol, and dried to give 42.5 g. of **ammonium ζ-truxinate,** yield 78%.

The ammonium truxinate was packed into a test-tube, placed in an oil-bath at 180°, and the bath heated to 200–210° for fifteen minutes, the resulting melt being stirred occasionally. The tube was cooled, benzene and petroleum ether added, and the mixture thoroughly triturated and filtered. The residue was treated with sodium carbonate solution, and the insoluble material filtered off. This precipitate was recrystallized from alcohol to give **ζ-truxinimide** (XV), m. p. 167–168°; literature,[14] 168–168.5°. From 38.5 g. of ammonium ζ-truxinate fused in seven batches was obtained 20.5 g. of the imide, a yield of 63%. The sodium carbonate solution was acidified to give 8.5 g. of a solid, m. p. 165°. Recrystallization from aqueous alcohol did not change the m. p. The m. p. of pure δ-truxinic acid was 174–175°; mixed with the above solid was 165–168°. The acid fraction was possibly the impure δ-acid.

To 20.5 g. of the ζ-truxinimide was added 150 cc. of 10% alcoholic potassium hydroxide. After five hours of standing, the initially clear solution became a crystalline mass. This was dissolved in 2 liters of water, and the aqueous solution filtered clear. Acidification of the filtrate yielded a precipitate which was filtered and dried, wt. 21.0 g., m. p. 215–216° (d.) when placed in bath at 200°. This represented an over-all yield of 43% based on the crude ζ-truxinic acid. Recrystallization from aqueous acetic acid gave crystals of m. p. 229–230° (d.) when placed in bath at 220°; literature[14] m. p. 225–226° (d.) when placed in bath at 200°.

Preparation of ζ-Truxinic-b-amino Acid (III).—The reaction was run at 38–40° for two hours, after which most of the insoluble sodium salt of the b-amido acid had disappeared. The remaining solid was filtered, and the preparation continued as above. From 16.7 g. of the ζ-truxinic-b-amido acid was obtained 12.0 g. of the amino acid, m. p. 171–173°, and 3.5 g. of starting material. The mixed m. p. of the a- and b-amino acids was 162–168° (d.). The net yield was practically quantitative. The acetyl derivative of ζ-truxinic-b-amino acid from aqueous alcohol had m. p. 124–125°.

Anal. Calcd. for $C_{19}H_{19}NO_3$: N, 4.53. Found: N, 4.48.

Reaction of ζ-Truxinic-a-amino Acid with Nitrosyl Bromide.—A nitrosyl bromide solution was made by pass-

(13) Melting points uncorrected.

(14) Stoermer and Scholtz, *Ber.*, **54**, 85 (1921).

(15) Bernstein and Quimby, THIS JOURNAL, **65**, 1845 (1943).

(16) Analyses through the courtesy of Dr. T. S. Ma, University of Chicago.

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ing nitric oxide into a mixture of 5.6 g. of bromine in 200 cc. of dry ether in an ice–salt bath. The solution was then slowly added to 7.0 g. of ζ-truxinic-a-amino acid just covered with dry ether. The temperature was kept below −5°. After addition was completed, the reaction mixture stood until the evolution of nitrogen ceased. It was then shaken with a sodium bisulfite solution until the ether was colorless, followed by a similar shaking with a potassium carbonate solution. Acidification of this latter solution yielded only a small amount of an oil from which no crystals could be obtained.

The ether solution was dried over anhydrous potassium carbonate, then concentrated to give a total of 3.5 g. of white needles, m. p. 130–133°. Upon decolorizing with charcoal from a benzene solution, crystals were formed by the addition of petroleum ether (b. p. 60–70°), m. p. 133°. The known m. p. of lactone II was 133°.[8]

The lactone was boiled with 10% alcoholic potassium hydroxide for one minute, diluted with water, and hydrochloric acid added. The resulting precipitate was filtered, dried and recrystallized from benzene to give crystals of m. p. 148–149° (d.). The m. p. of 1^c-carboxyl-2^c-benzoxyl-3^c-phenylcyclopropane was reported[8] as 145–146°. Treatment of the above acid in methyl alcohol with diazomethane in ether yielded lactone II, m. p. and mixed m. p. 132–133°. This dehydrating action of diazomethane had been observed previously with the optically active acid.[5]

Reaction of ζ-Truxinic-b-amino Acid with Nitrosyl Bromide.—The nitrosyl bromide solution was added to 7.0 g. of the b-amino acid as described in the previous experiment. The reaction seemed slower. There was a small amount of ether insoluble material, m. p. 230–233°, possibly α,γ-diphenylbutadiene tetrabromide.[8] The ether was shaken with sodium bisulfite solution, then a potassium carbonate solution as above. Acidification of the latter solution yielded an oil which gradually solidified to yield 3.5 g. of crystals, m. p. 125–137°. Recrystallization from aqueous alcohol gave needles of m. p. 137–139°. Elementary analysis showed bromine to be present. This product will be thoroughly studied at a later date.

The ether solution was dried over potassium carbonate, and the ether evaporated off leaving an oil from which no crystals could be obtained. Treatment of the oil with boiling 10% alcoholic potassium hydroxide for one minute, dilution with water, and acidification also yielded an oil. From this oil, by means of decolorization with charcoal and two recrystallizations was obtained a small quantity of crystals, m. p. 168–169°.

Reaction of ζ-Truxinic-a-amino Acid with Nitrous Acid.—A solution of 1.5 g. of ζ-truxinic-a-amino acid in 150 cc. of dilute hydrochloric acid was warmed to 40°, and 1.5 g. of sodium nitrite in 10 cc. of water was slowly added. A solid gradually formed, and a gas was evolved containing oxides of nitrogen. One hour after addition had been completed, the flask was cooled, and the contents filtered. There was obtained 0.5 g. of crystals, which when decolorized and recrystallized from a benzene–petroleum ether solution had a m. p. of 131–133°. The mixed m. p. with the lactone II prepared above was 131–132°, demonstrating their identity.

Reaction of ζ-Truxinic-b-amino Acid with Nitrous Acid.—The reaction with nitrous acid was performed as above. The initial product was an oil, which was extracted from the solution using ether. The ether extract was washed with potassium carbonate solution. Only an oil resulted from acidification of the latter. Evaporation of the ether resulted in an oil, from which by recrystallization from a benzene–petroleum ether solution was obtained a few mg. of solid of m. p. 188–189°.

We wish to thank Dean Frank C. Whitmore of the Pennsylvania State College for his many helpful suggestions.

Summary

Deamination of ζ-truxinic-a-amino acid (1^c-carboxyl-2^c-amino-3^c,4^t-diphenylcyclobutane) with both nitrosyl bromide and nitrous acid gave the lactone of 1^c-carboxyl-2^c-benzoxyl-3^c-phenylcyclopropane. This change cannot be explained by any existing theory of molecular rearrangements without the assumption of an inversion of a carbon atom not directly involved in the reaction. Only a bromo-acid of unknown structure could be isolated from the reaction of nitrosyl bromide and ζ-truxinic-b-amino acid.

CHICAGO, ILLINOIS RECEIVED JULY 19, 1943

[CONTRIBUTION FROM THE LABORATORY OF HIGH MOLECULAR CHEMISTRY, THE HEBREW UNIVERSITY]

Reaction of Diazomethane with Ammonium Salts of Organic Acids

BY MAX FRANKEL AND EPHRAIM KATCHALSKI

In a previous paper[1] dealing with derivatives of N-carboxy α-amino acid esters, it has been shown that diazomethane reacts with the salt formed between N-carboxyglycine ester and glycine ester (I), yielding N-carbomethoxyglycine ester and glycine ester in about equimolecular amounts. The reaction proceeds according the scheme

$$\underset{\text{COOR}}{\overset{\text{CH}_2\text{NHCOOH}_3\text{NCH}_2}{|}}\text{COOR} \quad \underset{\text{I}}{} \quad + \text{CH}_2\text{N}_2 = \underset{\text{COOR}}{\overset{\text{CH}_2\text{NHCOOCH}_3}{|}}\text{COOR} + \text{H}_2\text{NCH}_2\text{COOR}$$

$$\text{R} = \text{CH}_3 \text{ or } \text{C}_2\text{H}_5$$

(I) is a substituted ammonium salt of an organic acid; thus the above scheme represents a reaction between diazomethane and an ammonium salt of an organic acid. As far as we are aware the literature does not contain any references to reactions between diazomethane and ammonium or N-substituted ammonium salts of organic or inorganic acids (*cf.* ref. 2); we therefore included in the paper mentioned[1] experimental results concerning the action of diazomethane on ammonium propionate and on ammonium benzoate. In both cases the methyl esters of the corresponding acids, and ammonia, were obtained.

The object of the present paper is to extend the investigation of this reaction to ammonium salts of dibasic acids and to N-substituted ammonium salts.

(1) Frankel and Katchalski, THIS JOURNAL, **65**, 1670 (1943).

(2) Sidgwick, "Organic Chemistry of Nitrogen," 351–361 (1937); Smith, *Chem. Rev.*, **23**, 193 (1938).

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TABLE I

N-SUBSTITUTED DIAMMONIUM PHTHALATES

Phthalate prepared	Formula	Amine used, g.	Yield	Analyses, % N Calcd.	Found
Di-(methylammonium)	$C_{10}H_{16}N_2O_4$	1.1	Quant.[a]	12.28	12.40
Di-(ethylammonium)	$C_{12}H_{20}N_2O_4$	1.6	Quant.[a]	10.93	10.96
Di-(dimethylammonium)	$C_{12}H_{20}N_2O_4$	1.7	Quant.[b]	10.93	11.02
Di-(triethylammonium)	$C_{20}H_{36}N_2O_4$	3.6	90%[c]	7.67	7.69

[a] White crystals. [b] Separated as a viscous liquid which crystallized overnight in ice box. [c] Separated as oily drops which formed a viscous liquid but did not crystallize. Sixty ml. of ether required for the precipitation.

TABLE II

REACTION OF DIAZOMETHANE WITH AMMONIUM AND N-SUBSTITUTED AMMONIUM SALTS

Salt used	Dimethyl ester formed	Yield, %	B. p., °C., 690 mm.	Analyses for OCH_3, % Calcd.	Found
Diammonium malonate	Malonate	85	178	46.97	46.58
Diammonium succinate	Succinate	85	189	42.96	42.20
Diammonium phthalate[a]	Phthalate	88	278	31.96	32.21
Di-(methylammonium) phthalate	Phthalate	[b]	278	31.96	31.55
Di-(ethylammonium) phthalate	Phthalate	90	279	31.96	31.79
Di-(dimethylammonium) phthalate[a,c]	Phthalate	82	279	31.96	31.60
Di-(triethylammonium) phthalate[a,d]	Phthalate	72	278	31.96	32.10

[a] Solution of 0.8 g. of diazomethane in 70 ml. of ether used. [b] Reaction very slow. Ten ml. of alcohol added to accelerate. After standing for 48 hours, residue of 0.3 g. of ammonium salt was filtered off. Filtrate yielded 0.15 g. of product. [c] Residue of 0.05 g. remained after overnight treatment. [d] Fractionally distilled to remove triethylamine and redistilled twice for analysis.

Diazomethane was allowed to react with di-ammonium succinate, di-ammonium malonate, di-ammonium phthalate and with di-(methylammonium) phthalate, di-(ethylammonium) phthalate di-(dimethylammonium) phthalate and di-(triethylammonium) phthalate. The action of diazomethane on ammonium chloride, as representative of an inorganic ammonium salt, was also investigated.

In all cases a reaction analogous to that previously described[1] was observed, *i. e.*, the dimethyl esters of the corresponding dibasic organic acids were obtained, while ammonium chloride yielded methyl chloride. During these esterifications ammonia, methylamine, ethylamine, dimethylamine and triethylamine were evolved from the corresponding ammonium and substituted ammonium salts. In our experiments no appreciable methylation of the ammonia or amines liberated was observed.

Experimental

(a) Preparation of the Ammonium Salts.—The ammonium salts of malonic, succinic and phthalic acids were prepared by passing a stream of dried ammonia through an ethereal or alcoholic solution of the corresponding organic acid.[3] In the former case the ammonium salt was precipitated at once, while in the latter it was precipitated by the addition of ether.

The methylammonium, ethylammonium and dimethylammonium salts of phthalic acid were prepared by passing a stream of the appropriate dried gas through a suspension of 2 g. of *o*-phthalic acid in 10 ml. of alcohol. Di-(triethylammonium) phthalate was obtained by adding liquid triethylamine to a similar alcoholic solution of phthalic acid. After the addition was complete and the solution had cooled, separation of the salt was induced or completed by the addition of ether (generally 20 ml.). The products were filtered, washed with ether and dried.

All but the first of these salts seem to be described for the first time. Di-(methylammonium) phthalate has been obtained previously by a different method.[4] A tabulation of their yields and analyses is given in Table I.

(b) Reaction of Ammonium and N-Substituted Ammonium Salts with Diazomethane.—In all cases except those specified an ethereal solution of 1 g. of diazomethane in 70 ml. of ether prepared according to Adamson and Kenner[5] was used. This amount was greatly in excess of the theoretical quantity required in every instance. The ethereal solution of diazomethane was poured onto 0.5 g. of the solid ammonium salt. In general the evolution of nitrogen started immediately, but in some cases where the reaction was too slow it was accelerated by adding alcohol. The reaction mixtures were allowed to stand overnight at room temperature to complete the process. Moisture was excluded by means of a calcium chloride tube. The evolution of the ammonia or amines liberated in the reaction was indicated by their odor or their effect on litmus paper.

During the reaction the solid salt disappeared; the ethereal solution was filtered and the ether, excess of diazomethane and excess of ammonia were removed by distillation at normal pressure. The remaining viscous residue was dissolved in ether and dried over sodium sulfate. After filtration the ether was removed and the residue distilled to give the product. The esters thus obtained were redistilled before analysis. In addition to methoxyl determination a quantitative hydrolysis by alcoholic potassium hydroxide was carried out and the liberated carboxyl groups determined by back titration. In all cases this confirmed the formation of the methyl ester from the corresponding ammonium salt.

Data on the specific compounds are shown in Table II.

Action of Diazomethane on Ammonium Chloride.—One gram of diazomethane in 50 ml. of ether was added to 535 mg. of ammonium chloride. On adding 50 ml. of alcohol gas evolution started. The gases evolved were passed through a second vessel containing alcohol to absorb ammonia and methyl chloride which were only partly retained in the reaction vessel.

After twenty-four hours the residual solid ammonium chloride was filtered off (104 mg.). The alcohol–ether mixture of the reaction vessel contained a small amount of unchanged ammonium chloride in solution; this was de-

(3) McMaster, *Am. Chem. J.*, **49**, 294 (1913).

(4) Gibbs, THIS JOURNAL, **28**, 1411 (1906).

(5) Adamson and Kenner, *J. Chem. Soc.*, 1551 (1937).

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termined by a Volhard titration (43 mg.). The amount of ammonium chloride which underwent reaction was therefore 388 mg.

The methyl chloride was determined in both solutions as methyl iodide.[6] A total amount of 195 mg. of methyl chloride was found. Ammonia was determined by direct titration, 85 mg. was found. The yield of methyl chloride calculated on the basis of ammonium chloride which underwent reaction was 53%; that of ammonia 69%.

The authors acknowledge the assistance of Miss H. Berliner.

Summary

Diazomethane was allowed to react with di-ammonium malonate, di-ammonium succinate, di-ammonium phthalate, di-(methylammonium) phthalate, di-(ethylammonium) phthalate, di-(dimethylammonium) phthalate, and di-(triethylammonium) phthalate.

In all cases the dimethyl esters of the corresponding dibasic acids were obtained.

Reaction of diazomethane with ammonium chloride yielded methyl chloride.

During these esterifications ammonia, methylamine, ethylamine, dimethylamine and triethylamine were evolved from the corresponding ammonium and N-substituted ammonium salts.

(6) Roka and Fuchs, *Z. anal. Chem.*, **71**, 381 (1927).

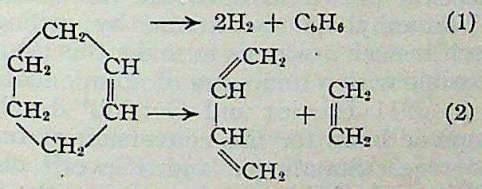
JERUSALEM, PALESTINE RECEIVED JANUARY 24, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE JOHNS HOPKINS UNIVERSITY]

The Thermal Decomposition of Substituted Cyclohexenes[1]

BY F. O. RICE[2a] AND MARY THOMAS MURPHY[2b]

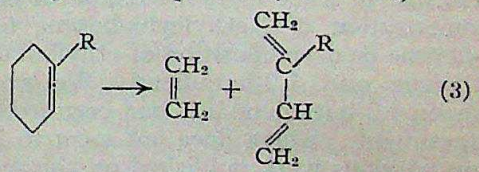
1. Introduction.—If cyclohexene is heated above its decomposition point, at low pressures and for a time sufficiently short that only a small fraction is decomposed, it undergoes a simple dissociation into smaller molecules. The particular conditions mentioned have been selected in order to avoid as far as possible bimolecular reactions of the products with each other or with the substrate. Several thermodynamically possible decompositions may occur such as



Reactions of these types have been discussed in a recent paper[3] in the light of a principle called the principle of least motion. In the case of several reactions such as those listed above which are all thermodynamically possible, the principle states that that reaction is favored which involves as little motion of the atoms as possible in passing from the old to the new configuration. The second half of the principle states that a reaction will be favored which involves least change of the electronic configuration of the reacting system. From both these standpoints, it is plausible to assume that the reaction will be favored which involves breaking or making as few bonds as possible.

On the basis of this principle we would predict with some confidence that reaction (2) would be greatly favored over reaction (1) and this has actually been found experimentally[4]; no benzene is found in the products but butadiene and ethylene are formed in almost theoretical yield. An investigation, therefore, of the decomposition of substituted cyclohexenes would provide not only a further test of the principle of least motion but also a method of preparing substituted butadienes.

2. 1-Methylcyclohexene.—We found that this compound decomposes to the extent of about 80% according to the equation (R = CH_3)



As might be expected, secondary reactions occur to a larger extent than in the decomposition of cyclohexene. For every 100 molecules of methylcyclohexene decomposed, about 40 molecules of hydrogen and 30 molecules of methane are formed in subsidiary reactions. Since separate experiments showed that isoprene itself is decomposed to the extent of only a few per cent. under the experimental conditions, doubtless the secondary reactions are due in greater part to attack of free radicals on the substrate.

Zelinski and co-workers[5] pyrolyzed a number of substituted cyclohexenes both alone and diluted with water vapor. They obtained a yield of 75% ethylene and 35.3% isoprene by heating 1-methylcyclohexene at 690°.

3. 1-Ethylcyclohexene.—There seems to be extensive decomposition which produces much methane and hydrogen; presumably there must be highly unsaturated C_8 or C_6 hydrocarbons formed although we could not identify anything in the higher fractions in spite of a careful search for ethylbutadiene which would be expected ac-

(1) Original manuscript received June 28, 1943.
(2) (a) Present address, Catholic University, Washington, D. C. (b) Present address, College of Chestnut Hill, Philadelphia, Pa.
(3) Rice and Teller, *J. Chem. Phys.*, **6**, 489 (1938).
(4) Rice, Ruoff and Rodowskas, THIS JOURNAL, **60**, 955 (1938).
(5) Zelinski, Mikhailov and Arbuzov, *J. Gen. Chem.* USSR, **4**, 856 (1934).

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TABLE I

PYROLYSIS DATA

	1-Methyl-cyclohexene	1-Ethyl-cyclohexene	1-Phenyl-cyclohexene	3-Vinyl-cyclohexene	Dipentene	3-*p*-Menthene
Moles used	0.516	0.664	0.493	1.05	0.98	0.50
% decomposed	10	14	23	61	33	6
Pressure in mm.	8	10	5–10	12	10	5
Furnace temp., °C.	750 ± 20	700 ± 10	750 ± 10	700 ± 10	700 ± 10	655 ± 10
Contact time, sec.	0.02	0.02	0.04	0.03	0.06	0.03
	Moles of product per mole of substrate decomposed					
H_2	0.42	0.21	0.17	0.06	0.13	0.36
CH_4	0.29	0.35	0.08	0.05	0.15	0.49
C_2H_2	..	..	..	0.02	..	..
C_2H_4	1.00	0.52	0.87	0.11	0.14	0.15
C_2H_6	..	0.02	..	..	..	0.01
C_3H_4	..	..	..	..	0.02	..
C_3H_6	0.08	0.05	..	..	0.10	0.73
C_4H_6	0.06	..	..	1.60	0.02	0.03
C_6H_8	0.81	..	..	..	1.62	..
C_6H_n	..	..	..	0.08	0.14	..
$C_{10}H_{10}$	..	..	0.41	..	..	..

cording to equation 3 (R = C_2H_5). The large amount of methane formed indicates that there is a considerable amount of chain decomposition.

We must remember, however, that in a previous discussion of the principle of least motion[6] it was pointed out that a molecule having a long carbon skeleton, when ruptured by heat, could coil around and react with itself to produce an isomer. Considerations of this kind from the principle of least motion suggest as possibilities isomerization of 1-ethylcyclohexene to 3-vinyl-2-hexene or decomposition of ethylbutadiene into ethylene and 1,2-butadiene. We would have missed 1,2-butadiene if it had been formed in our experiment. There does not seem to have been any previous work published on the pyrolysis of ethylcyclohexene.

4. 1-Phenylcyclohexene.—We did only one experiment and obtained 41 molecules of phenylbutadiene for every 100 molecules of phenylcyclohexene decomposed. It is possible that the low yield is due to polymerization of the phenylbutadiene during distillation. The pyrolysis of 1-phenylcyclohexene does not appear to have been studied previously.

5. 3-Vinylcyclohexene.—We have proved that this compound decomposes from 80–85% into 1,3-butadiene. In view of the fact that this molecule would produce a radical having a long carbon skeleton which could react with itself and isomerize, it is not surprising that there are some side reactions. From the principle of least motion, we would predict the formation of 1,3,6-octatriene caused by the radical, $CH_2CHCHCH_2CH_2CH$-$CHCH_2$, coiling around and reacting with itself.

The gas phase dimerization of butadiene has been studied by several workers[7,8] but the reverse reaction does not seem to have been investigated experimentally although Kistiakowsky has made some calculations on the rate of dissociation.

6. Dipentene.—The yield of isoprene was 81% of the amount of dipentene decomposed. From some other work we estimate that 3–4% of the isoprene formed decomposed under our experimental conditions so that the small amounts of methylacetylene and butadiene found probably come from decomposition of the isoprene. It seems plausible also that dipentene can isomerize into 3,7-dimethyl-1,3,6-octatriene by coiling around itself in such a way as to make this isomerization possible with a minimum of atomic motion.

In 1911 Harries and Gottlob[9] developed the isoprene lamp for the conversion of terpenes to isoprene. Staudinger and Klever[10] obtained a 60% yield of isoprene by passing the vapors of dipentene, diluted with nitrogen, over a hot platinum coil at 20–30 mm. pressure.

7. 3-*p*-Menthene.—This material gave a good yield of propylene on pyrolysis but the expected 2-isopropylbutadiene could not be detected. The only previous work relating to this compound that we could find[11] is that 3-*p*-menthene is a product of the pyrolysis of menthol and is stable at 500°.

8. Experimental.—Our sample of 1-methylcyclohexene (b. p. 108–109°, $n^{20}D$ 1.4510) was prepared by Dr. J. Greenberg from 1-methylcyclohexanol. The 1-ethylcyclohexene used was prepared by Dr. P. M. Ruoff according to the method of Signaigo and Cramer[12] and had a b. p. 135.5–136.8° and $n^{20}D$ 1.4577. 1-Phenylcyclohexene was prepared by Dr. J. Greenberg, using cyclohexanone and phenyl bromide as starting points.[13] It had b. p. (5 mm.) 102–103°, m. p. 10–11°.

(6) Kossiakoff and Rice, THIS JOURNAL, **65**, 593 (1943).

(7) Lebedev and Sergienko, *Compt. rend. acad. sci., U. S. S. R.*, **3**, 79 (1935).

(8) Kistiakowsky and Ransom, *J. Chem. Phys.*, **7**, 725 (1939).

(9) Harries and Gottlob, *Ann.*, **383**, 228 (1911).

(10) Staudinger and Klever, *Ber.*, **44**, 2212 (1911).

(11) Isikawa, Tosimitu, Miyata, Araki and Someno, *Science Repts., Tokyo Runrika Daigaku*, **A3**, 273 (1939); *C. A.*, **34**, 3240[1] (1940).

(12) Signaigo and Cramer, THIS JOURNAL, **55**, 3326 (1933).

(13) Sabatier and Mailhe, *Compt. rend.*, **138**, 1322 (1904); Noller and Kaneko, THIS JOURNAL, **57**, 2442 (1935).

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The 3-vinylcyclohexene was prepared by polymerizing butadiene at 450° and 600–700 mm. The dimer was twice distilled at 2 mm. pressure, the first and last samples being rejected each time. The sample had a b. p. 128–130° and $n^{20}D$ 1.4658. Our sample of limonene, b. p. (20 mm.) 67–68°, was purchased from Eastman Kodak Co. The 3-*p*-menthene was prepared by the dehydration of menthol. Sulfuric acid and aluminum oxide were both used as dehydrating agents but there was no difference in the products obtained by pyrolyzing the two samples. The material had a b. p. 168–169° and on hydrogenation gave 0.98 double bond.

The gaseous products were analyzed in a modified Shepherd[14] gas analysis apparatus containing a hydrogenation unit.[15] The products condensing in the traps were transferred to a low temperature Podbielniak still, fractionated, and then further analyzed in the gas analysis apparatus.

Isoprene was identified by its b. p., by giving two double bonds on hydrogenation and by the maleic anhydride derivative, m. p. 63°. 2-Phenylbutadiene was characterized by its b. p. and maleic anhydride derivative, m. p. 105°. 1,3-Butadiene was identified by its b. p. and hydrogenation value.

(14) Shepherd, *Bur. Standards J. Research*, **6**, 121 (1931).

(15) McMillan, Cole and Ritchie, *Ind. Eng. Chem., Anal. Ed.*, **8**, 105 (1936).

Summary

1. The thermal decomposition of a number of substituted cyclohexenes has been studied in the expectation that they would follow the pattern of the cyclohexene decomposition and yield a substituted butadiene and ethylene.

2. This was found to be the case for 1-methyl, 3-vinyl and 1-phenyl cyclohexene. In the case of ethylcyclohexene, we could not detect the expected ethylbutadiene.

3. Dipentene gave, as was to be expected, a high yield of isoprene. On the other hand, 3-*p*-menthene gave a high yield of propylene but no isopropylbutadiene could be detected.

WASHINGTON, D. C. RECEIVED FEBRUARY 19, 1944

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

The Effect of Dielectric Constant and Temperature on the Catalyzed Decomposition of Azodicarbonate Ion

BY CECIL V. KING AND JESSE J. JOSEPHS

In recent years much interest in reaction kinetics in solution has centered in two factors: (1) prediction by electrostatic theory of the effects of changing dielectric constant and ionic strength and (2) the interpretation of temperature coefficients in terms of activation energy and entropy.

(1) For a reaction between ions A and B present electrostatic theory may be summarized in the well-known Christiansen–Scatchard equation[1]

$$\log k = \log k_\infty - \frac{Z_A Z_B \epsilon^2 N}{2.3DRT} \cdot \frac{1}{r_A + r_B} + \frac{Z_A Z_B \epsilon^2 N}{2.3DRT} \cdot \frac{\kappa}{1 + a\kappa} \quad (1)$$

where the symbols have their usual significance and the last term refers to the salt effect, the next to last term to the dielectric constant effect. A similar equation has been developed by Eyring and his associates and includes a separate estimation of the radius of each ion and the critical complex.[2,3] (2) Introduction of the Eyring theory that rates may be expressed in terms of a universal frequency and an equilibrium constant K^* (reactants-critical complex) necessitates

$$k = RT/Nh \times K^*$$

defining the Arrhenius "energy of activation" as a free energy, and leads to the equation, for reactions in solution[4,5]

$$\log k = \log e \frac{RT}{Nh} - \frac{E_{exp.}}{2.3RT} + \frac{\Delta S^*}{2.3R} \quad (2)$$

where $E_{exp.}$ is the activation energy as determined from the slope of log k *vs.* $1/T$ plots and ΔS^* has been defined as the entropy of activation. This may be compared with the corresponding "collision theory" equation

$$\log k = \log Z - \frac{E_{exp.}}{2.3RT} + \log P \quad (3)$$

where the collision frequency Z may be calculated from the equations of the kinetic theory and P is the probability factor for effective collision.

As usually determined, in iso-composition solutions, both $E_{exp.}$ and ΔS^* contain factors due to the change in dielectric constant with temperature; and it has been suggested[6] that temperature coefficients for use in these equations should be determined in media of the same dielectric constant rather than the same composition.

Presumably there should be no entropy of activation unless the free energy of activation varies with temperature, or if the dielectric constant is kept unchanged as the temperature is varied (using rate constants at zero ionic strength).[7,8] However, since ΔS^* is deter-

(1) Scatchard, *Chem. Rev.*, **10**, 229 (1932).

(2) Laidler and Eyring, *Ann. N. Y. Acad. Sci.*, **39**, 303 (1940).

(3) Glasstone, Laidler and Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, pp. 428, 430.

(4) Ref. 3, p. 199.

(5) LaMer, *J. Franklin Inst.*, **225**, 709 (1938).

(6) Svirbely and Warner, THIS JOURNAL, **57**, 1883 (1935); Warner, *Ann. N. Y. Acad. Sci.*, **39**, 345 (1940).

(7) LaMer, *J. Chem. Phys.*, **1**, 289 (1933).

(8) Ref. 3, pp. 433–434.

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mined as a difference it does not represent correct entropy values unless all other factors in equation (2) can be properly evaluated. For instance there may be a fractional "transmission coefficient" by which the Eyring frequency factor eRT/Nh should be multiplied in any particular case, but there is no independent method of ascertaining this. Also it has been suggested that the rate constant k should be based on mole fraction rather than volume concentrations for the calculation of $E_{exp.}$.[9,10,11]

The Azodicarbonate Decomposition.—This reaction has been studied in detail.[12] It is highly sensitive to general acid catalysis; the hydrogen ion catalyzed rate is measurable in dilute sodium hydroxide solutions, while catalysis by molecular water is small. The rate-controlling process is second order, presumably

$$N_2(COO)_2^{=} + H_3O^{+} \longrightarrow X^{-1}$$

while the stoichiometric equation is

$$2N_2(COO)_2^{=} + 4OH^{-} \longrightarrow N_2 + N_2H_4 + 4CO_3^{=}$$

The rate equation is, neglecting water catalysis and change in ionic strength μ during the reaction

$$\frac{k_\mu^H K_\mu^w t}{2.3(b-2a)} = \log\frac{a}{a-x} + \frac{2x}{2.3(b-2a)} \quad (4)$$

where a and b are initial molar concentrations of azodicarbonate and hydroxyl ions, respectively, k_μ^H and K_μ^w are molar rate constant and the water constant ($C_{H_3O^+}$ C_{OH^-}) at finite values of μ, and x and t have their usual meaning.

Experimental.—Sodium azodicarbonate was prepared as before[12]; two samples evolved 95 and 98% of the theoretical nitrogen, in acid solution. The rates were followed by measuring the pressure of the nitrogen evolved as before. Five temperatures were used, 14.9, 19.9, 24.9, 29.9 and 34.9°, each ±0.02°. Slight condensation of water vapor in exposed parts of the apparatus at the two higher temperatures did not seem to affect the measurements. Since the temperature coefficient is approximately 2% per 0.1° throughout, all rate constants were arbitrarily increased by 2% to correspond to round temperatures.

To vary the dielectric constant dioxane–water mixtures were used. Solutions were made up at approximately 25°, using, per 100 cc., 0, 10, 20, 30, 40, 50 and 60 cc. of dioxane (purified as described by Kraus and Fuoss.)[13] Using the density data of Hertz and Lorentz[14] these solutions are calculated to contain 0, 10.2, 20.2, 30.1, 39.9, 49.7 and 59.5% dioxane by weight. Dielectric constants of these mixtures were interpolated from the measurements of Åkerlöf and Short[15] and the water dissociation constants from a large plot of the data of Harned and Fallon.[16] The latter values were corrected to the volume concentration scale.

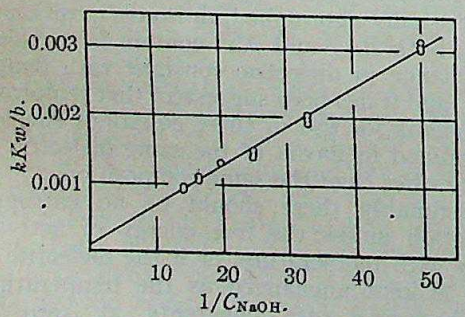

Fig. 1.—The rate in 30% dioxane, at constant ionic strength.

Solutions were made with carbonate-free sodium hydroxide and carbon dioxide free water and no attempt was made to study the effect of other acids than the hydrogen ion. All experiments were made at least in duplicate. Average values only are given except in Table I.

Results.—To check the nature of the reaction in dioxane mixtures experiments were carried out in 30% dioxane (by volume), with varying sodium hydroxide concentration and the ionic strength maintained constant at 0.1225 by additions of sodium chloride. The rates are given in Table I and plotted *vs.* the reciprocal of hydroxyl concentration in Fig. 1. The rate is proportional to the hydrogen ion concentration except for the small water catalysis whose value is obtained by extrapolation to $1/C_{OH^-} = 0$.

TABLE I

The rate in 30% dioxane (by volume) as a function of sodium hydroxide concentration; 25°, μ = 0.1225, C azo-salt = 0.0075 M.

C_{NaOH}, M	kKw/b	C_{NaOH}, M	kKw/b
0.02	0.00302	0.05	0.00131
	.00305		.00131
	.00314		.00130
.03	.00194		
	.00197	.06	.00106
	.00205		.00111
	.00205		
		.07	.000966
.04	.00141		.000938
	.00144		.000938
	.00147		.000966

In Table I rate constants are given as kKw/b since these values are comparable to first order rate constants with unchanging hydrogen ion concentration.[12] In Table II averaged constants with C_{OH^-} = 0.02 and varying temperatures and dioxane concentration are given in terms of $k_\mu^H K_\mu^w$ since these are used directly to evaluate k_0^H, the molar hydrogen ion catalytic constant at zero ionic strength.

In the application of equation (1) it is customary to evaluate and eliminate the last term (effect of ionic strength), usually by determining rate constants at a number of ionic strengths and extrapolating to $\mu = 0$. In the present case the accuracy attainable did not seem to justify the very large number of experiments necessary to make satisfactory extrapolations.

Instead, the salt effect term, including the effect of ionic strength on the water constant

(9) Scatchard, *J. Chem. Phys.*, **7**, 657 (1939); *Ann. N. Y. Acad. Sci.*, **39**, 341 (1940).
(10) Davis and LaMer, *J. Chem. Phys.*, **10**, 585 (1942).
(11) Svirbely and Peterson, THIS JOURNAL, **65**, 166 (1943).
(12) King, *ibid.*, **62**, 379 (1940).
(13) Kraus and Fuoss, *ibid.*, **55**, 21 (footnote 7) (1933).
(14) Hertz and Lorentz, *Z. physik. Chem.*, **A140**, 406 (1929).
(15) Åkerlöf and Short, THIS JOURNAL, **58**, 1241 (1936).
(16) Harned and Fallon, *ibid.*, **61**, 2374 (1939).

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TABLE II

The rate in dioxane mixtures. C azo-salt = 0.0075 M, C_{NaOH} = 0.02 M, μ = 0.0425.

Dioxane, vol. %	$k_\mu^H K_\mu^w \times 10^5$ 15°	20°	25°	30°	35°
0	3.25	6.78	13.54	26.8	43.3
10	3.34	5.95	11.32	23.0	41.0
20	2.75	4.91	8.96	18.1	35.5
30	2.12	3.46	6.60	14.3	26.1
40	1.47	2.53	4.94	10.2	16.8
50	1.00	1.78	3.51	6.40	12.9
60	0.64	1.12	2.19	3.94	8.30

(since this is known only at zero ionic strength), was calculated as follows. Introducing activity coefficients (f) for the ions involved

$$k_\mu^H K_\mu^w = k_0^H K_0^w f_2/f_1^2 \quad (5)$$

and using the Debye–Hückel "second approximation" for log f, k_0^H becomes

$$\log k_0^H = \log k_\mu^H K_\mu^w - \log K_0^w + \frac{\epsilon^2 N}{2.3DRT}\frac{\kappa}{1+a\kappa} \quad (6)$$

The value to be used for a was estimated from the salt effect experiments with sodium chloride recorded in Table II of the previous paper.[12] Log $k_\mu^H K_\mu^w$ was plotted *vs.* the last term of the equation

$$\log k_\mu^H K_\mu^w = \log k_0^H K_0^w - 1.02\sqrt{\mu}/(1 + 0.328a\sqrt{\mu}) \quad (7)$$

using various values for a (in Å.) until the points conformed to the slope 1.02. The plot, using a = 6 Å., is shown in Fig. 2. This method has the disadvantage of using one average a value for all the ions involved. Previous work indicates that a varies little with changing temperature or dielectric constant.

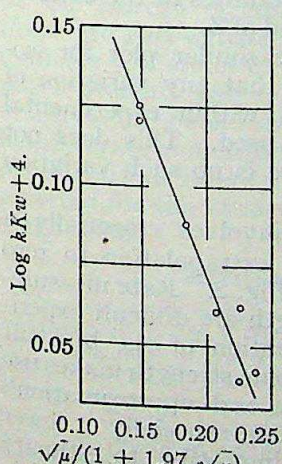

Fig. 2.—Evaluation of a from salt effect data; slope of line = −1.02.

Table III shows in detail the calculation of k_0^H. Equation (1) may now be put in the form

$$\log k_0^H = \log_{D=\infty} k_0^H - \frac{Z_A Z_B \epsilon^2 N}{2.3DRT}\frac{1}{r_A + r_B} \quad (8)$$

from which it is seen that a plot of log k_0^H *vs.* $1/D$, at each temperature, should be linear, with a slope from which ($r_A + r_B$) can be calculated.

These plots are shown in Fig. 3. The points approximate a linear relation at dielectric constant above 50. Previous work[5,6,17] has shown that departure from linearity at lower dielectric constant, in the direction found here, is to be expected. It has been possible to measure rate constants of some reactions with higher dielectric constants than in water, by the addition of amino-acids to the solutions, in which case the linear relation is found to hold over a wider range. That could not be done in this case because of the general acid catalysis.

(17) Amis and Potts, THIS JOURNAL, 63, 2883 (1941).

TABLE III

THE EVALUATION OF LOG k_0^H; a = 6 Å.

t, °C.	Dioxane, vol.%	D	log $k_\mu^H K_\mu^w$	log K_0^w	$\frac{\epsilon^2 N}{2.3DRT}\cdot\frac{\kappa}{1+a\kappa}$	log k_0^H
15	0	82.3	−4.49	−14.35	0.21	10.07
	10	73.0	−4.48	−14.64	.24	10.40
	20	63.8	−4.56	−14.99	.29	10.72
	30	54.8	−4.67	−15.39	.35	11.07
	40	45.5	−4.83	−15.83	.44	11.44
	50	36.6	−5.00	−16.40	.58	11.98
	60	27.8	−5.19	−17.09	.82	12.72
20	0	80.4	−4.17	−14.16	.21	10.20
	10	71.2	−4.23	−14.47	.24	10.48
	20	62.2	−4.31	−14.81	.29	10.79
	30	53.5	−4.46	−15.31	.35	11.20
	40	44.3	−4.60	−15.66	.45	11.51
	50	35.6	−4.75	−16.19	.59	12.06
	60	27.0	−4.95	−16.93	.83	12.81
25	0	78.5	−3.87	−14.00	.21	10.34
	10	69.5	−3.95	−14.30	.25	10.60
	20	60.5	−4.05	−14.64	.30	10.89
	30	52.1	−4.18	−15.04	.36	11.22
	40	43.1	−4.31	−15.50	.45	11.64
	50	34.6	−4.45	−16.05	.60	12.20
	60	26.2	−4.66	−16.77	.84	12.95
30	0	76.7	−3.57	−13.83	.21	10.47
	10	67.8	−3.64	−14.13	.25	10.74
	20	59.0	−3.74	−14.48	.30	11.04
	30	50.8	−3.84	−14.88	.36	11.40
	40	41.9	−3.99	−15.33	.46	11.80
	50	33.6	−4.19	−15.90	.61	12.32
	60	25.5	−4.40	−16.72	.85	13.17
35	0	74.9	−3.36	−13.68	.21	10.53
	10	66.1	−3.39	−13.98	.25	10.84
	20	57.5	−3.45	−14.33	.30	11.18
	30	49.5	−3.58	−14.72	.37	11.51
	40	40.8	−3.77	−15 18	.47	11.88
	50	32.6	−3.89	−15.74	.62	12.47
	60	24.8	−4.08	−16.45	.87	13.24

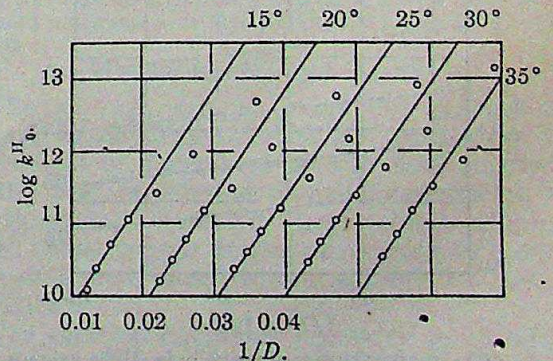

Fig. 3.—Log molar rate constants at zero ionic strength *vs.* $1/D$. Subtract 0.01 from abscissa for 20°, 0.02 for 25°, etc.

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From the slopes of the lines of Fig. 3, the average value of $(r_A + r_B)$ is calculated to be 3.42 Å.

The Temperature Coefficient.—Values of log k_0^H were plotted *vs.* $1/T$, and in Table IV the values of $E_{exp.}/2.3\ RT$ obtained from the slopes are given; also values of log A of the Arrhenius equation

$$\log k_0^H = \log A - E_{exp.}/2.3\ RT \qquad (9)$$

For comparison a plot was made of log k_0^H *vs.* dielectric constant and interpolated values at $D = 75$, 65, 55 and 45 (for 25°) are given in Table V with the corresponding values of $E_{exp.}/2.3\ RT$ and log A. Finally $\Delta S^*/2.3\ R$ was calculated from the equation

$$\log A = \log eRT/Nh + \Delta S^*/2.3R \qquad (10)$$

and these values are also given in Tables IV and V.

TABLE IV

VALUES DERIVED FROM THE TEMPERATURE COEFFICIENTS IN ISO-COMPOSITION MEDIA AT 25°

$\log e\frac{RT}{Nh} = 15.01$ with the minute as time unit.

Dioxane, vol.%	$E_{exp.}/2.3RT$	log A	$\Delta S^*/2.3R$
0	7.49	17.83	2.82
10	7.49	18.08	3.07
20	7.38	18.26	3.25
30	7.16	18.36	3.35
40	6.82	18.43	3.42
50	7.27	19.43	4.42
60	7.61	20.53	5.52

TABLE V

VALUES DERIVED FROM THE TEMPERATURE COEFFICIENTS IN ISO-DIELECTRIC MEDIA AT 25°

D	log k_0^H	$E_{exp.}/2.3RT$	log A	$\Delta S^*/2.3R$
75	10.45	3.80	14.25	−0.76
65	10.77	3.80	14.57	− .44
55	11.14	3.47	14.61	− .40
45	11.61	3.35	14.96	− .05

The temperature coefficients in iso-dielectric media are shown in Fig. 4.

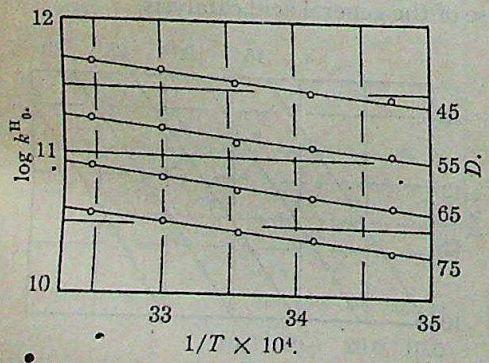

Fig. 4.—The temperature coefficient in iso-dielectric media.

Finally, in Table VI are given the corresponding values using "normalized" rate constants as

TABLE VI

VALUES DERIVED FROM THE TEMPERATURE COEFFICIENTS USING "NORMALIZED" RATE CONSTANTS AT 25°

D	log $^Nk_0^H$	$E_{exp.}/2.3RT$	log A	$\Delta S^*/2.3R$
75	10.44	3.88	14.32	−0.69
65	10.69	3.73	14.42	− .59
55	11.05	3.88	14.93	− .08
45	11.42	3.88	15.30	+ .29

suggested by Davis and LaMer,[4] using the water solution at 25° as the reference

$$^Nk_0^H = k_0^H \frac{\Sigma \text{ moles(solution)/liter}}{\Sigma \text{ moles(standard)/liter}} \qquad (11)$$

Discussion.—The nature of the reaction studied and the approximations in the calculations involved do not justify extensive conclusions concerning the theory. The low values of ΔS^* in iso-dielectric media—the largest (from Table V) being −3.5 e. u.—suggest that entropy of activation may really be small or negligible; negative values actually found could be due to a fractional "transmission coefficient" or other factors. The use of "normalized" or mole fraction rate constants makes comparatively little difference. The value of log Z of the collision theory is 15.31 in terms of moles, liters and minutes at 25° with $r_A + r_B = 3.42$ Å., making log P of equation (3) 0.3 unit smaller (or more negative) than $\Delta S^*/2.3$ R. Here, as in other cases,[6] agreement with the collision theory is not unreasonable, considering the uncertainties in the calculation of the rate constants and of Z.

Figure 4, as well as the similar plot for iso-composition media, shows that any variation of $E_{exp.}$ with temperature is within experimental error over the 20° range used. This does not mean, of course, that there is no such variation but only that it is small.

The estimation of k_0^H involves essentially a long and rather uncertain extrapolation to zero ionic strength as shown in Fig. 2. Rate measurements at lower ionic strength are difficult experimentally, and the contribution of the bivalent azodicarbonate ion to the ionic strength makes use of the Debye–Hückel "second approximation" equation somewhat uncertain, especially at lower dielectric constant. It is impossible to estimate the error introduced in this way, but it is probable that the errors are consistent throughout and do not greatly affect the conclusions.

The previous interpretation of the nature and mechanism of the reaction[12] seems fully confirmed, and the reaction is essentially unaltered in the dioxane mixtures. As shown in Table II the effect of dioxane is to diminish the observed rate greatly, but this is due to the decrease in water concentration, the water constant and the hydrogen ion concentration; the molar catalytic constant increases exactly as required by the theory. As expected, the exceedingly high molar

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rate constants are associated with low activation energies—*ca.* 5000 cal. in iso-dielectric media.

In conclusion, it may be said that the equations of Amis and Cook[18] and Amis and Potts[17] allow reasonably good calculation of the differences of log A in iso-composition and iso-dielectric media, and of the differences of $E_{exp.}$ in similar media. Also it should be mentioned that while the last term of equation (8) accounts reasonably for the variation in rate with dielectric constant it does not account for the variation with temperature. This situation has been studied in detail by Amis and Jaffe.[19]

Summary

The rate of decomposition of the azodicarbonate ion has been measured, in dilute sodium hydroxide in water and with addition of dioxane up to 60%, at five temperatures from 15 to 35°.

From these rates, molar hydrogen ion catalysis constants at zero ionic strength were calculated. Their variation with dielectric constant was found to agree satisfactorily with the predictions of electrostatic theory.

Temperature coefficients were determined for iso-composition and iso-dielectric solvents and energies and entropies of activation were calculated for comparison with the Eyring "absolute rate" and the collision rate theories. The results, especially in the isodielectric media, show agreement with theory quite comparable to that in other reactions reported in the literature.

Previous interpretation of the nature and mechanism of the reaction is substantiated.

(18) Amis and Cook, THIS JOURNAL, **63**, 2621 (1941).
(19) Amis and Jaffe, *J. Chem. Phys.*, **10**, 646 (1942).

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[CONTRIBUTION FROM THE WESTERN REGION, BUREAU OF MINES, U. S. DEPARTMENT OF THE INTERIOR, BERKELEY, CALIFORNIA]

Heats of Formation of Solid and Liquid $Mn(NO_3)_2 \cdot 6H_2O$[1]

BY C. HOWARD SHOMATE[2] AND FRANK E. YOUNG[2]

The heats of fusion of certain nitrates are important factors in thermal calculations pertaining to the nitrogen dioxide[3] process for extracting manganese from low-grade ores, now being studied by the Bureau of Mines. Available values for these nitrates antedate modern thermochemical methods and are of questionable accuracy. This paper presents new determinations of the heats of formation of solid and liquid manganous nitrate hexahydrate and of the heat of fusion of this compound. In a later paper, similar data will be reported for the nitrates of barium, calcium, and magnesium.

Method and Materials

The manganous nitrate hexahydrate used in this work was prepared by Dr. E. H. Huffman by dissolving electrolytic manganese (purity at least 99.9 per cent) in reagent-grade nitric acid. The manganese was added slowly to control the temperature until the acid had been largely used up. Finally, an excess of manganese was contacted until brown oxide of manganese just started to form, indicating virtually complete exhaustion of the acid. After filtration, a small amount of 30% hydrogen peroxide was added to clear up a slight discoloration remaining in the solution. The material then was evacuated with an oil pump and stored over a mixture of potassium hydroxide and calcium chloride. At this stage, the product was solid at room temperature, and analysis showed 4.13 moles of water per mole of manganous nitrate. Melting, with addition of enough water to bring the composition to the hexahydrate, yielded material with a melting point of 24.9°. Two fractional crystallizations produced crystals melting at 25.0°, which was not raised by further fractionation. The latter material constituted the final product. It analyzed 19.15% manganese (theoretical, 19.14%).

Heats of formation and the heat of fusion were determined by measuring the heat of solution of the salt in 1 N sulfuric acid in the apparatus described by Southard.[4] The 1.000 N sulfuric acid was prepared by dilution of reagent grade concentrated sulfuric acid and was standardized against sodium carbonate.

The calorimetric system was calibrated electrically, using a 100-ohm manganin heater. The heater current was measured by the potential drop across a 0.01-ohm standard resistance calibrated by the National Bureau of Standards. The usual heating period during a calibration was 600 seconds, which gave a temperature rise of about 400 μv. (about 0.36°). The temperature readings were estimated to 0.01 μv. from galvanometer deflections. All measurements were made with a White double potentiometer.

The results are expressed in defined calories (1 cal. = 4.1833 int. joules),[5] and all formula weights were calculated from the 1941 International Atomic Weights. All weights were corrected to a vacuum basis, using 1.8 for the density of solid manganous nitrate hexahydrate and 1.7 for the liquid.

Measurements and Results

The average sample weight of manganous nitrate hexahydrate (5.2895 g.) corresponds to the weight of manganese used in determinations of the heat of solution of manganese metal by Southard and Shomate,[6] whose value is adopted here. This sample weight corresponds to a dilution of 1 mole of anhydrous salt in $49.23H_2SO_4 \cdot 5{,}355H_2O$.

The skeleton equations necessary to calculate the heats of formation of solid and liquid man-

(1) Published by permission of the Director, Bureau of Mines, U. S. Department of the Interior. Not copyrighted.
(2) Chemists, Western Region, Bureau of Mines.
(3) Dean, Fox and Back, Bureau of Mines, Rept. of Investigations 3626, 30 pp. (1942).
(4) Southard, *Ind. Eng. Chem.*, **32**, 442 (1940).
(5) Mueller and Rossini, *Am. J. Physics*, **12**, 1 (1944).
(6) Southard and Shomate, THIS JOURNAL, **64**, 1770 (1942).

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ganous nitrate hexahydrate and its heat of fusion are given in Tables I, II and III. The uncertainties given in the last column of each table are twice the standard deviations of the means of the experimental results involved. This method of calculating uncertainties was discussed by Rossini and Deming[7] and was adopted by Shomate[8] in a previous paper on the thermochemistry of manganese compounds. In the tables, the resulting values of the heats of formation and the corresponding uncertainties have been rounded to the nearest 10 calories.

Heat of Formation of $Mn(NO_3)_2 \cdot 6H_2O(l)$.—A summary of the data needed to calculate the heat of formation of liquid manganese nitrate hexahydrate is given in Table I.

TABLE I

HEAT OF FORMATION OF $Mn(NO_3)_2 \cdot 6H_2O(l)$ (CAL. PER MOLE)

Reaction	$\Delta H_{298.16}$	Uncertainty
(1) $Mn + 2H^+ \longrightarrow Mn^{++} + H_2$	−54,406	50
(2) $H_2 + N_2 + 3O_2 \longrightarrow 2H^+ + 2NO_3^-$	−97,853	305
(3) $Mn(NO_3)_2 \cdot 6H_2O(l) \longrightarrow Mn^{++} + 2NO_3^- + 6H_2O(l)$	−5,096	6
(4) $6H_2 + 3O_2 \longrightarrow 6H_2O(l)$	−409,908	60
(5) $Mn + N_2 + 6O_2 + 6H_2 \longrightarrow Mn(NO_3)_2 \cdot 6H_2O(l)$	−557,070	310

$\Delta H_5 = \Delta H_1 + \Delta H_2 - \Delta H_3 + \Delta H_4$

The heat of reaction (1) in 1.000 *N* sulfuric acid was obtained from the value of Southard and Shomate[6] by applying a small correction to change from their acid strength, 1.006 *N*, to the present strength, 1.000 *N*. This correction was estimated from the data of Grau and Roth[9] as 50 ± 10 cal. per mole to give $\Delta H_{298.16} = -54,406$ from Southard and Shomate's value of $\Delta H_{298.16} = -54,356$ for 1.006 *N* acid.

Reaction (2) represents the heat of formation of nitric acid in $MnSO_4 \cdot 48.23H_2SO_4 \cdot 5,355H_2O$. The heat of this reaction was obtained by considering the following series of reactions

(6) $H_2 + N_2 + 3O_2 + 26.50H_2O \longrightarrow 2HNO_3 \cdot 26.50H_2O$

(7) $2HNO_3 \cdot 26.50H_2O + MnSO_4 \cdot 48.23H_2SO_4 \cdot 5,355H_2O \longrightarrow Mn(NO_3)_2 \cdot 49.23H_2SO_4 \cdot 5,381.5H_2O$

(8) $Mn(NO_3)_2 \cdot 49.23H_2SO_4 \cdot 5,355H_2O + 26.50H_2O \longrightarrow Mn(NO_3)_2 \cdot 49.23H_2SO_4 \cdot 5,381.5H_2O$

The desired heat of formation is $\Delta H_2 = \Delta H_6 + \Delta H_7 - \Delta H_8$. The heat of reaction (6) is obtainable from the work of Becker and Roth,[10] who reported $\Delta H_{293.1} = -14,855$ for the reaction, $Aq + 1/2N_2 + 5/4O_2 + 1/2H_2O(l) = HNO_3(0.05M)$. Forsythe and Giauque[11] have corrected this value to 25°, making $\Delta H_{298.16} = -15,075$. Employing Rossini's[12] heat of formation of liquid water, there is obtained $\Delta H_{298.16} = -49,234 \pm 151$ as the heat of formation of $HNO_3(0.05M)$ from the elements. The correction to the degree of dilution of reaction (6) may be made from the data of Becker and Roth,[13] +37 ± 4 cal., to yield finally $\Delta H_{298.16} = 2(-49,197 \pm 152) = -98,394 \pm 304$ cal. for the heat of reaction (6).

The heats of reactions (7) and (8) were directly determined in the present work as 460 ± 21 and −81 ± 10 calories, respectively, thus yielding $\Delta H_{298.16} = -97,853 \pm 305$ for reaction 2.

Six determinations of ΔH_3 were made, the results being −5098, −5091, −5101, −5085, −5102, and −5085, with a mean of −5096 ± 6 calories, after applying a correction of +18 ± 2 calories for the directly determined heat of dilution of the solution by the water of hydration. The average final temperature of the solution experiments was 25.5°. Data are not available for making the minor correction to 25.0°. It was necessary to carry out the solution experiments at slightly above 25° to avoid freezing any of the liquid manganous nitrate hexahydrate before solution.

The heat of formation obtained by subtracting ΔH_3 from the sum of ΔH_1, ΔH_2, and ΔH_4 is −557,070 ± 310 calories per mole.

Heat of Fusion of Manganous Nitrate Hexahydrate.—The heat of fusion was determined from the heats of solution of the solid and liquid as shown in Table II.

TABLE II

HEAT OF FUSION OF $Mn(NO_3)_2 \cdot 6H_2O$

Reaction	ΔH, room temp.	Uncertainty
(9) $Mn(NO_3)_2 \cdot 6H_2O(c) \longrightarrow Mn^{++} + 2NO_3^- + 6H_2O$	+4,510	11
(10) $Mn(N_3)O_2 \cdot 6H_2O(l) \longrightarrow Mn^{++} + 2NO_3^- + 6H_2O$	−5,096	6
(11) $Mn(NO_3)_2 \cdot 6H_2O(c) \longrightarrow Mn(NO_3)_2 \cdot 6H_2O(l)$	+9,610	10

$\Delta H_{11} = \Delta H_9 - \Delta H_{10}$

The heat of solution (9) was determined in the same way as the heat of solution of the liquid (10), previously discussed as reaction (3). The value +4510 ± 11 for ΔH_9 is the mean of five results: +4499, +4500, +4520, +4504, and +4524. The correction for dilution by the water of hydration (+18 calories) is included. Because of glass formation when the liquid nitrate was frozen in ice, it was necessary to freeze each sample in a sealed glass bulb in carbon dioxide–ethyl alcohol mixture and allow it to warm slowly to about 21° before putting it into the calorimeter. It was found best to measure the heat of solution of the solid at a mean final temperature of 21.9°. Unfortunately, no data are available to permit accurate correction to 25°. For this reason, the calculated uncertainty, 10

(7) Rossini and Deming, *J. Wash. Acad. Sci.*, **29**, 416 (1939).
(8) Shomate, THIS JOURNAL, **65**, 785 (1943).
(9) Grau and Roth, *Z. anorg. Chem.*, **188**, 195 (1930).
(10) Becker and Roth, *Z. Elektrochem.*, **40**, 842 (1934).
(11) Forsythe and Giauque, THIS JOURNAL, **64**, 48 (1942).
(12) Rossini, *Bur. Standards J. Research*, **22**, 407 (1939).
(13) Becker and Roth, *Z. physik. Chem.*, **A174**, 104 (1935).

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calories, may be somewhat smaller than the true uncertainty in the heat of fusion.

Heat of Formation of Solid Manganous Nitrate Hexahydrate.—The heat of formation of the solid salt may be found by adding the heat of formation of the liquid and the heat of solidification. The skeleton equations for this calculation are shown in Table III.

TABLE III

HEAT OF FORMATION OF $Mn(NO_3)_2 \cdot 6H_2O(c)$

Reaction	$\Delta H_{298.16}$	Uncertainty
(12) $Mn + N_2 + 6O_2 + 6H_2 \longrightarrow Mn(N_3O)_2 \cdot 6H_2O(l)$	−557,070	310
(13) $Mn(NO_3)_2 \cdot 6H_2O(c) \longrightarrow Mn(NO_3)_2 \cdot 6H_2O(l)$	+9,610	10
(14) $Mn + N_2 + 6O_2 + 6H_2 \longrightarrow Mn(NO_3)_2 \cdot 6H_2O(c)$	−566,680	310

$\Delta H_{14} = \Delta H_{12} - \Delta H_{13}$

Reactions (12) and (13) were discussed above as reactions (5) and (11), respectively. The value of the heat of formation of solid manganous nitrate, −566,680 ± 310 calories, is subject to the same lack of correction to 25° as the heat of fusion discussed under equation (9). By comparison with the uncertainty of 310 calories, however, this correction probably is not significant.

Discussion.—The results of this investigation are summarized in Table IV. In the reactions involving liquid water, Rossini's[12] value of the heat of formation of water is used.

The previous values for the reactions in Table IV, as summarized in the compilation of Bichowsky and Rossini,[14] are not in good agreement with the present results and emphasize the necessity of being critical of the older heat of formation data of nitrates. They tabulate −564.2 kilocalories

(14) Bichowsky and Rossini, Thermochemistry of the Chemical Substances, Reinhold Publishing Corporation, New York, N. Y., 1936.

TABLE IV

HEATS OF REACTION (CAL. PER MOLE)

Reaction	$\Delta H_{298.16}$	Uncertainty
$Mn + N_2 + 6O_2 + 6H_2 \longrightarrow Mn(NO_3)_2 \cdot 6H_2O(l)$	−557,070	310
$Mn + N_2 + 6O_2 + 6H_2(l) \longrightarrow Mn(NO_3)_2 \cdot 6H_2O(c)$	−566,680	310
$Mn + N_2 + 3O_2 + 6H_2O(l) \longrightarrow Mn(NO_3)_2 \cdot 6H_2O(l)$	−147,160	310
$Mn + N_2 + 3O_2 + 6H_2O(l) \longrightarrow Mn(NO_3)_2 \cdot 6H_2O(c)$	−156,770	310
$Mn(NO_3)_2 \cdot 6H_2O(c) \longrightarrow Mn(NO_3)_2 \cdot 6H_2O(l)$	+9,610	10

for the heat of formation of solid manganous nitrate hexahydrate based upon Thomsen's data for the heat of formation of manganous hydroxide, the heat of solution of manganous nitrate hexahydrate in water, for which Thomsen reported +6.15 kilocalories, and the heat of reaction of manganous hydroxide with nitric acid. Combining the above value for the solid with the heat of fusion, 8.26 kilocalories, from the data of Riesenfeld and Milchsack,[15] Bichowsky and Rossini give −555.9 kilocalories for the heat of formation of the liquid nitrate from the elements. These older data, except for the heat of fusion, are reported at 291.16°K.

Summary

The heats of formation from the elements of liquid and solid manganous nitrate hexahydrate and the heat of fusion of this compound have been determined at room temperature by measuring the heats of solution in 1 *N* sulfuric acid. The results are, respectively, $\Delta H_{298.16} = -557{,}070 \pm 310$, $-566{,}680 \pm 310$, and $+9{,}610 \pm 10$ calories per mole.

(15) Riesenfeld and Milchsack, *Z. anorg. allgem. Chem.*, **85**, 401 (1914).

BERKELEY, CALIF. RECEIVED FEBRUARY 7, 1944

[CONTRIBUTION FROM THE WESTERN REGION, BUREAU OF MINES, U. S. DEPARTMENT OF THE INTERIOR, BERKELEY, CALIFORNIA]

Heats of Formation of $Mg(NO_3)_2$, $Mg(NO_3)_2 \cdot 6H_2O$, $Ca(NO_3)_2$, $Ca(NO_3)_2 \cdot 4H_2O$ and $Ba(NO_3)_2$[1]

BY FRANK E. YOUNG[2]

Thermal calculations pertaining to the nitrogen dioxide cyclic process for the hydrometallurgical extraction of manganese from ores require accurate values of the heats of formation of the nitrates of several constituents, particularly manganese, barium, calcium, and magnesium. No value of the heat of formation of anhydrous magnesium nitrate is available, and the existing heats of formation of the other nitrates are based largely on older data of uncertain reliability. New values of the heats of formation of solid and liquid manganous nitrate hexahydrate were reported in a previous paper.[3] The present paper records new determinations of the heats of formation of anhydrous magnesium, calcium, and barium nitrates, magnesium nitrate hexahydrate and calcium nitrate tetrahydrate.

(1) Published by permission of the Director, Bureau of Mines, U. S. Department of the Interior. (Not copyrighted.)

(2) Chemist, Western Region, Bureau of Mines.

(3) Shomate and Young, THIS JOURNAL, **66**, 771 (1944).

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Materials[4]

Magnesium nitrate hexahydrate was prepared from Merck C. P. product, containing a maximum of 0.07% impurities, by allowing it to stand for fifteen hours over potassium hydroxide to remove excess water and nitric acid. Analysis showed 9.50% Mg (theoretical, 9.48%). The average sample weight used in the present experiments was 6.0357 g.

Anhydrous magnesium nitrate was prepared by heating Merck C. P. magnesium nitrate hexahydrate *in vacuo*, beginning at 65° and raising the temperature gradually to 129° over a period of eleven hours, followed by fifteen hours at 129°. The flask then was opened and the solid cake broken up and pulverized, after which the heating at 129° was continued for six more hours. The temperature then was allowed to rise over a period of thirteen hours to 150°, and the heating was completed by a final half-hour at 150°. Analysis of the product showed 16.43% Mg (theoretical 16.40%) and 0.170% MgO (by titration). Correction was made in the thermal results for the presence of this oxide. The average sample size was 3.5024 g.

Calcium nitrate tetrahydrate was prepared by drying Mallinckrodt reagent-quality product over 78% sulfuric acid for twenty-two hours. Analysis showed 17.00% Ca (theoretical, 16.97%). No detectable amount of CaO was present. The average sample size was 5.2219 g.

Anhydrous calcium nitrate was prepared by melting Mallinckrodt reagent-quality calcium nitrate tetrahydrate and boiling off most of the water under reduced pressure. The material was then broken up and heated at 300° for twenty-four hours in an electric furnace. The product contained 24.43% Ca (theoretical, 24.42%) and 0.043% CaO. A correction was made for the presence of this calcium oxide. The average sample weight was 3.1962 g.

Calcium oxide was prepared by heating Mallinckrodt reagent-quality calcium carbonate to 900° for ninety hours in platinum, using an electric furnace. When the heating was completed, the calcium oxide was stored over dehydrite until the sample bulbs for the heats of solution were filled. These bulbs were filled allowing as little exposure to air as possible during filling and were sealed immediately after weighing. Analysis as sulfate showed 71.23% Ca, corresponding to 99.67% CaO. Titration gave 99.68% CaO. Samples of an average weight of 1.1156 g. were used.

Anhydrous barium chloride was prepared from Baker analyzed barium chloride dihydrate by drying at 135° for nineteen hours. Analyses by precipitation as barium sulfate gave an average of 65.90% Ba, corresponding to 99.92% $BaCl_2$. No oxide could be detected. The average sample weight was 8.3310 g. This size of sample was necessary because of the small heat of solution of barium chloride, the temperature rise being only 53.57 μv. with the sample used, corresponding to 0.04870°.

Anhydrous barium nitrate was prepared by grinding and drying Mallinckrodt analytical reagent barium nitrate at 115°. Analysis showed 99.89% $Ba(NO_3)_2$. The product was ground to pass an 80-mesh screen in order to decrease the time of solution. The average sample weight, 10.4550 g., corresponds to the weight of barium chloride used.

The 1.000 *N* hydrochloric acid used in the heat of solution measurements was prepared by dilution of reagent quality hydrochloric acid and standardization against sodium carbonate.

Method

The heats of formation were determined by measuring the heats of solution of the compounds in 1.000 *N* hydrochloric acid in the calorimeter previously described by Southard[5] and later by Shomate and Young.[3]

The results are expressed in defined calories (1 cal. = 4.1833 int. joules) and all formula weights were calculated from the 1941 International Atomic Weights. Corrections of weights to vacuum basis were made using the following densities: anhydrous magnesium nitrate, 2.2; magnesium nitrate hexahydrate, 1.46; calcium oxide, 3.40; calcium nitrate, 2.36; calcium nitrate tetrahydrate, 1.82; anhydrous barium chloride, 3.86; and anhydrous barium nitrate, 3.24. As the final temperature in each measurement was within a few hundredths of a degree of 25°, no correction of the results to 25° is necessary.

Measurements and Results

Each of the heats of formation has been obtained from the heats of the reactions represented by skeleton equations in the pertinent table below. The uncertainties, given in the last column of each table, are twice the standard deviations of the means of the experimental results involved. This method of calculating uncertainties has been discussed more fully by Rossini and Deming.[6] The final values for the heats of formation and the uncertainties have been rounded to the nearest 10 calories.

The Heat of Formation of Anhydrous Magnesium Nitrate.—The skeleton equations for the present method of obtaining the heat of formation of anhydrous magnesium nitrate are shown in Table I.

TABLE I

THE HEAT OF FORMATION OF $Mg(NO_3)_2$ (CAL. PER MOLE)

Reaction	$\Delta H_{298.16}$	Uncertainty
(1) $Mg + 2H^+ \longrightarrow Mg^{++} + H_2$	−111,322	41
(2) $H_2 + N_2 + 3O_2 \longrightarrow 2H^+ + 2NO_3^-$	−98,087	304
(3) $Mg(NO_3)_2 \longrightarrow Mg^{++} + 2NO_3^-$	−20,636	14
(4) $Mg + N_2 + 3O_2 \longrightarrow Mg(NO_3)_2$	−188,770	310

$\Delta H_4 = \Delta H_1 + \Delta H_2 - \Delta H_3$

The value for ΔH_1 was taken directly from the work of Shomate and Huffman,[7] who determined the heat of solution of magnesium metal under the same conditions as in the present measurements.

Reaction (2) represents the heat of formation of nitric acid in the final solution of reaction (1) or $MgCl_2 \cdot 75.2\ HCl \cdot 4190\ H_2O$. This value may be obtained by the use of the following equations:

(5) $H_2 + N_2 + 3O_2 + 26.5\ H_2O \longrightarrow 2\ HNO_3 \cdot 26.5\ H_2O$

(6) $2HNO_3 \cdot 26.5\ H_2O + MgCl_2 \cdot 75.2\ HCl \cdot 4190\ H_2O \longrightarrow Mg(NO_3)_2 \cdot 77.2\ HCl \cdot 4216.5\ H_2O$

(7) $Mg(NO_3)_2 \cdot 77.2\ HCl \cdot 4190\ H_2O + 26.5\ H_2O \longrightarrow Mg(NO_3)_2 \cdot 77.2\ HCl \cdot 4216.5\ H_2O$

The required heat of formation, ΔH_2, is equal to $\Delta H_5 + \Delta H_6 - \Delta H_7$. The value −98,398 ± 304 was adopted for ΔH_5. This value was obtained from the heat-of-formation and dilution data of Becker and Roth[8] as explained in the previous paper.[3] The values for ΔH_6 and ΔH_7 were determined in the present work by direct experiment as +198 ± 4 and −113 ± 4 calories, respectively.

(4) The materials used in this research were prepared by Dr. E. H. Huffman, formerly chemist in this laboratory.

(5) Southard, *Ind. Eng. Chem.*, **32**, 442 (1940).

(6) Rossini and Deming, *J. Wash. Acad. Sci.*, **29**, 416 (1939).

(7) Shomate and Huffman, THIS JOURNAL, **65**, 1625 (1943).

(8) Becker and Roth, *Z. Elektrochem.*, **40**, 842 (1934); *Z. physik. Chem.*, **A174**, 104 (1935).

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Six determinations of ΔH_3 were made, giving $-20,619$, $-20,621$, $-20,639$, $-20,647$, $-20,627$, and $-20,664$, with a mean of $-20,636 \pm 14$. These results have been corrected by $+189$ calories for the presence of 0.170% magnesium oxide and for variations in sample size which had a noticeable effect on the heats of solution, the average correction being 12 calories.

The heat of formation of anhydrous magnesium nitrate, ΔH_4, obtained by subtracting ΔH_3 from the sum of $\Delta H_1 + \Delta H_2$ is $-188,770 \pm 310$ calories.

The Heat of Formation of Magnesium Nitrate Hexahydrate.—Table II summarizes the data necessary for obtaining the heat of formation of magnesium nitrate hexahydrate.

TABLE II

THE HEAT OF FORMATION OF $Mg(NO_3)_2 \cdot 6H_2O$ (CAL. PER MOLE)

Reaction	$\Delta H_{298.16}$	Uncertainty
(8) $Mg + 2H^+ \longrightarrow Mg^{++} + H_2$	$-111,322$	41
(9) $H_2 + N_2 + 3O_2 \longrightarrow 2H^+ + 2NO_3^-$	$-98,087$	304
(10) $Mg(NO_3)_2 \cdot 6H_2O \longrightarrow Mg^{++} + 2NO_3^- + 6H_2O$	$+5,095$	2
(11) $6H_2 + 3O_2 \longrightarrow 6H_2O$	$-409,908$	60
(12) $Mg + N_2 + 6O_2 + 6H_2 \longrightarrow Mg(NO_3)_2 \cdot 6H_2O$	$-624,410$	310

$\Delta H_{12} = \Delta H_8 + \Delta H_9 - \Delta H_{10} + \Delta H_{11}$

Reactions (8) and (9) are identical with reactions (1) and (2) which have been discussed previously.

Six determinations of ΔH_{10} were made, giving $+5096$, $+5092$, $+5094$, $+5096$, $+5096$, $+5095$, with a mean of $+5095 \pm 1$ calories after applying a correction of $+26 \pm 1$ calories for the heat of dilution by the water of hydration. The mean value for ΔH_{10} corresponds to a temperature drop of 76.34 μv. or 0.06940° in the calorimeter.

Rossini's[9] value for the heat of formation of water, $-68,318 \pm 10$ calories per mole, was multiplied by six to obtain ΔH_{11}, giving $-409,908 \pm 60$ calories.

$\Delta H_8 + \Delta H_9 - \Delta H_{10} + \Delta H_{11}$ gives the heat of formation of magnesium nitrate hexahydrate from the elements as $\Delta H_{12} = -624,410 \pm 310$ calories.

Anhydrous Calcium Nitrate.—Table III outlines the reactions for determining the heat of formation of anhydrous calcium nitrate.

The heat of reaction (13) was taken from the compilation of Bichowsky and Rossini,[10] the correction of 25° being negligible.

Six determinations were made of ΔH_{14}, giving $-46,220 \pm 14$ as the mean of: $-46,216$, $-46,235$, $-46,230$, $-46,204$, $-46,197$, $-46,240$. These values include a correction of -151 calories

(9) Rossini, *Bur. Standards J. Research*, **22**, 407 (1939).

(10) Bichowsky and Rossini, "Thermochemistry of Chemical Substances," Reinhold Publishing Corporation, New York, N. Y., 1936.

TABLE III

THE HEAT OF FORMATION OF $Ca(NO_3)_2$ (CAL. PER MOLE)

Reaction	$\Delta H_{298.16}$	Uncertainty
(13) $Ca + {}^1/_2O_2 \longrightarrow CaO$	$-151,800$	200
(14) $CaO + 2H^+ \longrightarrow Ca^{++} + H_2O$	$-46,220$	14
(15) $H_2 + N_2 + 3O_2 \longrightarrow 2H^+ + 2NO_3^-$	$-98,087$	304
(16) $Ca(NO_3)_2 \longrightarrow Ca^{++} + 2NO_3^-$	$-3,740$	9
(17) $H_2 + {}^1/_2O_2 \longrightarrow H_2O$	$-68,318$	10
(18) $Ca + N_2 + 3O_2 \longrightarrow Ca(NO_3)_2$	$-224,050$	360

$\Delta H_{18} = \Delta H_{13} + \Delta H_{14} + \Delta H_{15} - \Delta H_{16} - \Delta H_{17}$

for the presence of impurities and a correction of $+4$ calories for the heat of dilution by the water formed in the reaction.

The heat of formation of nitric acid in $CaCl_2 \cdot 85.25\ HCl \cdot 4775\ H_2O$ is found in the same way as ΔH_2, discussed previously. The heats of solution of nitric acid and water in the calcium chloride solution were determined by direct experiment and were found to have the same values as corresponding heats of solution in the magnesium chloride solution discussed before, namely, $+194 \pm 4$ and -113 ± 4 calories, respectively.

The heat of solution of anhydrous calcium nitrate, ΔH_{16}, is the mean of seven results: -3742, -3759, -3736, -3742, -3749, -3725, and -3725 calories, after application of a $+57$-calorie correction for calcium oxide content. It was thought that the abnormally large spread in these results might be attributed to the effects of a transition of small thermal magnitude near room temperature. In order to test this the fifth sample (-3749 cal.) was heated to 110° for forty hours immediately before measuring its heat of solution; the sixth result (-3725) was obtained using a sample that had been kept at 0° for sixty-four hours and the seventh result (-3725) using a sample that had been cooled in a carbon dioxide–ethyl alcohol mixture and allowed to warm up over a period of twenty-four hours to 10° before it was put into the calorimeter. After completion of these heat of solution measurements, a minor transition actually was found in the heat capacity of anhydrous calcium nitrate at 288°K.[11] It thus appears that the larger heats of solution correspond to the high-temperature form and the smaller values to the low-temperature form, as might be expected.

ΔH_{17} is Rossini's[9] value of the heat of formation of water.

The heat of formation of anhydrous calcium nitrate from the elements, ΔH_{18}, is $-224,050 \pm 360$ calories per mole.

The Heat of Formation of Calcium Nitrate Tetrahydrate.—The skeleton equations representing the reactions necessary to obtain the heat of formation of calcium nitrate tetrahydrate are shown in Table IV.

The first three reactions, ΔH_{19}, ΔH_{20} and

(11) Shomate and Kelley, unpublished measurements.

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TABLE IV

THE HEAT OF FORMATION OF $Ca(NO_3)_2 \cdot 4H_2O$ (CAL. PER MOLE)

Reaction	$\Delta H_{298.16}$	Uncertainty
(19) $Ca + {}^1/_2O_2 \longrightarrow CaO$	−151,800	200
(20) $CaO + 2H^+ \longrightarrow Ca^{++} + H_2O$	−46,220	14
(21) $H_2 + N_2 + 3O_2 \longrightarrow 2H^+ + 2NO_3^-$	−98,087	304
(22) $Ca(NO_3)_2 \cdot 4H_2O \longrightarrow Ca^{++} + 2NO_3^- + 4H_2O$	+8,360	3
(23) $3H_2 + {}^3/_2O_2 \longrightarrow 3H_2O$	−204,954	30
(24) $Ca + N_2 + 5O_2 + 4H_2 \longrightarrow Ca(NO_3)_2 \cdot 4H_2O$	−509,420	370

$\Delta H_{24} = \Delta H_{19} + \Delta H_{20} + \Delta H_{21} - \Delta H_{22} + \Delta H_{23}$

ΔH_{21}, were discussed above as ΔH_{13}, ΔH_{14} and ΔH_{15}, respectively.

ΔH_{22} is the mean of six results after applying a correction of +17 ± 1 calories for the heat of dilution by the water of hydration. These corrected heats of solution are +8353, 8361, 8360, 8358, 8363, and 8365, with a mean of 8360 ± 3 calories.

ΔH_{23} represents the heat of formation of 3 molecules of water or three times Rossini's[9] value for the heat of formation of water.

The heat of formation of calcium nitrate tetrahydrate, ΔH_{24}, is −509,420 ± 370.

The Heat of Formation of Anhydrous Barium Nitrate.—Table V summarizes the reactions used to obtain the heat of formation of anhydrous barium nitrate.

TABLE V

THE HEAT OF FORMATION OF $Ba(NO_3)_2$ (CAL. PER MOLE)

Reaction	$\Delta H_{298.1}$	Uncertainty
(25) $Ba + Cl_2 \longrightarrow BaCl_2$	−205,260	210
(26) $BaCl_2 \longrightarrow Ba^{++} + 2Cl^-$	−2,086	4
(27) $H_2 + Cl_2 \longrightarrow 2H^+ + 2Cl^-$	−78,466	100
(28) $H_2 + N_2 + 3O_2 \longrightarrow 2H^+ + 2NO_3^-$	−98,164	304
(29) $Ba(NO_3)_2 \longrightarrow Ba^{++} + 2NO_3^-$	+9,944	8
(30) $Ba + N_2 + 3O_2 \longrightarrow Ba(NO_3)_2$	−236,990	380

$\Delta H_{30} = \Delta H_{25} + \Delta H_{26} - \Delta H_{27} + \Delta H_{28} - \Delta H_{29}$

The heat of formation of barium chloride given by Bichowsky and Rossini,[10] corrected to 25°, was adopted for reaction (25).

Six determinations were made of the heat of solution of barium chloride in 1.000 *N* hydrochloric acid, reaction (26), giving −2088, −2080, −2086, −2090, −2084 and −2095 calories, with a mean of −2086 ± 4 calories per mole. It was necessary to correct these heats of solution for variations in sample size. The average correction was 5 calories.

Equation (27) represents the heat of formation of hydrogen chloride in $Ba(NO_3)_2 \cdot 45.5HCl \cdot 2474H_2O$. This heat of formation was estimated by assuming it to be the same in the above solution as in a solution in which the barium nitrate had been replaced by enough hydrogen chloride to maintain the same ionic strength, giving the equation:

(31) $48.5HCl \cdot 2474H_2O + H_2 + Cl_2 \longrightarrow 50.5HCl \cdot 2474H_2O$

The heat of reaction (31) may be calculated from the difference of the two reactions

(32) $24.25H_2 + 24.25Cl_2 + 2474H_2O \longrightarrow 48.5HCl \cdot 2474H_2O$

(33) $25.25H_2 + 25.25Cl_2 + 2474H_2O \longrightarrow 50.5HCl \cdot 2474H_2O$

using the heat of formation of hydrochloric acid at infinite dilution given by Rossini[12] and the heats of dilution reported by Sturtevant.[13] The heat of reaction (27) calculated in this manner is −78,466 for 2 moles of hydrochloric acid, in which the uncertainty is estimated as ±100 calories.

ΔH_{28} is found in the same way as ΔH_2 and ΔH_{15}, using the directly determined values of +115 ± 10 and −113 ± 4 for the heats of solution of nitric acid and the corresponding amount of water in the barium chloride solution, respectively.

The value given for ΔH_{29} is the mean of six results, +9950, 9950, 9931, 9951, 9930 and 9951, or 9944 ± 8 calories. As with the barium chloride, it was necessary to make a small correction for variations in sample weights. In this instance, the average correction was 2 calories.

The heat of formation of barium nitrate, $\Delta H_{30} = \Delta H_{25} + \Delta H_{26} - \Delta H_{27} + \Delta H_{28} - \Delta H_{29}$, is −236,990 ± 380 calories per mole.

Discussion.—The results obtained in this research are compared in Table VI with previous values taken from the compilation of Bichowsky and Rossini.[10]

TABLE VI

HEATS OF FORMATION (CAL. PER MOLE)

Substance	Heat of formation: From elements, This research	From elements, Previous value	From elements and $H_2O(l)$, This research	From elements and $H_2O(l)$, Previous value
$Mg(NO_3)_2$	−188,770	...	...	...
$Mg(NO_3)_2 \cdot 6H_2O$	−624,410	−622,500	−214,500	−212,590
$Ca(NO_3)_2$	−224,050	−224,040	...	...
$Ca(NO_3)_2 \cdot 4H_2O$	−509,420	−509,590	−236,150	−236,320
$Ba(NO)_3$	−236,990	−236,900	...	...

The previous values are for a temperature of 18° and have not been corrected to the base temperature of the present work, 25°. They are based on heats of solution of metallic calcium and barium reported by Guntz and Benoit,[14] the heat of solution of calcium oxide determined by Gautier,[15] the heat of solution of calcium nitrate tetrahydrate determined by Ewing, Rogers, Miller and McGovern,[16] and various heats of solution and reaction measured by Thomsen. The agreement is satisfactory, except for the mag-

(12) Rossini, *Bur. Standards J. Research*, **9**, 679 (1932).
(13) Sturtevant, THIS JOURNAL, **62**, 584 and 3265 (1940).
(14) Guntz and Benoit, *Ann. chim.*, **20**, 5 (1923).
(15) Gautier, *Compt. rend.*, **128**, 939 (1899).
(16) Ewing, Rogers, Miller and McGovern, THIS JOURNAL, **54**, 1335 (1932).

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nesium nitrate hexahydrate results. The difference between the values for this material again illustrates the necessity for redetermination of heats of formation which are based on data antedating modern methods, *i. e.*, the data of Thomsen in the present instance.

It will be noted that the part of the uncertainty in the heats of formation attributable to the heat of formation of the nitric acid alone ranges from 44 to 86% of the total uncertainty. Correction of the present results may be made readily whenever a better heat of formation of nitric acid becomes available.

Summary

The heats of formation of several nitrates of magnesium, calcium and barium have been determined at 25° by measuring heats of solution in 1.000 *N* hydrochloric acid. These heats of formation from the elements are: magnesium nitrate, −188,770 ± 310; magnesium nitrate hexahydrate, −624,410 ± 310; calcium nitrate, −224,050 ± 360; calcium nitrate tetrahydrate, −509,420 ± 370, and barium nitrate, −236,990 ± 380 calories per mole.

BERKELEY, CALIF. RECEIVED FEBRUARY 14, 1944

[CONTRIBUTION FROM THE WESTERN REGION, BUREAU OF MINES, U. S. DEPARTMENT OF THE INTERIOR]

The Heats of Formation of $Al(NO_3)_3 \cdot 6H_2O$ and $Al(NO_3)_3 \cdot 9H_2O$[1]

BY FRANK E. YOUNG[2]

The heats of formation of several metallurgically important nitrates have been determined recently at the Pacific Experiment Station of the Bureau of Mines. Previous papers have described determinations of the heats of formation of solid and liquid manganous nitrate hexahydrate[3] and the anhydrous nitrates of barium, calcium and magnesium, as well as calcium nitrate tetrahydrate and magnesium nitrate hexahydrate.[4] The present paper reports values of the heats of formation for two hydrated aluminum nitrates for which no previous results are available.

Materials and Method

The aluminum metal used in the measurements was cut from the center of a small ingot of 99.78% aluminum. The principal impurities were 0.10% magnesium and 0.10% iron. The only other impurity, except a negligible amount of surface oxide, was 0.02% copper. The magnesium and copper were determined chemically and the iron was determined both chemically and spectrographically. Titanium and manganese were shown to be absent by the spectrograph. After the aluminum was cut, it was washed several times with benzene, dried *in vacuo*, and weighed into bulbs which were sealed immediately. Corrections in the thermal measurements were made for the impurities.

Aluminum nitrate enneahydrate was prepared by Dr. E. H. Huffman, formerly of this Laboratory, by recrystallization of Mallinckrodt analytical reagent grade of aluminum nitrate from 4 *N* nitric acid. After air drying, the material was stored over 80% sulfuric acid for seventeen hours to remove excess water. Direct ignition to aluminum oxide, in platinum, over a gas–oxygen blast lamp, gave 13.58% Al_2O_3 (theoretical, 13.59%).

Aluminum nitrate hexahydrate was prepared by storing the enneahydrate over Dehydrite for five days. Analysis by direct ignition in platinum over the blast lamp gave 15.86% Al_2O_3 (theoretical, 15.87% Al_2O_3).

The heats of formation were determined by measuring the heats of solution in 4.000 *N* hydrochloric acid, which was prepared by diluting concentrated reagent quality hydrochloric acid and standardized against sodium carbonate.

To shorten the time required for taking the aluminum into solution, 1 ml. of chloroplatinic acid solution was added to the hydrochloric acid in the calorimeter before each determination. The chloroplatinic acid solution was prepared by dissolving 0.1002 g. of Mallinckrodt Analytical Reagent chloroplatinic acid hexahydrate in enough 4.000 *N* hydrochloric acid to make 100 ml. of solution. A correction was applied to the thermal results for the reduction of the chloroplatinic acid by the aluminum. The use of chloroplatinic acid reduced the solution time of the aluminum from several hours to twenty or thirty minutes.

The calorimetric measurements were made in the apparatus described by Southard[5] and later by Shomate and Young.[3] The results are expressed in defined calories (1 cal. = 4.1833 int. joules). All formula weights were calculated in accordance with the 1941 International Atomic Weights. Corrections of weights to vacuum were made using the following densities: aluminum metal, 2.70; aluminum nitrate enneahydrate, 1.4; aluminum nitrate hexahydrate, 1.7 (estimated).

Measurements and Results

The reactions by which the heats of formation of aluminum nitrate enneahydrate and aluminum nitrate hexahydrate were obtained are shown as skeleton equations in Tables I and II, respectively. The uncertainties in the last column of each table are twice the standard deviations of the means of the experimental results. This method of ascribing uncertainties has been discussed by Rossini and Deming.[6] The final values of the heats of formation and the corresponding uncertainties have been rounded to the nearest ten calories. The final temperatures in the solution measurements were always within a few hundredths of a degree of 25°, so that no correction was needed. The average sample weights, aluminum, 0.5394 g.; aluminum nitrate enneahydrate, 7.5028 g.; and aluminum nitrate hexahydrate, 6.4214 g., correspond to a dilution of 1 mole of anhydrous salt in $361.6HCl \cdot 4585H_2O$. The calorimetric

(1) Published by permission of the Director, Bureau of Mines, U. S. Department of the Interior. (Not copyrighted.)
(2) Chemist, Western Region, Bureau of Mines.
(3) Shomate and Young, THIS JOURNAL, **66**, 771 (1944).
(4) Young, *ibid.*, **66**, 773 (1944).
(5) Southard, *Ind. Eng. Chem.*, **32**, 442 (1940).
(6) Rossini and Deming, *J. Wash. Acad. Sci.*, **29**, 416 (1939).

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temperature changes accompanying solution of these samples were: aluminum, 1.67155°; aluminum nitrate enneahydrate, 0.13869°; and aluminum nitrate hexahydrate, 0.01310°.

The Heat of Formation of Aluminum Nitrate Enneahydrate.—Table I gives the skeleton equations of the reactions used in obtaining the heat of formation of aluminum nitrate enneahydrate.

TABLE I

THE HEAT OF FORMATION OF $Al(NO_3)_3 \cdot 9H_2O$ (CAL. PER MOLE)

Reactions	$\Delta H_{298.16}$	Uncertainty
(1) $Al + 3H^+ \longrightarrow Al^{+++} + {}^3/_2H_2$	−126,834	62
(2) ${}^3/_2H_2 + {}^3/_2N_2 + {}^9/_2O_2 \longrightarrow 3H^+ + 3NO_3^-$	−144,695	456
(3) $Al(NO_3)_3 \cdot 9H_2O \longrightarrow Al^{+++} + 3NO_3^- + 9H_2O$	+11,194	11
(4) $9H_2 + {}^9/_2O_2 \longrightarrow 9H_2O$	−614,862	90
(5) $Al + {}^3/_2N_2 + 9H_2 + 9O_2 \longrightarrow Al(NO_3)_3 \cdot 9H_2O$	−897,590	470

$\Delta H_5 = \Delta H_1 + \Delta H_2 - \Delta H_3 + \Delta H_4$

The heat of solution of aluminum in 4 *N* hydrochloric acid, ΔH_1, is the mean of six results: −126,810, −126,824, −126,727, −126,868, −126,884, and −126,875 cal. A correction of −143 cal. has been applied to these results for the presence of the impurities discussed above. It was also necessary to correct for the heat absorbed in the vaporization of water by the escaping hydrogen. This correction was made on the assumption that none of the hydrogen was left in the solution by the time thermal equilibrium was attained and that the hydrogen was completely saturated with water vapor when it left the solution. The partial pressure of water vapor over the solution was taken as 18.1 mm. and the heat of vaporization as 10,500 cal. per gram formula mass at 25°. Allowing an uncertainty of 10%, this correction was −376 ± 38 cal. for the 1.5 moles of hydrogen involved. The correction for vaporization of hydrogen chloride was nearly negligible, being only 1 cal. The total vaporization correction of −377 cal. has already been applied to the above results. The heat evolved in the reduction of the chloroplatinic acid used to increase the rate of solution of the aluminum made an additional correction of +16 cal. necessary. In making this correction, it was assumed that all of the chloroplatinic acid was reduced to the metal. Data for this correction were obtained from the compilation of Bichowsky and Rossini.[7]

Equation (2) represents the heat of formation of nitric acid in $AlCl_3 \cdot 358.6HCl \cdot 4585H_2O$. This heat of formation may be obtained from the reactions

(6) ${}^3/_2H_2 + {}^3/_2N_2 + {}^9/_2O_2 + 37.11H_2O \longrightarrow 3HNO_3 \cdot 37.11H_2O$

(7) $3HNO_3 \cdot 37.11H_2O + AlCl_3 \cdot 358.6HCl \cdot 4585H_2O \longrightarrow Al(NO_3)_3 \cdot 361.6HCl \cdot 4622.11H_2O$

(8) $Al(NO_3)_3 \cdot 361.6HCl \cdot 4585H_2O + 37.11H_2O \longrightarrow Al(NO_3)_3 \cdot 361.6HCl \cdot 4622.11H_2O$

The value for the heat of formation of nitric acid in 0.05 *M* solution, −49,234 ± 152 cal., was obtained from the data of Becker and Roth,[8] as explained in a previous paper.[3] The correction for the difference in acid strengths from 0.05 *M* to the present concentration of $3HNO_3 \cdot 37.11H_2O$ was obtained from the heats of dilution given by Becker and Roth.[9] This correction amounted to 56 cal., making $\Delta H_6 = 3(-49{,}178 \pm 152)$ or −147,534 ± 456 cal. The heats of solution of nitric acid, ΔH_7, and the corresponding amount of water, ΔH_8, in the aluminum chloride solution were measured directly as $\Delta H_7 = +53 \pm 5$ cal. and $\Delta H_8 = -2786 \pm 2$ cal. The required ΔH_2 is $\Delta H_6 + \Delta H_7 - \Delta H_8$ or −144,695 ± 456 cal.

Six measurements of the heat of solution of aluminum nitrate enneahydrate, ΔH_3, were made to obtain +11,194 ± 11 cal., the mean of +11,192, +11,173, +11,216, +11,186, +11,196, and +11,201 cal., after application of a +676 ± 1 cal. correction for the measured heat of dilution by the water of hydration.

The heat of formation of 9 moles of water, ΔH_4, was obtained by multiplying Rossini's[10] heat of formation of water by 9: $9(-68{,}318 \pm 10) = -614{,}862 \pm 90$ cal. The heat of formation of aluminum nitrate enneahydrate from the elements, ΔH_5, is −897,590 ± 470 cal. per mole. The heat of formation of this compound from the elements and liquid water, $\Delta H_1 + \Delta H_2 - \Delta H_3$, is −282,720 ± 260 cal. per mole.

The Heat of Formation of Aluminum Nitrate Hexahydrate.—Table II summarizes the reactions used in this work in obtaining the heat of formation of aluminum nitrate hexahydrate.

TABLE II

THE HEAT OF FORMATION OF $Al(NO_3)_3 \cdot 6H_2O$ (CAL. PER MOLE)

Reaction	$\Delta H_{298.16}$	Uncertainty
(9) $Al + 3H^+ \longrightarrow Al^{+++} + {}^3/_2H_2$	−126,834	62
(10) ${}^3/_2H_2 + {}^3/_2N_2 + {}^9/_2O_2 \longrightarrow 3H^+ + 3NO_3^-$	−144,695	456
(11) $Al(NO_3)_3 \cdot 6H_2O \longrightarrow Al^{+++} + 3NO_3^- + 6H_2O$	−543	6
(12) $6H_2 + 3O_2 \longrightarrow 6H_2O$	−409,908	60
(13) $Al + {}^3/_2N_2 + {}^{15}/_2O_2 + 6H_2 \longrightarrow Al(NO_3)_3 \cdot 6H_2O$	−680,890	460

$\Delta H_{13} = \Delta H_9 + \Delta H_{10} - \Delta H_{11} + \Delta H_{12}$

Reactions (9) and (10) have been discussed already as reactions (1) and (2), respectively.

Six measurements of the heat of solution of aluminum nitrate hexahydrate in 4 *N* hydro-

(7) Bichowsky and Rossini, "Thermochemistry of the Chemical Substances," Reinhold Publishing Corporation, New York, N. Y., 1936.

(8) Becker and Roth, *Z. Elektrochem.*, **40**, 842 (1934).

(9) Becker and Roth, *Z. physik. Chem.*, **A174**, 104 (1935).

(10) Rossini, *Bur. Standards J. Research*, **22**, 407 (1939).

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chloric acid gave −543, −531, −550, −539, −550, and −546, with a mean of −543 ± 6 cal. per mole after application of a measured 450 ± 1 cal. correction for the heat of dilution by the water of hydration.

Reaction (12) again involves Rossini's heat of formation of water, −409,908 ± 60 cal. for 6 moles.

The heat of formation of aluminum nitrate hexahydrate from the elements, ΔH_{13}, is −680,890 ± 460 cal. per mole. The heat of formation of this hydrate from the elements and liquid water, $\Delta H_9 + \Delta H_{10} - \Delta H_{11}$, is −270,990 ± 460 cal. per mole.

Whenever a better heat of formation of nitric acid becomes available, the present measurements may be corrected accordingly.

Summary

The heats of formation of aluminum nitrate enneahydrate and aluminum nitrate hexahydrate have been determined by measuring the heats of solution of these compounds and aluminum in 4.000 *N* hydrochloric acid. The heats of formation from the elements are −897,590 ± 470 cal. per mole for aluminum nitrate enneahydrate and −680,890 ± 460 cal. per mole for aluminum nitrate hexahydrate.

BERKELEY, CALIFORNIA RECEIVED FEBRUARY 14, 1944

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF KANSAS]

The System Acetic Acid–Ammonia

BY ARTHUR W. DAVIDSON, HARRY H. SISLER AND RAYMOND STOENNER

The familiar salt ammonium acetate, $NH_4C_2H_3O_2$, as well as solutions of this salt in acetic acid, may readily be prepared by the direct combination of dry ammonia and anhydrous acetic acid. It is obvious, then, that the entire system acetic acid–ammonium acetate, freezing point data for which have previously been presented,[1] may be regarded as constituting only one-half of the more comprehensive binary system acetic acid–ammonia, in which ammonium acetate assumes the role merely of an especially stable addition compound.[2] Although ammonium acetate has long been known to be readily soluble in liquid ammonia,[3] and a determination of its solubility at a single temperature has indeed been reported,[4] no attempt has thus far been made to study the system throughout the entire range of concentrations.

It will readily be appreciated that the investigation of liquid solutions consisting of ammonium acetate and excess ammonia presents experimental difficulties which are not encountered with solutions of ammonium acetate in acetic acid. Especially is this true at room temperatures and above, since the lowering of the vapor pressure of liquid ammonia produced by ammonium acetate is not nearly so great as might be expected.[5] Other similar systems, consisting of ammonia and ammonium nitrate,[6] ammonium thiocyanate,[7] and the ammonium halides,[8] have been successfully studied, although only in the first two instances was it found possible to cover the entire range of concentrations from ammonia to pure ammonium salt.

The present work consisted mainly of a study of the ammonium acetate–ammonia portion of the system. A part of the earlier work[1] was repeated, also, and somewhat more accurate data were obtained for temperatures above 60°. Three new addition compounds of ammonia and acetic acid, two of them stable at their melting points, have been discovered.

Method

Preparation of Materials.—Anhydrous acetic acid was prepared as described in previous papers from this Laboratory.[1] No sample used had a freezing point of less than 16.60°.

Commercial synthetic anhydrous ammonia, which was stated to be at least 99.95% pure, was found to have a freezing point of −77.5 ± 0.4°, in good agreement with the values of −77.7 to −77.8° found in the literature. Distillation over metallic sodium was found to bring about no change in freezing point; hence this product was used without further purification.

Ammonium acetate was obtained, as described previously,[1] by the passage of dry ammonia over anhydrous acetic acid in a desiccator over calcium oxide. The preparation of pure ammonium acetate (50 mole % of ammonia) by this process is very slow, and requires the use of a large excess of ammonia; furthermore, there is no advantage to be gained by the use of a salt of exactly this composition. Hence, various solid products containing from 38 to 43 mole % of ammonia were used as starting materials, after determination of their compositions by treatment with sodium hydroxide solution and distillation of the ammonia into standard hydrochloric acid.

Determination of Equilibrium.—A few mixtures, containing from 23 to 43 mole % of ammonia, were made up by the addition of acetic acid to the solid starting material, and their freezing points were determined in sealed tubes, as previously described,[1] as a check on the earlier results. For all other mixtures of f. p. higher than −10° (45 to 82 mole % of ammonia), the method used was essentially that of Bradley and Alexander.[7] A small quantity (0.5 to 0.6 g.) of a solid mixture of known composition was introduced into the bend of a U-shaped glass tube of 8 mm. internal diameter and a total length of about 30 cm., and its weight was determined by difference. The lower part of the tube

(1) Davidson and McAllister, THIS JOURNAL, **52**, 507 (1930).
(2) Davidson, *Chem. Rev.*, **8**, 175 (1931).
(3) Franklin and Kraus, *Am. Chem. J.*, **20**, 820 (1898).
(4) Hunt and Boncyk, THIS JOURNAL, **55**, 3528 (1933).
(5) Shatenshtein and Uskova, *Acta Physicochim., U. R. S. S.*, **2**, 337 (1935); *C. A.*, **29**, 6489 (1935).
(6) Kuriloff, *Z. physik. Chem.*, **25**, 107 (1898).
(7) Bradley and Alexander, THIS JOURNAL, **34**, 15 (1912).
(8) Kendall and J. G. Davidson, *ibid.*, **42**, 1141 (1920).

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was then immersed in a bath of solid carbon dioxide, carbon tetrachloride and chloroform, which maintained a temperature of −78°, and dry ammonia was passed through the tube.[9] The quantity of ammonia condensed under these conditions could be readily controlled by maintenance of a constant rate of flow and regulation of the time of absorption, which varied, in different samples, from thirty seconds to three minutes. After a little practice, it was found possible to attain any desired composition by this means. Then, with the bend of the U-tube still in the cold bath, both ends of the tube were sealed in the blast-lamp, and it was allowed to come to room temperature and weighed. After the mixture had completely liquefied, it was again cooled until solidification occurred; the equilibrium temperature was then determined as that at which the last trace of crystals disappeared, while the tube was being slowly heated. Each f. p. was determined at least twice; the temperatures reported are believed to be correct to within 0.5°, except in the range from 67 to 75 mole % of ammonia, where, because of the extremely high rate of change of equilibrium temperature with concentration, the values are accurate only to ±2°.

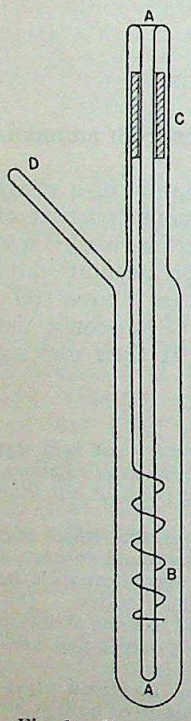

Fig. 1.—Freezing point cell.

At temperatures much below 0°, the mixtures became so viscous and equilibrium was attained so slowly that the procedure just described was no longer satisfactory. The method adopted for solutions of f. p. below −10° was similar to that described by Cady and Jones,[10] except that equilibrium temperatures were determined by means of cooling curves instead of by visual observation. The cells used were as pictured in Fig. 1; their outer dimensions were 35 by 2.5 cm., with a thermocouple well, AA, about 5 mm. in diameter. The stirrer, B, was of stainless steel wire, the upper end of which was attached to a short piece of iron pipe, C, which had been coated with stainless steel. The stirrer was operated by means of a solenoid, which was wired through a motor-driven interrupter making contact approximately 120 times per minute.

Mixtures of the desired composition were made by the following procedure. The weighed cell, surrounded by a weighed test-tube of slightly larger diameter which served as an air jacket, was one-third immersed in liquid air. About 20 cc. of ammonia was introduced by distillation through the side arm D, which was then closed by means of a rubber cap. After the ammonia had solidified, the jacketed cell was removed from the bath, the outer tube was warmed to room temperature, and the weight of the ammonia was determined. The air jacket provided sufficient insulation so that but little of the ammonia melted, and no appreciable amount vaporized, during the weighing. The desired quantity of acetic acid was introduced through the side arm, the end of which was then sealed. The jacket was removed, and the cell was warmed to room temperature and again weighed.

For the determination of equilibrium temperatures, the well, AA, was filled with a mixture of carbon tetrachloride and chloroform, in order to minimize convection effects. A copper–constantan thermocouple was introduced, and the cell was surrounded by several concentric tubes to provide air jackets. It was then immersed in a bath of solid carbon dioxide, or of liquid air, in a Dewar flask, so that cooling took place at a rate not exceeding one degree per minute. The rate of cooling in the neighborhood of the f. p. was kept approximately the same for all the determinations by the expedient of decreasing the number of jackets for mixtures of lower f. p.

The temperature–time curves were recorded directly by means of a Leeds and Northrup Micromax recorder, which had been calibrated at the b. p. of ammonia, the f. p. of pyridine, the sublimation point of carbon dioxide, and the b. p. of oxygen. The level to which the temperature rose immediately after the first break in the cooling curve was taken as the equilibrium temperature.[11] Data so obtained are believed to be correct to ±1.5°.

Analysis of Solid Phases.—Two of the three new compounds encountered in this work exist only under such conditions of temperature and pressure that the obtaining of samples for analysis would have been extremely difficult, if not impossible. Fortunately, however, both of these compounds melt congruently, so that the composition of each is clearly indicated by the position of the corresponding maximum in the f. p. curve. In the case of the third compound, the probable composition is indicated by the course of the curve, but an attempt was made to confirm this by direct analysis. A solution of appropriate composi-

TABLE I

ACETIC ACID–AMMONIA

S	T	S	T
(a) Solid phase $NH_3 \cdot 2HC_2H_3O_2$		(c) Solid phase $5NH_3 \cdot 4HC_2H_3O_2$ (cont.)	
23.7	50.1	69.2	100.0
26.3	59.5	71.2	91.0
30.2	66.0	71.9	87.0
31.3	66.5	72.2	85.0
32.6	67.0	72.7	81.0
		73.2	78.0
(b) Solid phase $NH_3 \cdot HC_2H_3O_2$		73.7	68.5
		74.2	40.0
34.0	69.0		
34.9	73.5	(d) Solid phase $2NH_3 \cdot HC_2H_3O_2$ (?)	
35.9	79.5		
39.6	96.5	74.4	6.5
40.8	100.5	75.7	4.5
43.3	106.5	76.2	3.0
45.6	112.0	78.0	−1.0
46.7	114.0	78.6	−3.0
48.0	115.5	80.2	−7.0
50.0	117.0	81.2	−9.0
51.0	117.0	84.6	−20.5
51.6	117.0	87.3	−29.5
(c) Solid phase $5NH_3 \cdot 4HC_2H_3O_2$		(e) Solid phase $9NH_3 \cdot HC_2H_3O_2$	
53.1	119.0	88.8	−35.5
54.5	120.0	89.6	−34.0
55.2	119.5	90.9	−34.5
55.7	119.5	92.6	−40.5
56.0	119.5	97.6	−61.5
59.0	118.0	98.0	−64.0
61.4	116.4	98.9	−77.5
63.9	113.0	(f) Solid phase NH_3	
66.0	109.5	99.3	−78.5
67.8	104.5	100.0	−77.5

(9) It was attempted, at first, to carry out the absorption of ammonia in an ice–salt bath; under these conditions, however, condensation occurred so extremely slowly that the method proved to be impracticable.

(10) Cady and Jones, *J. Phys. Chem.*, **37**, 303 (1933).

(11) The difference in the rates of cooling above and below the equilibrium point was usually not sufficiently great to make it possible to fix this point by extrapolation of the lower portion of the curve.

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tion was made up in the lower end of a cell consisting of two bulbs, about 8 by 2 cm. each, connected by a vertical tube 10 cm. long and 8 mm. in diameter. The upper end of the cell was then sealed. After equilibrium had been reached at the desired temperature, the cell was inverted and the mother liquor allowed to drain into the lower bulb, both bulbs being maintained at the same temperature throughout the process. After two days, the narrow portion of the cell was sealed and the bulbs separated. The one containing the crystalline solid was weighed, broken under dilute acid, washed out, and weighed again; the amount of ammonium salt formed in the solution was then determined in the usual manner.

Results

In the preceding table, S denotes the mole percentage of ammonia, and T the corresponding equilibrium temperature. These data, together with those of Davidson and McAllister, are presented graphically in Fig. 2, in which, however, a few of the points have been omitted in order to avoid crowding.

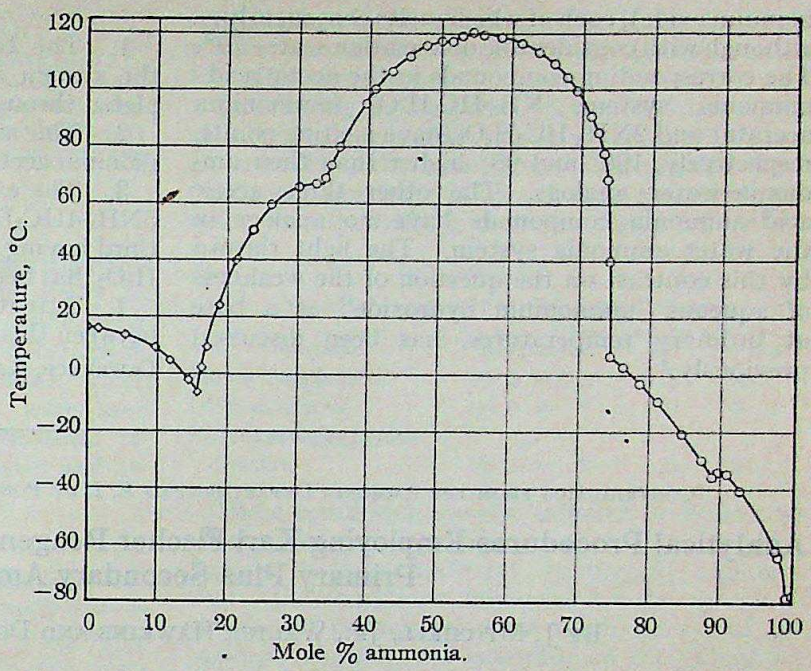

Fig. 2.—System acetic acid–ammonia; the data of Davidson and McAllister (recalculated) are indicated by squares, those of the present work by circles.

The equilibrium temperatures in the range from 25 to 50 mole % of ammonia were found to be a little higher than those previously reported, the difference increasing with increasing ammonia content. Thus, the melting point of the compound $NH_3 \cdot 2HC_2H_3O_2$ (or $NH_4C_2H_3O_2 \cdot HC_2H_3O_2$) was found to be 67.0° instead of 66.5°, and that of ammonium acetate ($NH_3 \cdot HC_2H_3O_2$ or $NH_4C_2H_3O_2$) to be 117° instead of 113°.

Because of the decidedly unexpected course of the curve just beyond the mid-point, this region was studied with special care; the data reported above are representative of a much larger number of determinations. The evidence for the existence of a eutectic point at about 52 mole % of ammonia, and of a surprisingly stable compound of ammonia content but slightly higher than that of ammonium acetate, is unmistakable. The composition of this compound (55.6 mole % of ammonia) corresponds to the formula $5NH_3 \cdot 4HC_2H_3O_2$ (or $4NH_4C_2H_3O_2 \cdot NH_3$), and its melting point is 119.5 ± 0.5°. Its saturated solution in liquid ammonia at 25° is found to contain 25.7 mole % of acetic acid. This figure agrees fairly well with that of 26.4% calculated from the data of Hunt and Boncyk,[4] who, however, do not mention the solvation of ammonium acetate under these conditions.

At about 6.5° this compound undergoes transition to solid phase (d), which is stable in contact with solutions containing from 74.4 to 88.8 mole % of ammonia. Because of the impossibility of freeing the crystals completely from the rather viscous mother liquor, especially since suction could not be applied, accuracy in direct analysis was unattainable; the proportion of ammonia found would inevitably be too high. Three analyses of samples obtained from solutions of different initial concentration gave fairly concordant results averaging 71.9 mole % NH_3. This figure, together with the course of the curve in this region, indicates that the compound is probably $2NH_3 \cdot HC_2H_3O_2$, although the possibility of its having the composition $5NH_3 \cdot 2HC_2H_3O_2$ is not altogether exluded. If the first supposition is correct, the m. p. of the compound, by extrapolation, would appear to be about 16°.

A marked halt in the cooling curves for solutions in the concentration range just mentioned clearly indicated a eutectic point at −35.5°. Beyond 88.8 mole % of ammonia, the stable solid phase is a compound $9NH_3 \cdot HC_2H_3O_2$ (or $NH_4C_2H_3O_2 \cdot 8NH_3$), which melts congruently at −34°. A saturated solution of this compound in liquid ammonia at the f. p. of the latter contains little more than 1 mole % of acetic acid, and the last eutectic temperature is no more than 1° below the f. p. of ammonia.

Discussion

It is of interest to compare the freezing point curve just described with that for the system water–ammonia, first investigated in its entirety by Rupert.[12] Such comparison clearly brings out the enormous difference in stability of the addition compounds in the two cases, which is undoubtedly a consequence of the much greater tendency of acetic acid than of water to act as a proton donor. There are two solid compounds of water and ammonia, $NH_3 \cdot H_2O$ (ammonium hydroxide) and $2NH_3 \cdot H_2O$ ($NH_4OH \cdot NH_3$, or am-

(12) Rupert, THIS JOURNAL, **32**, 748 (1910); *cf.* Postma, *Rec. trav. chim.*, **39**, 515 (1920); and Elliott, *J. Phys. Chem.*, **28**, 887 (1924).

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monium oxide), each of which melts congruently—although with considerable dissociation—at −79°. The corresponding compounds in the acetic acid–ammonia system, $NH_3 \cdot HC_2H_3O_2$ (ammonium acetate) and $2NH_3 \cdot HC_2H_3O_2$, have melting points, respectively, 196° and 95° higher than their ammonia–water analogs. The other three acetic acid–ammonia compounds have no analogs in the water–ammonia system. The light thrown by this contrast on the question of the weakness of aqueous "ammonium hydroxide" as a base at ordinary temperatures, has been discussed previously.[2]

Summary

1. The temperature–concentration curve for the system acetic acid–ammonia has been completed throughout the entire concentration range.
2. The melting point of pure anhydrous ammonium acetate has been found to be 117°.
3. The existence of the new solid compounds $5NH_3 \cdot 4HC_2H_3O_2$ and $9NH_3 \cdot HC_2H_3O_2$, and of a third having the probable composition $2NH_3 \cdot HC_2H_3O_2$, has been demonstrated.
4. Attention has been directed to the contrast between this system and that of water–ammonia.

LAWRENCE, KANSAS RECEIVED FEBRUARY 14, 1944

[CONTRIBUTION FROM THE AMMONIA DEPARTMENT OF E. I. DU PONT DE NEMOURS & COMPANY, INC.]

Analytical Procedures Employing Karl Fischer Reagent. XI. The Determination of Primary Plus Secondary Amines[1]

BY J. MITCHELL, JR., WALTER HAWKINS AND DONALD MILTON SMITH

The identification of amines by acylation techniques has been used to some extent,[2,3] but little has been done on their quantitative acetylation. Olson and Feldman[4] modified the acidimetric acetyl chloride procedure of Smith and Bryant[5] so that most amines reacted 90% or better. However, some amides also reacted so that this technique did not differentiate between these classes of compounds. Although acetic anhydride has been used in the determination of tertiary amines,[6,7] it apparently has not been used in the quantitative estimation of primary and secondary amines.

In the present research an acetylation method has been developed which is based on the selective reaction of acetic anhydride with the primary and secondary amines, according to the equations

$$RNH_2 + (CH_3CO)_2O = CH_3CONHR + CH_3COOH$$
$$RNHR' + (CH_3CO)_2O = CH_3CONRR' + CH_3COOH$$
$$(CH_3CO)_2O + H_2O = 2CH_3COOH$$

The new technique, independent of acid–base titrimetry, determines the excess acetic anhydride, after acetylation, by hydrolysis followed by titration of excess water with Karl Fischer reagent under conditions reported in an earlier publication for the determination of anhydrides.[8]

The new procedure is applicable to primary and secondary amines generally including aliphatic, alicyclic, heterocyclic and aromatic types. However, diaryl secondary amines and pyrrole fail to react. Since tertiary amines do not interfere, the method can be used indirectly for the determination of tertiary amine by correcting the total base titer for primary plus secondary amine.

In the presence of primary alcoholic hydroxyl the procedure is modified to effect quantitative acetylation of both the amine and alcohol.

Experimental

Reagents.—The acetylating reagent is prepared by mixing 1.5 moles (142 ml.) of pure acetic anhydride in sufficient dry pyridine to make one liter of solution.[9] The hydrolysis reagent consists of 100 g. of J. T. Baker C. P. or Merck A. R. grade dry sodium iodide and 22 ml. of water in 1 liter of pyridine solution. The preparation of the Karl Fischer reagent has been reported in a previous publication.[10]

Analytical Procedure.—In the absence of hydroxyl the sample, containing up to 10 milliequivalents of primary plus secondary amine, is transferred to a 250-ml. glass-stoppered volumetric flask.[11] To this is added exactly 20 ml. of the acetylating reagent. The flask together with a blank is then stoppered, shaken and allowed to stand for thirty minutes at room temperature.[12] At the end of this time 25 ml. (calibrated pipet) of the hydrolysis reagent is added. The flask is placed in a water-bath at 60 ± 1°, and after momentarily raising the stopper to allow for expansion of the included air, is firmly stoppered and maintained at that temperature for thirty minutes. After cooling spontaneously to room temperature, the contents are titrated directly for water with Karl Fischer reagent.

Ten ml. (calibrated pipet) of the hydrolysis reagent is titrated for water. Free water in the sample is determined by titration of a portion of the sample acidified with glacial acetic acid.

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(1) Presented in part before the Division of Analytical and Micro Chemistry at the Pittsburgh meeting of the American Chemical Society, Sept. 9, 1943.

(2) Alexander and McElvain, THIS JOURNAL, 60, 2285 (1938).

(3) Billman and O'Mahony, *ibid.*, 61, 2340 (1939).

(4) Olson and Feldman, *ibid.*, 59, 2003 (1937).

(5) Smith and Bryant, *ibid.*, 57, 61 (1935).

(6) Blumrich, *Angew. Chem.*, 374 (1941), used excess acetic anhydride to acetylate primary and secondary amines in order to titrate tertiary amine in glacial acetic acid solution.

(7) Haslam and Guthrie, *Analyst*, 68, 328 (1943); acetylated ethylaniline quantitatively to determine diethylaniline.

(8) Smith, Bryant and Mitchell, THIS JOURNAL, 63, 1700 (1941).

(9) Eastman Kodak Co. No. 4 acetic anhydride and J. T. Baker C. P. or Eastman Kodak Co. No. 214-H pyridine meet these requirements.

(10) Smith, Bryant and Mitchell, THIS JOURNAL, 61, 2407 (1939).

(11) The sample may be weighed directly or added volumetrically in pyridine solution.

(12) In the presence of primary hydroxyl an additional thirty minutes at 60 ± 1° is required to effect complete esterification. In this case sample size is limited to 10 milliequivalents of amine plus hydroxyl.

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Total anhydride added is equivalent to the net water used up during hydrolysis of the blank. This is found by subtraction of the water found from total water added before hydrolysis. Excess anhydride after acetylation is determined by subtracting water found from total water added to the sample, including free water originally present. The net anhydride is equivalent to the primary plus secondary amine in the sample.

Analytical Results

Thirteen primary amines were analyzed by this method; some were checked acidimetrically by titration to brom phenol blue. The trade products with the exception of hexamethylenediamine, which was sublimed, and *p*-bromoaniline, which was recrystallized from chloroform, were used without further purification. Experimental results are given in Table I. The precision and accuracy are usually within ±0.2%.

TABLE I

ANALYTICAL DATA FOR PRIMARY AMINES

Amine		Found, wt. %: Acidimetric	Acetylation	H_2O	Total
n-Butylamine	(10)[a]	97.7	98.0 ± 0.5	1.7	99.7
Propylenediamine[b]	(2)		84.1 ± .2	13.9	98.0
Hexamethylenediamine[c]	(4)		99.9 ± .1	0.1	100.0
Cyclohexylamine	(2)		100.2 ± .2	.0	100.2
o-Aminodicyclohexyl[d]	(2)	96.2[h]	96.7 ± .3	.0	96.7
Benzylamine	(2)	92.8	92.7 ± .2	.2	92.9
Aniline	(4)		100.8 ± .1	.0	100.8
p-Toluidine[e]	(2)		99.2 ± .1	.0	99.2
p-Phenylenediamine	(4)		99.6 ± .1	.0	99.6
p-Bromoaniline	(4)		99.4 ± .1	.0	99.4
β-Naphthylamine[f]		97.5	97.1 ± .2	.0	97.1
o-Aminodiphenyl[d]	(2)		99.0 ± .2	.0	99.0
2-Aminopyridine[g]	(2)		100.0 ± .3	.0	100.0

[a] Figures in parentheses represent number of indivdual determinations. [b] Carbide & Carbon Chemical, 85%. [c] du Pont. [d] Monsanto. [e] Arthur H. Thomas Co. [f] J. T. Baker. [g] Reilly Tar and Chemical Co.; all others Eastman Kodak Chemicals. [h] Calculated from Kjeldahl nitrogen value.

Analytical data for several secondary amines are given in Table II. Results with diphenylamine, carbazole and phenothiazine were 0.0 ± 0.0%.

TABLE II

ANALYTICAL DATA FOR SECONDARY AMINES

		Found, wt. %: Acidimetric	Acetylation	H_2O	Total
Diethylamine	(2)[a]	99.7	99.7 ± 0.1	0.3	100.0
Di-*n*-butylamine	(10)	98.3	98.4 ± .2	.1	98.5
Di-*s*-butylamine	(4)	99.5	83.5 ± .2	.1	83.6
Di-isobutylamine	(2)	100.1	100.1 ± .1	.0	100.1
Methylaniline	(4)		98.8 ± .1	.0	98.8
Pyrrole	(6)		0.0 ± .1	.0	0.0
Morpholine[b]	(2)		104.1 ± .2	.0	104.1
Piperidine	(2)	99.4	99.8 ± .2	.0	99.8
Piperazine hydrate	(2)		45.8 ± .2	53.8	99.6

[a] Figures in parentheses represent number of determinations. [b] Eastman Kodak Co. practical grade chemical; all others Eastman Kodak.

The low result obtained on di-*s*-butylamine probably indicates the presence of some tertiary amine. It is quite surprising that pyrrole failed to react. Experiments conducted at 60° on the sample as received and on freshly distilled pyrrole gave values of only 0.6% after thirty minutes and 2% after three hours.

Interfering Substances.—Since the above procedure is based on acetylation, alcohols will react. By modifying the technique to include the short additional heating period primary hydroxyl will react quantitatively as shown in Table III.[13]

TABLE III

ANALYTICAL DATA FOR HYDROXYAMINES

Substance	Found, wt. %: Acetylation	H_2O	Total
Monoethanolamine	99.5 ± 0.1	0.2	99.7
Diethanolamine	99.6 ± .1	.0	99.6
Hydroxyethylethylenediamine	99.1 ± .2	.0	99.1

These conditions are not sufficiently drastic to effect quantitative esterification of secondary hydroxyl; tertiary hydroxyl reacts only slightly. Under the conditions employed for the complete reaction of primary alcohols the hydroxyl of diisopropanolamine was esterified to the extent of 80%. By increasing the heating period to one hour at 60° this value was raised to 92%.

The effect of the type of alcohol is given in Table IV. In this case 5 milliequivalents of butanol was analyzed alone and in the presence of an equivalent amount of amine.

TABLE IV

RELATIVE REACTIVITY OF ACETIC ANHYDRIDE WITH *n*-, *s*- AND *t*-BUTANOL

Substances	% OH Esterified
n-Butanol	100
n-Butanol + *n*-butylamine	100[a]
s-Butanol	71
s-Butanol + isobutylamine	72[a]
t-Butanol	6
t-Butanol + isobutylamine	13[a]

[a] Corrected for quantitative amine reaction.

In general the presence of amine had little or no effect on the acetylation of the alcohol.

No interference is encountered from amides, urethans, nitriles or tertiary amines. Acetamide, urea and acetanilide did not react. Acetonitrile and adiponitrile gave 0.7 and 0.4% reaction, respectively. Dimethylaniline reacted to the extent of 1.3 ± 0.1%. This may have been due to secondary amine impurity.

Summary

1. An accurate and precise quantitative procedure for the determination of primary plus secondary amine, based on acetylation with acetic anhydride, has been described. Analytical results for more than twenty-two primary and secondary amines are reported.

(13) When necessary the results may be corrected for primary hydroxyl by the specific esterification procedure described in the preceding paper of this series, Smith, Mitchell and Hawkins, Paper No. X.

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2. The interference of alcoholic hydroxyl has been investigated, including the relative reactivity of primary, secondary and tertiary hydroxyl.

3. The method can be used indirectly for the determination of tertiary amine.

WILMINGTON, DELAWARE RECEIVED FEBRUARY 17, 1944

[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 956]

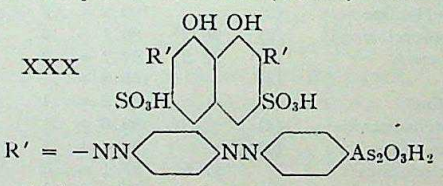
The Serological Properties of Simple Substances. VII. A Quantitative Theory of the Inhibition by Haptens of the Precipitation of Heterogeneous Antisera with Antigens, and Comparison with Experimental Results for Polyhaptenic Simple Substances and for Azoproteins

BY LINUS PAULING, DAVID PRESSMAN, AND ALLAN L. GROSSBERG

In an earlier paper in this series[1] there was developed a simple physicochemical theory of the precipitation of bivalent antibody molecules and bivalent antigen molecules and the inhibition of precipitation by haptens, and it was shown[1,2] that the results of experiments on the precipitation of specific antisera by polyhaptenic substances agree qualitatively but not quantitatively with the theory: in particular, the predicted linear decrease in amount of precipitate with increase in amount of hapten was observed only in the region of small inhibition. The deviation from linearity for larger amounts of hapten was attributed to the heterogeneity of the antisera, which were assumed, as is indicated by many experimental observations, to contain antibody molecules with greatly varying combining powers. We have now developed an extended quantitative theory of hapten inhibition on the assumption of an error-function distribution of antibody molecules with different combining powers in a heterogeneous antiserum, and have found it to be in generally satisfactory quantitative agreement with experiment. The theory permits the evaluation of two constants from each hapten-inhibition experiment, an average bond-strength constant for antibody and hapten (in competition with antigen) and an effective heterogeneity index for the antiserum; values of each of these constants can be interpreted in relation to the molecular structure of the hapten and the antigen.

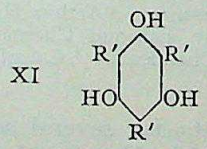
There have previously been reported[2,3] the results of quantitative investigations of the inhibition by haptens of the precipitation of polyhaptenic simple substances by antisera made by inoculating rabbits with sheep serum coupled either with diazotized *p*-arsanilic acid[2] (anti-R sera) or with diazotized *p*-(*p*-aminophenylazo)-phenylarsonic acid[3] (anti-R′ sera). It was found that the relative inhibiting powers of various haptens are essentially the same for different polyhaptenic simple substances precipitated by the same pool of antiserum, but are somewhat different for different pools of anti-R serum or of anti-R′ serum precipitated by the same polyhaptenic substance. Still greater differences are observed between anti-R sera and anti-R′ sera in general. We have now carried out a comparative study of hapten inhibition of the precipitation of a polyhaptenic simple substance (XXX) and an azo

XXX



protein (R′-ovalbumin) by anti-R serum and anti-R′ serum, and of a polyhaptenic substance (XI) by anti-R serum obtained by a single three

XI



weeks' course of inoculations, with the results described below. The data obtained in these and the earlier experiments have been analyzed by use of the new theory, and the results are discussed in relation to the molecular structure of the interacting substances.

Experimental Methods

Materials.—There have been previously described the methods of preparation of the antisera,[3,4] the haptens and antigens,[2,3,4] and the R′-ovalbumin,[3] which contained 2 per cent. arsenic.

The Reaction of Antiserum with Antigen and Hapten.—The reaction mixtures were set up in triplicate, with use in each series of experiments of the amount of antigen giving the largest amount of precipitate in the absence of hapten; borate buffer was used as diluent.[2] The tubes were allowed to stand one hour at room temperature and over two nights in the refrigerator, and the precipitates were then analyzed by our standard method.[5]

The results of the study of the inhibition by each of 24 haptens of the precipitation of antiserum with antigen

(1) L. Pauling, D. Pressman, D. H. Campbell, and C. Ikeda, THIS JOURNAL, **64**, 3003 (1942).

(2) D. Pressman, D. H. Brown, and L. Pauling, *ibid.*, **64**, 3015 (1942).

(3) D. Pressman, J. T. Maynard, A. L. Grossberg, and Linus Pauling, *ibid.*, **65**, 728 (1943).

(4) L. Pauling, D. Pressman, D. H. Campbell, C. Ikeda, and M. Ikawa, *ibid.*, **64**, 2994 (1942).

(5) D. Pressman, *Ind. Eng. Chem., Anal. Ed.*, **15**, 357 (1943).

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TABLE I

HAPTEN INHIBITION OF PRECIPITATION OF ANTI-R SERUM WITH ANTIGEN XXX AND WITH R′-OVALBUMIN

For antigen XXX: antigen solution, 1.75 ml. (22 μg.); anti-R serum, 0.25 ml.; hapten solution, 1 ml. For R′-ovalbumin: antigen solution, 1.80 ml. (140 μg.); anti-R serum, 0.20 ml.; hapten solution, 1 ml. *p*H of all supernates 8.05–8.10.

Acid	Antigen XXX K_0'	Antigen XXX σ	R′-ovalbumin K_0'	R′-ovalbumin σ	Moles of hapten added, × 10^9: 2.4	4.7	9.4	18.8	37.5	75	150	9.4	18.8	37.5	75	150	300
					Amount of precipitate with antigen XXX[a]							Amount of precipitate with R′-ovalbumin[a]					
p-(*p*-Aminophenylazo)-phenylarsonic	1.00	2.0	1.34	1.0	906[b]	872[b]	813[b]					954[b]	895[b]	830[b]			
p-(*p*-Hydroxyphenylazo)-phenylarsonic	1.00	1.5	1.34	1.0	945[b]	920[b]	843[b]					955[b]	914[b]	828[b]			
p-Acetaminophenylarsonic	1.00	1.2	1.07	1.5	815	663	440					760	634	421			
p-(*p*-Nitrobenzoylamino)-phenylarsonic	0.43	2.1	0.98	1.2	849	765	627					821	666	440			
p-(*p*-Aminobenzoylamino)-phenylarsonic	.54	2.0	.77	1.5	815	758	578					844	710	530			
p-Benzoylaminophenylarsonic	.63	1.5	.71	1.2	859	760	585					[865]	[745]	[555]			
p-Nitrophenylarsonic	1.52	1.2	2.06	1.2	719	540	291					648	437	193			
m-Nitrophenylarsonic	0.47	1.0	0.46	1.5			696	[452]	218				813	673	474		
o-Nitrophenylarsonic	.095	1.2	.089	1.2					725	527	288				880	775	600
p-Iodophenylarsonic	.89	1.0	.98	1.2			494	226	80				661	469	216		
p-Bromophenylarsonic	.81	1.0	.81	1.5			521	252	99				687	514	291		
p-Chlorophenylarsonic	.71	1.0	.69	1.2			562	301	122				759	562	322		
p-Methylphenylarsonic	.50	1.1	.50	1.0			660	448	192				839	669	453		
m-Methylphenylarsonic	.22	1.0	.18	1.5			835	732	500				915	844	743		
o-Methylphenylarsonic	.022	1.8	.031	1.0					913	846	725				980	918	832
β-Naphthylarsonic	.41	1.1	.49	1.2			723	518	262				820	668	445		
α-Naphthylarsonic	.061	1.5	.049	1.5					802	645	453				919	832	707
1,4-Aminonaphthylarsonic	.088	1.0	.079	1.0					764	558	321				884	798	602
p-Hydroxyphenylarsonic	.22	1.8	.20	1.5			795	655	480				919	824	700		
p-Carboxyphenylarsonic	.19	1.0	.17	1.5					543	282	122				751	576	358
Phenylarsonic	.137	1.2	.125	1.5					630	410	179				804	660	434
p-Aminophenylarsonic	.19	0.9	.18	1.5			895	765	540				909	851	733		
m-Aminophenylarsonic	.127	1.1	.125	1.5					657	428	192				781	661	437
o-Aminophenylarsonic	.027	1.5	.035	1.0					915	807	679				964	906	804

[a] The amounts are tabulated as fractions per mille of the amount precipitated in absence of hapten: for antigen XXX this was 715 μg. and for R′-ovalbumin 769 μg. Values for R′-ovalbumin include the precipitated antigen protein. Values are averages for triplicate analyses, with mean deviation ±2%; single analyses are given in brackets. [b] These values are for hapten concentrations one-fifth of those indicated.

XXX and with R′-ovalbumin are given for anti-R serum in Table I and for anti-R′ serum in Table II. These antisera were obtained by successive inoculations and bleedings of several rabbits over a period of several months; for comparison a study was also made of the effect of fifteen haptens on the precipitation by antigen XI of an anti-R serum obtained after a single three-weeks' course of inoculations, with the results given in Table III.

Discussion

In an earlier paper[1] it was shown that in a system containing bivalent antigen, A, homogeneous bivalent antibody, B, and univalent hapten, H, and capable of forming the soluble complexes AB, ABA, HB, HBA, and HBH and the precipitate AB the amount of precipitate, calculated according to the principles of chemical equilibrium with use of reasonable values for the pertinent equilibrium constants, falls off, in the region of the equivalence zone, in linear relation to the amount of hapten present. The slope of the curve for a system containing equivalent amounts of antigen and antibody was found to be given by the equation

$$\frac{dAB\ (pp)}{dH_{total}} = -\frac{1/2 + Ks + (K^2s^2 + Ks)^{1/2}}{1 + Ks + \left(1 + \frac{1}{K's}\right)(K^2s^2 + Ks)^{1/2}} \qquad (1)$$

in which AB (pp) is the amount of precipitate, H_{total} the total amount of hapten present in all forms, K the equilibrium constant for combination of a haptenic group of the antigen and a complementary region of the antibody, K' the corresponding constant for hapten and antibody, and s the solubility of the precipitate. This equation may be rewritten[2] in the form

$$-\frac{dH_{total}}{dAB\ (pp)} = \frac{C}{K'} + C' \qquad (2)$$

with C and C' independent of hapten, and constant for a given antigen–antibody system; and it has been suggested[2] that, as an approximation, the constant C' may be neglected, and the hapten inhibition constants K' for a series of haptens be taken as proportional to the negative slopes $-dAB\ (pp)/dH_{total}$.

It has been found,[1,2,3] however, that the experimental points showing the dependence of the amount of precipitate on the amount of added hapten do not fall on a straight line except in the region of very low hapten concentration—with larger amounts of hapten the inhibition of precipitation is less than predicted by the theory (see Fig. 1 of ref. 2); and this deviation from linearity has been attributed to heterogeneity

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TABLE II

HAPTEN INHIBITION OF PRECIPITATION OF ANTI-R′ SERUM WITH ANTIGEN XXX AND WITH R′-OVALBUMIN

For antigen XXX: antigen solution, 1.25 ml. (67 μg.); anti-R′ serum, 0.75 ml.; hapten solution, 1.0 ml. For R′-ovalbumin: antigen solution, 1.50 ml. (175 μg.); anti-R′ serum, 0.50 ml.; hapten solution, 1.0 ml. *p*H of all supernates 8.1–8.2.

	Antigen XXX		R′-ovalbumin		Moles of hapten added, × 10^9											
					12.5	25	50	100	200	400	12.5	25	50	100	200	400
					Amount of precipitate with antigen XXX[a]						Amount of precipitate with R′-ovalbumin[a]					
Acid	K_0'	σ	K_0'	σ												
p-(*p*-Aminophenylazo)-phenylarsonic	1.20	1.9	1.20	2.0	629	452	270				680	481	340			
p-(*p*-Hydroxyphenylazo)-phenylarsonic	1.05	1.8	1.02	2.0	651	501	305				690	541	386			
p-Acetaminophenylarsonic	0.24	1.7	0.20	2.0		812	670	510				813	772	605		
p-(*p*-Nitrobenzoylamino)-phenylarsonic	.32	2.0	.30	2.5		736	619	436				755	648	497		
p-(*p*-Aminobenzoylamino)-phenylarsonic	.47	2.0	.38	2.0		675	501	343				775	571	446		
p-Benzoylaminophenylarsonic	.37	1.8	.29	2.5		754	568	424				780	648	521		
p-Nitrophenylarsonic	.22	1.8	.30	1.0		825	701	539				903	773	541		
m-Nitrophenylarsonic	.25	2.0	.22	2.0				502	318	190				588	413	260
o-Nitrophenylarsonic	.16	2.0	.11	2.5				602	426	288				706	566	445
p-Iodophenylarsonic	.32	1.5	.34	2.0				420	234	134				483	282	187
p-Bromophenylarsonic	.22	2.0	.19	1.5				531	357	198				656	454	278
p-Chlorophenylarsonic	.17	1.5	.17	1.5				596	417	250				694	457	295
p-Methylphenylarsonic	.17	2.0	.16	2.0				602	411	268				660	465	324
m-Methylphenylarsonic	.089	1.5	.063	3.0				750	607	404				744	655	530
o-Methylphenylarsonic	.084	2.0	.060	2.5				725	575	430				795	684	550
β-Naphthylarsonic	.19	1.5	.15	2.0				603	404	196				664	468	349
α-Naphthylarsonic	.25	1.5	.15	2.0				516	313	182				678	494	347
1,4-Aminonaphthylarsonic	.32	1.7	.19	1.7				431	252	137				641	434	276
p-Hydroxyphenylarsonic	.095	1.5	.069	1.5				800	600	381				884	687	557
p-Carboxyphenylarsonic	.074	1.5	.054	1.5				827	620	482				890	720	655
Phenylarsonic	.067	1.5	.060	1.5				821	680	495				875	703	606
p-Aminophenylarsonic	.074	1.5	.062	1.5				801	669	460				880	709	598
m-Aminophenylarsonic	.054	1.0	.041	1.5				915	778	578				957	834	686
o-Aminophenylarsonic	.029	2.0	.038	2.0				867	809	671				880	765	673

[a] The amounts are tabulated as fractions per mille of the amount precipitated in absence of hapten: for antigen XXX this was 748 μg. and for R′-ovalbumin 562 μg. Values for R′-ovalbumin include the precipitated antigen protein. Values are averages of triplicate analyses, with mean deviation ±4%.

TABLE III

HAPTEN INHIBITION OF PRECIPITATION OF ANTIGEN XI AND ANTI-R SERUM PRODUCED BY A BRIEF COURSE OF INOCULATIONS

Antigen solution, 2 ml. (40 μg.); anti-R serum, 2 ml.; hapten solution, 2 ml. *p*H of supernates 8.16–8.18.

			Moles of hapten added, × 10^9				
			12.5	25	50	100	200
Acid	K_0'	σ	Amount of precipitate[a]				
p-(*p*-Hydroxyphenylazo)-phenylarsonic	1.1	(2.0)	[b]				
p-Acetaminophenylarsonic	1.15	2.5	759	729	568		
p-Benzoylaminophenylarsonic	1.04	1.7			629	429	(263)
p-Nitrophenylarsonic	1.58	2.0	795	610	520		
m-Nitrophenylarsonic	0.39	2.5			(756)	624	511
o-Nitrophenylarsonic	.22	3.5			756	690	590
p-Methylphenylarsonic	.56	3.0			667	529	450
m-Methylphenylarsonic	.44	2.5			689	635	502
o-Methylphenylarsonic	.13	1.5			953	876	770
β-Naphthylarsonic	.33	2.0			812	665	535
α-Naphthylarsonic	.12	2.8			762	795	702
Phenylarsonic	.44	2.5			710	635	478
p-Aminophenylarsonic	.61	3.0			(650)	514	(454)
m-Aminophenylarsonic	.35	2.0			816	662	523
o-Aminophenylarsonic	.22	1.5			914	820	686

[a] The amounts are tabulated as fractions per mille of the amount precipitated in absence of hapten, which was 331 μg. Values are averages for triplicate analyses, with mean deviation ±4%; duplicate analyses are given in parentheses. [b] Values of 946 and 867 found for 5 and 10 × 10^{-9} mole of hapten, respectively; the value 2.0 for σ was assumed.

of the antiserum, which appears to contain antibodies of greatly varying combining powers. We have now extended the theory to cover heterogeneous antisera of a particular sort, and have found that the extended theory agrees in a generally satisfactory way with experiment.

Let us assume that the heterogeneity of the antiserum is such that it can be described by a probability distribution function which is an error function in the effective free energy of combination of hapten and antibody (in competition with antigen); that is, in the quantity $\ln(K'/K_0')$, where K' is the effective hapten inhibition constant of the particular antibody molecule under consideration and K_0' is an average effective hapten inhibition constant. The normalized distribution function itself is

$$\frac{1}{\sqrt{\pi}\,\sigma}\, e^{-\{\ln (K'/K_0')\}^2/\sigma^2} \qquad (3)$$

and the fractional number of antibody molecules with given value of K' in a differential region is

$$\frac{dN}{N} = \frac{1}{\sqrt{\pi}\,\sigma} e^{-\{\ln (K'/K_0')\}^2/\sigma^2} d \ln (K'/K_0') \qquad (4)$$

Curves showing the distribution function for several values of the heterogeneity index σ are shown in Fig. 1. For $\sigma = 1$ most of the antibody molecules (84%) have K' values in the range from 0.368 K_0' to 2.718 K_0', for $\sigma = 2$ this range is from 0.135 K_0' to 7.48 K_0', for $\sigma = 3$ from 0.050 K_0' to 20.1 K_0', and for $\sigma = 4$ from 0.018 K_0' to 54.5 K_0'. The corresponding ranges of values of free energy of interaction of antibody and hapten have widths of 1200, 2400, · · ·, cal. per mole for $\sigma = 1, 2, \cdots$.

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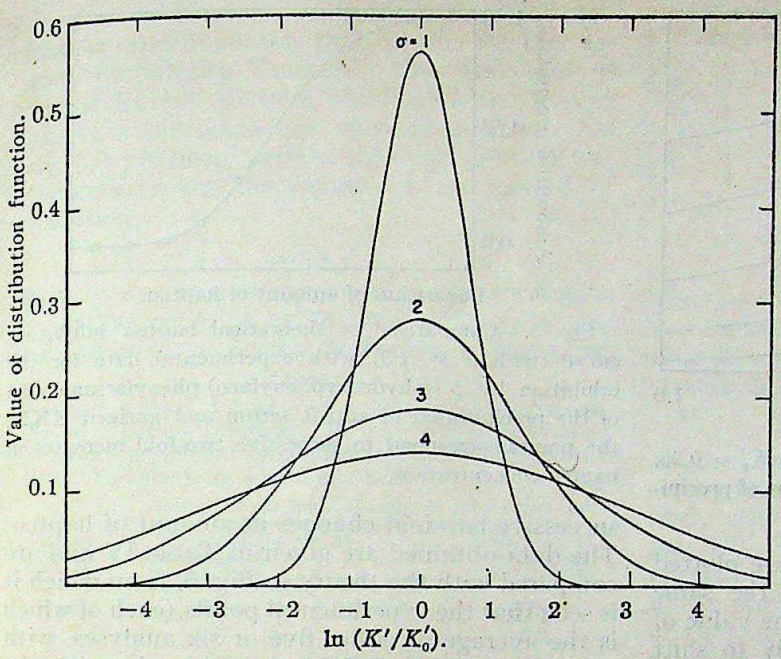

Fig. 1.—Assumed distribution function for values 1, 2, 3, and 4 of the heterogeneity index σ, plotted against ln (K'/K'_0).

This distribution of antibodies would occur in an antiserum if the heterogeneity were the result of a very large number of independent influences, each of which could increase or decrease the free energy of bond formation by an additive contribution. Since this is not unreasonable, in the light of current concepts of the structure of antibodies, we may well expect this distribution to be rather closely approximated by the antiserum from a single animal or by the combined antisera from a large number of animals.[6] On the other hand, the combined antisera from only a few animals or a combination of unlike fractions obtained in the course of fractionation of antibodies might not have an error-function distribution and might not correspond in their properties to the present theory; the theory could, however, easily be extended to cover such special cases.

If we assume that for each kind of antibody the amount of precipitate is linear in the amount of hapten, with slope proportional to K', the amount of precipitate formed by the heterogeneous antiserum is given by the equation

$$P = \frac{AB\ (\text{pp})}{AB\ (\text{pp})_{H_{\text{total}}=0}} = \frac{1}{\sqrt{\pi}\,\sigma}\int_{-\infty}^{\ln (1/H_{\text{total}} K'_0)} (1 - K'H_{\text{total}})\, e^{-\{\ln (K'/K'_0)\}^2/\sigma^2}\, \mathrm{d} \ln (K'/K'_0) \quad (5)$$

The upper limit of the integral represents the value of K' at which the hapten just inhibits completely the precipitation of the corresponding antibody: no precipitate is formed by antibody with larger values of K'. The integral is easily evaluated in terms of the Gaussian probability integral $\mathrm{H}(x)$, for which numerical values are given in tables[7]; the equation then assumes the form

$$P = \frac{1}{2}\{1 + \mathrm{H}(x_1)\} - \frac{1}{2} H_{\text{total}} K_0\, e^{\sigma^2/4}\{1 + \mathrm{H}(x_2)\} \quad (6)$$

with $x_1 = \frac{1}{\sigma} \ln (1/H_{\text{total}} K'_0)$ and $x_2 = x_1 - \sigma/2$. The function $\mathrm{H}(x)$ is to be taken with the same sign as x.

Curves of the calculated amounts of precipitate for $\sigma = 0$, 1, 2, 3, 4, and 5 plotted against H_{total} are shown in Fig. 2. It is seen that with increase in σ there is increasing deviation from the linear relation, which holds for $\sigma = 0$. The similarity in form of the theoretical and experimental curves is evident from a comparison of Fig. 3, which shows calculated curves for $\sigma = 1.5$ and a sequence of values of K'_0, with Fig. 1 of reference 2, in which experimental data for several haptens with the same antigen–antibody system are plotted.

The values of K'_0 for each antigen–antibody system have been normalized by assigning the value 1.00 to an azo hapten or, for some systems, to an average of several haptens.

A very satisfactory way of comparing experiment and theory is to use a logarithmic scale for the amount of hapten. Since K'_0 and H_{total} occur in Equation 6 only as their product, the

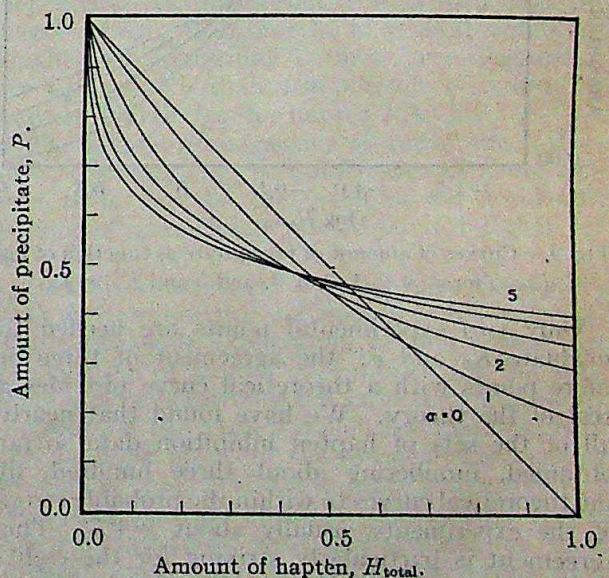

Fig. 2.—Theoretical curves showing dependence of amount of precipitate P on amount of hapten H_{total} for $\sigma = 0$, 1, 2, 3, 4, and 5 and $K'_0 = 1$.

(6) It would not be surprising if the antiserum from a single rabbit inoculated with an azoprotein were to have a different type of distribution. The antibodies produced by the rabbit would be influenced by the nature of the place of attachment of the hapten to the protein (histidine or tyrosine side-chains). The distribution function for such an antiserum might be closely approximated by the sum of two or more error functions.

(7) "Tables of Probability Functions," Vol. I, Federal Works Agency, Works Projects Administration, New York, 1941.

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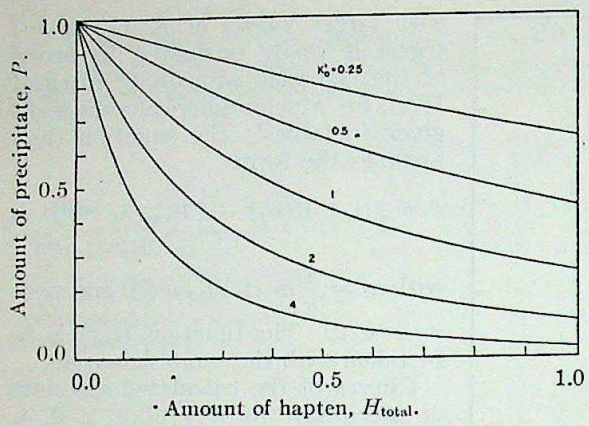

Fig. 3.—Family of curves with $\sigma = 1.5$ and $K_0' = 0.25$, 0.5, 1, 2, and 4, showing dependence of amount of precipitate on K_0' for fixed σ.

curves showing the amount of precipitate plotted against the logarithm of H_{total} have the same shape when they correspond to the same value of σ; the effect of changing K_0' is simply to shift the curve along the log H_{total} axis. Hence only a single family of such curves, covering a range of values of σ, is needed for the evaluation of σ and K_0' from a set of experimental points. Such a set of curves,[8] for $\sigma = 0$, 1, 2, 3, 4, and 5, is shown in Fig. 4.

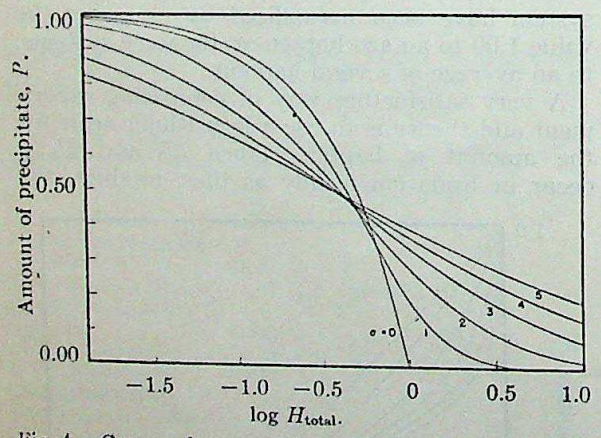

Fig. 4.—Curves of amount of precipitate as function of log H_{total}, for $\sigma = 0$, 1, 2, 3, 4, and 5 and $K_0' = 1$.

Only two experimental points are needed to evaluate K_0' and σ; the agreement of three or more points with a theoretical curve provides a test of the theory. We have found that nearly all of the sets of hapten inhibition data so far obtained, numbering about three hundred, fit the theoretical curves to within the probable errors of the experiments, usually about ±4%. This agreement is particularly striking for the eight-point sets in Tables IV and VI of reference 2. In order to test the theory further a set of analyses was made with special care over a range of ten

(8) In interpreting the experimental data it was found convenient to prepare and use a set of transparent templates, covering the range $\sigma = 0$ to 5 at intervals of 0.5.

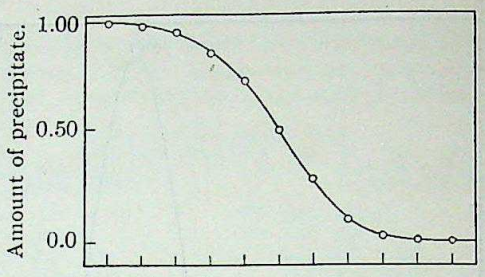

Fig. 5.—Comparison of theoretical hapten inhibition curve (with $\sigma = 1.3$) with experimental data for the inhibition by *p*-(*p*-hydroxyphenylazo)-phenylarsonic acid of the precipitation of anti-R serum and antigen XXX; the points correspond to successive two-fold increases in hapten concentration.

successive two-fold changes in amount of hapten. The data obtained are given in Table IV and are compared with the theory in Fig. 5, from which it is seen that the experimental points (each of which is the average of either five or six analyses, with mean deviation ±1.5%) agree closely with the indicated theoretical curve, which corresponds to $\sigma = 1.3$.

TABLE IV

INHIBITION BY *p*-(*p*-HYDROXYPHENYLAZO)-PHENYLARSONIC ACID OF PRECIPITATION OF ANTI-R SERUM AND ANTIGEN XXX

Antigen solution, 2 ml. (6.7×10^{-8} mole); antiserum, 0.33 ml.; hapten solution, 2.67 ml.; *p*H of supernates, 8.0; amount of precipitate in absence of hapten, 762 μg.; values corrected by 17 μg., the blank for serum and buffer.

Moles of added hapten, $\times 10^9$	Amount of precipitated antibody, in fractions per mille of amount for zero hapten[a]
2.44	965
4.88	950
9.75	925
19.5	833
39	707
78	490
156	277
313	91
625	25
1250	15
2500	12

[a] Each value is the average of five or six replicate analyses, with mean deviation ±1.5%.

The antiserum used in this experiment was, like most of those which we have used, a pooled serum made by mixing the sera obtained in several bleedings of a number of rabbits (usually about six). Since the mixing of sera would be expected to produce a serum with increased heterogeneity, some experiments were carried out with antisera obtained by single bleedings of individual rabbits, which had been inoculated over a period of months. The results are given in Table V and Fig. 6. It is seen that these antisera are heterogeneous, with $\sigma = 1$ for Rabbit 35 and $\sigma = 1.5$ for Rabbit 43, and that the agreement with the

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theory is satisfactory, indicating that the distribution approximates that given by the assumed probability function. The two sets of data for Rabbit 35 were obtained with antisera from two bleedings on successive days. No study has yet been made of the dependence of the heterogeneity on the length of the period of inoculation.

TABLE V

INHIBITION BY *p*-(*p*-HYDROXYPHENYLAZO)-PHENYLARSONIC ACID OF PRECIPITATION OF ANTIGEN XXX AND ANTI-R SERA OBTAINED BY SINGLE BLEEDINGS OF INDIVIDUAL RABBITS

Antigen solution, 1.5 ml. (7.5×10^{-8} mole); antiserum, 0.187 ml.; hapten solution, 2.81 ml.; *p*H of supernates, 8.0; values of amount of precipitated antibody corrected by 9 μg., the blank for serum and buffer.

Moles of added hapten, $\times 10^9$	Amount of precipitated antibody, in fractions per mille of amount for zero hapten[a] Rabbit No. 35 Bleedings of Nov. 8, 1943	Rabbit No. 35 Nov. 9, 1943	Rabbit No. 43 Bleeding of Nov. 8, 1943
1.85	960	910	1000
3.7	950	877	970
7.4	866	870	964
14.8	741	757	850
29.5	602	575	750
59	333	303	551
118	113	71	340
235	40	9	143
470	24	1	86
940	4	0	70
Amount of pptd. antibody for zero hapten, μg.[b]	963	919	815

[a] Averages of triplicate analyses, with mean deviation ±1%. [b] Averages of sextuplicate analyses.

It is of interest to know how sensitive the parameters of the hapten inhibition function are to change in the amount of antigen in the system—the theory as developed applies only in the region of the equivalence zone, and might be expected not to agree with experiment in the region of excess of antigen and the region of excess of antibody. Several sets of hapten inhibition experiments were carried out with anti-R serum and antigen XXX, the amount of antigen used with 0.33 ml. of antiserum in different sets being 13, 32, 80, and 200 $\times 10^{-9}$ mole; the first corresponds to excess of antibody, the second and third approximately to the equivalence zone, and the fourth to excess of antigen, the amounts of precipitate in absence of hapten being 413, 769, 693, and 323 μg., respectively. A strongly inhibiting hapten, *p*-(*p*-hydroxyphenylazo)-phenylarsonic acid, and a weakly inhibiting hapten, *o*-methylphenylarsonic acid, were used. The results of the experiments, which extended over six two-fold changes in amount of hapten, are shown in Fig. 7, in comparison with the theoretical curves. The agreement with theory is satisfactory for each set of points, and for each hapten the four sets of points lead to the same value of

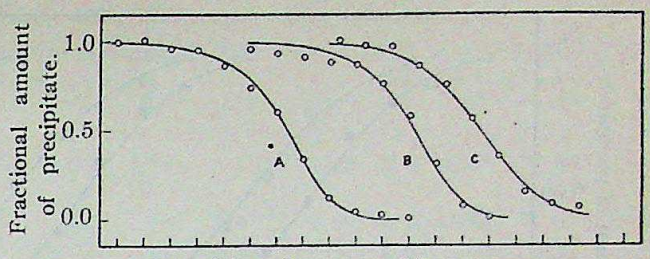

Fig. 6.—Comparison of theoretical hapten inhibition curves (A and B with $\sigma = 1$, C with $\sigma = 1.5$) with experimental data for antisera obtained by single bleedings of individual rabbits: A and B, Rabbit No. 35; C, Rabbit No. 43.

σ, the heterogeneity parameter—1.5 for the strong hapten and 1.8 for the weak one. Moreover, although the amount of hapten required for 50% inhibition increases with increase in amount of antigen (somewhat less rapidly than in linear proportion), the relative inhibiting power of the two haptens remains essentially constant: the four pairs of curves correspond, respectively, to $K_0' = 0.022$, 0.019, 0.023, and 0.026 for *o*-methylphenylarsonic acid relative to the value 1.00 for the other hapten, in excellent agreement with the ratio 0.022:1 given for the two haptens in Table I, for the same antigen–antibody system. We conclude that it is not necessary in comparative hapten inhibition experiments to select the antigen–antibody ratio with extreme care.

Some of the characteristics found for the parameters K_0' and σ may be seen from Table VI, in which there are given values determined from the data in Tables IV and V of reference 2. It is to be noted that the heterogeneity index σ depends on the antiserum, the antigen, and the hapten, being, for example, in general somewhat smaller for antiserum T than for antiserum S, for antigen VI than for antigen III, and for hapten XXIII than for hapten XXVIII.

The greater homogeneity of antiserum T than of S, corresponding to a difference of about one unit in σ, may be the result of the accidental pooling of more closely related sera for T than for S.

Usually σ increases for a sequence of haptens with given antiserum and antigen as K_0' decreases. The presumable explanation of this is that the competition of hapten and antigen for the antibody will be essentially the same for all antibody molecules if the hapten is identical in action with the haptenic group of the antigen—this leading to small σ—whereas if the hapten is much different from the haptenic group of the antigen it will compete favorably with the antigen for those antibody molecules of the heterogeneous antiserum which happen to be more closely complementary in structure to the hapten than to the antigen, and unfavorably for those which are more closely complementary to the antigen than to the hapten, and this variance in nature

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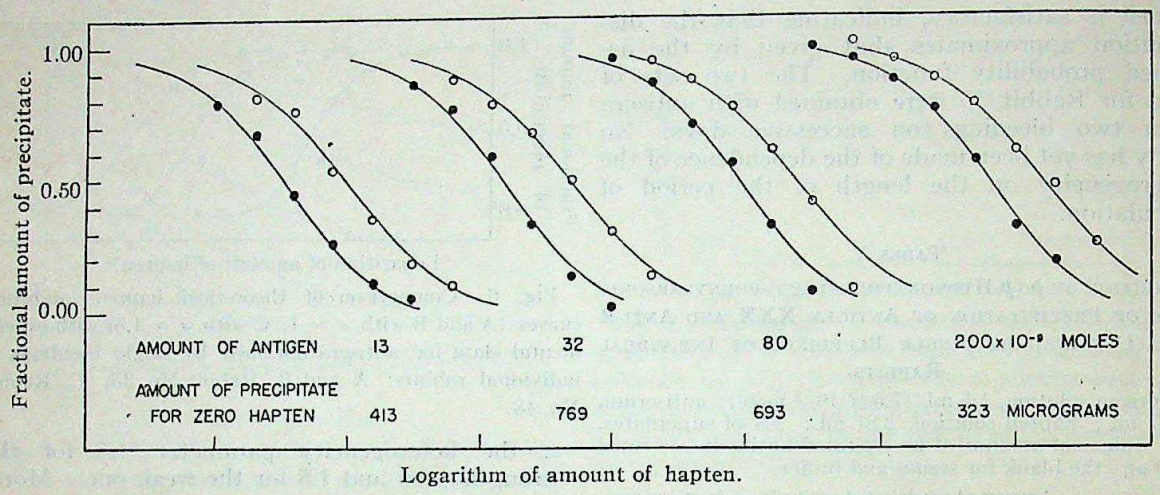


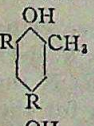
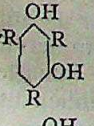
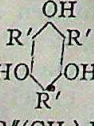
Fig. 7.—Comparison of experimental values of amount of precipitate in presence of hapten with theoretical curves. Fractional amounts of precipitate relative to amount for zero hapten are plotted as ordinates against the logarithm of amount of hapten. The successive curves were obtained with use of different amounts of antigen, as given below the curves. Solution of antigen XXX, 2 ml.; anti-R serum, 0.33 ml.; hapten solution, 2.67 ml.; *p*H of supernates, 8.0; most of the points are averages for triplicate analyses. The point farthest left corresponds to 9.8×10^{-9} mole of hapten in each sequence of points for hapten *p*-(*p*-hydroxyphenylazo)-phenylarsonic acid, represented by solid circles, and to 313×10^{-9} mole of hapten in each sequence for hapten *o*-methylphenylarsonic acid, represented by open circles; the theoretical curves are for $\sigma = 1.5$ and 1.8 for the two haptens, respectively.

of the competition of hapten and antigen for antibody would become evident in a large value of σ. Since a good precipitating antigen is one which combines strongly with most of the antibody molecules in the antiserum, a strong hapten, with large K_0', would be similar in structure to the antigen, and so would have σ small, whereas a weak hapten would have σ large, as observed. It is to be expected from this argument, however, that in the inhibition of precipitation of an antiserum by an antigen with haptenic group different from that of the immunizing antigen used in making the antiserum a hapten similar to the immunizing antigen might have both σ and K_0' larger than a hapten similar to the precipitating antigen.

It is found in practice that, although the theory has been developed only for dihaptenic antigens, it applies equally well also to polyhaptenic antigens, including azoproteins. Values of σ and K_0' determined from the data in Tables I, II, and III are given in these tables, and values determined from the data in Table IV of reference 2 and Table V of reference 3 are included in Table VII. The range of σ values for the twenty-four haptens studied is usually about 2 units

TABLE VI

VALUES OF THE PARAMETERS K_0' AND σ FOR SEVERAL ANTIGENS AND HAPTENS[a]

Antigen	Antiserum	Hapten XXIII K_0'	Hapten XXIII σ	XXVIII K'	XXVIII σ	XXI K'	XXI σ	XXIX K_0'	XXIX σ
III 	S	1.00	(2.0)	0.34	(2.5)	0.10	(4.0)	0.033	(4.0)
VI 	S	1:00	(1.5)	0.91	(2.0)	.30	(2.5)	0.76	(2.5)
	T	1.00	(0.5)	3.16	(0.5)	.55	(1.5)	.38	(1.5)
XI 	S	1.00	(1.5)	0.68	(2.0)	.15	(3.0)	.049	(2.0)
	T	1.00	(1.5)	2.40	(2)	.73	(1.5)	.45	(3.0)
XV $R''(CH_2)_2R''$	S	1.00	(1.0)	0.52	(1.5)	.077	(2.5)	.00	
XX R'' R''	S	1.00	(1.5)	.82	(1.5)	.34	(1.5)	.017	(3.0)
	T	1.0	(0.5)	1.9	(0.5)				

[a] From the data in Tables IV and V of Ref. 2.

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TABLE VII

COMPARISON OF VALUES OF HAPTEN INHIBITION CONSTANTS FOR ANTI-R AND ANTI-R′ SERA AND SEVERAL ANTIGENS

Hapten (acid)	Constants for anti-R sera						Constants for anti-R′ sera				
	K'^a	σ^a	K'^a	$K_0'^b$	$K_0'^c$	K'^d	K'^e	σ^e	$K_0'^e$	$K_0'^f$	$K_0'^g$
p-(*p*-Aminophenylazo)-phenylarsonic	1.02	1.3	1.02	1.00	1.34		1.06	2.0	1.86	1.80	2.16
p-(*p*-Hydroxyphenylazo)-phenylarsonic	0.98	2.0	0.98	1.00	1.34	1.1	0.94	1.5	0.89	1.58	1.84
p-Acetaminophenylarsonic	1.02	1.8	1.19	1.00	1.07	1.15	.48	3.0	.38	0.36	0.36
p-(*p*-Nitrobenzoylamino)-phenylarsonic	0.89	2.2	0.88	0.43	0.98		.50	3.0	.50	.48	.55
p-(*p*-Aminobenzoylamino)-phenylarsonic	.89	1.5	.81	.54	.77		.46	2.0	.43	.70	.68
p-Benzoylaminophenylarsonic	.80	1.8	.75	.63	.71	1.04	.35	1.5	.34	.54	.52
p-Nitrophenylarsonic	1.40	1.7	1.64	1.52	2.06	1.58	.39	2.0	.31	.33	.48
m-Nitrophenylarsonic	0.75	3.0	0.76	0.47	0.46	0.39	.40	2.5	.38	.38	.39
o-Nitrophenylarsonic	.28	3.5	.22	.095	.089	.22	.39	2.0	.32	.24	.194
p-Iodophenylarsonic	.80	2.2	.91	.89	.98		.31	1.7	.24	.49	.61
p-Bromophenylarsonic	.80	2.2	.87	.81	.81		.27	1.5	.19	.33	.33
p-Chlorophenylarsonic	.80	2.5	.88	.71	.69		.25	2.0	.15	.26	.31
p-Methylphenylarsonic	.80	2.5	.86	.50	.50	.56	.18	2.0	.11	.25	.29
m-Methylphenylarsonic	.53	2.5	.38	.22	.18	.44	.19	2.5	.12	.134	.113
o-Methylphenylarsonic	.13	3.0	.057	.022	.031	.13	.20	2.5	.16	.126	.108
β-Naphthylarsonic	.66	3.5	.55	.41	.49	.33	.21	2.0	.15	.37	.28
α-Naphthylarsonic	.23	3.2	.13	.061	.049	.12	.59	3.0	.71	.28	.27
1,4-Aminonaphthylarsonic	.17	3.0	.080	.088	.079		.65	2.5	.68	.49	.34
p-Hydroxyphenylarsonic	.60	2.5	.48	.22	.20		.16	3.0	.078	.143	.124
p-Carboxyphenylarsonic	.29	3.0	.25	.19	.17		.14	3.5	.040	.111	.097
Phenylarsonic	.26	2.0	.24	.137	.125	.44	.15	3.5	.054	.101	.108
p-Aminophenylarsonic	.44	2.3	.33	.19	.18	.61	.15	3.5	.048	.111	.112
m-Aminophenylarsonic	.29	2.5	.25	.127	.125	.35	.11	3.5	.024	.081	.074
o-Aminophenylarsonic	.13	3.0	.052	.027	.035	.22	.10	3.5	.017	.044	.068

[a] For anti-R serum and antigen VI, Table VI, ref. 2. [b] For anti-R serum and antigen XXX, Table I, this paper. [c] For anti-R serum and R′-ovalbumin, Table I, this paper. [d] For anti-R serum (with short period of inoculation) and antigen XI, Table III, this paper. [e] For anti-R′ serum and antigen XXX, Table VI, ref. 3. [f] For anti-R′ serum and antigen XXX, Table II, this paper. [g] For anti-R′ serum and R′-ovalbumin, Table II, this paper.

(1.0 to 3.0 or 1.5 to 3.5); it is especially small for the anti-R serum of Table I, being only 1.0 to 1.5 for precipitation with R′-ovalbumin and 0.9 to 2.1 for precipitation with antigen XXX.

In our earlier papers[2,3] values were assigned to the hapten inhibition constant K' on the basis of the estimated initial slopes of the hapten inhibition curves. These values, which are given in Table VII for comparison with those of K_0', cover for the series of haptens much smaller ranges than do those of K_0', the range for K' being one-third of that of K_0' for the anti-R serum and one-tenth for the anti-R′ serum. This is as expected: Equation 6 for H_{total} small assumes the form

$$P = 1 - e^{\sigma^2/4} K_0' H_{\text{total}} \qquad (7)$$

which is similar to the equation used to determine K' from the initial slope, with $e^{\sigma^2/4} K_0'$ in place of K'; the effect of the factor $e^{\sigma^2/4}$ would be to increase the range of K_0' over that of K' by the factor 5 for a change in σ from 1.5 to 3.0 (anti-R serum) and by the factor 12 for a change in σ from 1.5 to 3.5 (anti-R′ serum).[9]

(9) The evaluation of K_0' from the data is of course more reliable than that of K' from the estimated initial slopes.

It is of interest to examine the correlations among the K_0' values collected in Table VII. Most striking is the agreement between the values for antigen XXX and those for the greatly different antigen R′-ovalbumin with the same antiserum; this agreement is somewhat better for anti-R′ serum (mean difference 15%) than for anti-R serum (20%). There is similar general agreement between the values for different pools of anti-R serum with simple antigens VI ($K_0'^a$) and XXX ($K_0'^b$) and between the values for two different pools of anti-R′ serum and antigen XXX ($K_0'^e$ and $K_0'^f$).

The most pronounced difference between anti-R sera and anti-R′ sera—the much smaller effect of position of substituents in the benzene ring for the latter than for the former—has been already pointed out[3] in the discussion of the values of K' originally assigned, and a tentative interpretation of the difference as resulting from a greater looseness of fit of the anti-R′ antibody to the larger R′ haptenic group of the immunizing antigen than of the anti-R antibody to the R haptenic group has been proposed. The extent of the difference can be seen from Table VIII, in which the ratios of K_0' values for meta and ortho to

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those for the corresponding para compounds are presented. It is seen that for the nitro and methyl groups a twenty-fold change in K_0' is caused by changed position in the ring in the precipitation of anti-R serum, and only a two-fold change for anti-R′ serum. The effect of the amino group with anti-R serum is much smaller than that of the nitro group and the methyl group —only about six-fold; but the same two-fold change is shown with anti-R′ serum. The structural significance of these observations is not clear.

TABLE VIII

EFFECT OF POSITION OF SUBSTITUENTS ON HAPTEN INHIBITION CONSTANT

Substituent*	Anti-R sera			Anti-R serum, short inoculation	Anti-R′ sera		
	a	*b*	*c*	*d*	*e*	*f*	*g*
	Meta/para						
Nitro	0.46	0.31	0.22	0.25	1.23	1.15	0.81
Methyl	.44	.44	.36	.79	1.09	0.54	.39
Amino	.76	.67	.69	.57	0.50	.73	.66
	Ortho/para						
Nitro	.134	.063	.043	.14	1.03	.73	.40
Methyl	.066	.044	.062	.23	1.45	.50	.37
Amino	.16	.14	.19	.36	0.35	.40	.60

* Letters *a* to *g* refer to Table VII.

The effect of the nature of the substituent group is just as pronounced for anti-R′ serum as for anti-R serum; for each antiserum an approximately fifty-fold range of values is covered by K_0' for the twenty-four haptens. The general order of effectiveness of groups is indicated by the order of the para-substituted haptens in the table.

The anti-R serum obtained after a short course of inoculations (*d* in Tables VII and VIII) shows much lower specificity of interaction with haptens than the other antisera, with respect both to the nature of the substituent group and to its position.

This investigation was carried on with the aid of a grant from The Rockefeller Foundation. We are grateful to Professor Dan H. Campbell and Dr. V. Schomaker for assistance.

Summary

A quantitative theory of the inhibition by haptens of the precipitation of heterogeneous antisera by antigens has been developed on the basis of the assumption that the heterogeneity of an antiserum can be described by a distribution function which is an error function of the free energy of interaction of antibody and hapten in competition with the precipitating antigen. The theory has been found to be in satisfactory agreement with experiment. It has been applied to data obtained in previous investigations and to data from new experiments on the inhibition by each of twenty-four haptens of the precipitation of anti-R serum and of anti-R′ serum with a dihaptenic simple antigen and with R′-ovalbumin, yielding values of the average effective inhibition constant of the haptens and of the heterogeneity index of the antisera. A discussion of the structural significance of these quantities is presented.

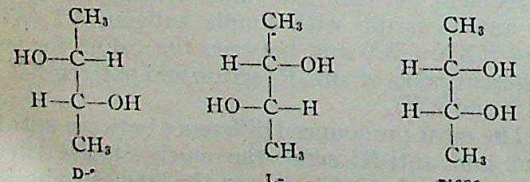
PASADENA, CALIFORNIA RECEIVED FEBRUARY 1, 1944

[CONTRIBUTION FROM THE NORTHERN REGIONAL RESEARCH LABORATORY[1]]

Configuration of the 2,3-Butylene Glycols[1]

BY S. A. MORELL AND A. H. AUERNHEIMER[2]

2,3-Butylene glycol is a symmetrical molecule containing two asymmetric carbon atoms. Like tartaric acid, it can occur in only three stereoisomeric forms, D-, L- and *meso*-, which are formulated configurationally as follows



2,3-Butylene glycols

Previous investigations[3,4,5] on the configuration of the 2,3-butylene glycols have been limited to the distinction between the optically inactive *meso*- and D, L- forms, rather than with relating the active forms to their respective configurational series. In order to accomplish the latter, one of the enantiomorphs must be converted to a compound whose configuration is known.

In studying the conversion of optically active 2,3-butylene glycols to butadiene, by pyrolysis of their diacetates according to the method of Hill and Isaacs,[6] the isolation of several optically active intermediates has made it possible to establish the configuration of the glycols. Both the dextro- and levorotatory glycols were used in the present investigation. From the former, a levorotatory methylvinylcarbinol acetate was obtained which yielded a dextrorotatory methylvinylcarbinol on hydrolysis. From the latter, a levorotatory methylvinylcarbinol was obtained, without isolating its intermediate acetate. The optical purity of the glycols used differed con-

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(2) Chemist and Junior Chemist, respectively, Industrial Chemical Section, Agricultural Residues Division.

(3) J. Böeseken and R. Cohen, *Rec. trav. chim.*, **47**, 839 (1928).

(4) C. E. Wilson and H. J. Lucas, THIS JOURNAL, **58**, 2396 (1936).

(5) S. Winstein and H. J. Lucas, *ibid.*, **61**, 1581 (1939).

(6) R. Hill and E. Isaacs, U. S. Patent 2,224,912, Dec. 17, 1940.

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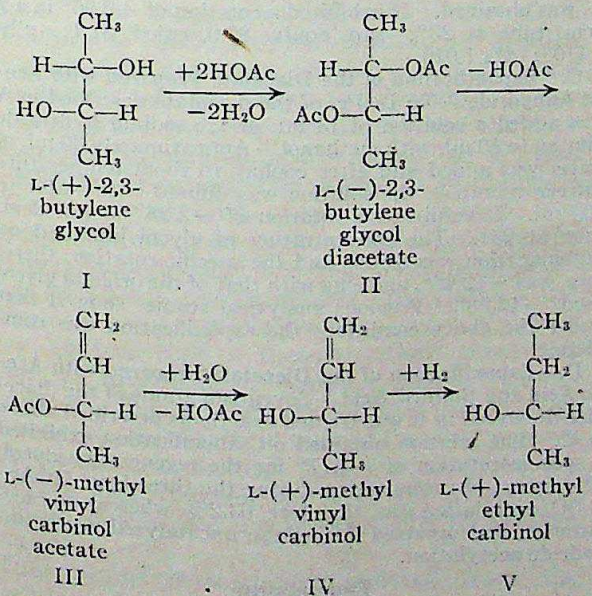
siderably, but it will be evident from the following discussion that the sign of rotation alone, rather than the magnitude of rotation, was sufficient to establish the necessary configurational relationships.

Winstein and Lucas[5] have found that the acetylation of an optically active, 2,3-butylene glycol proceeds with an inversion in the sign of rotation. In confirming this observation, it was found that extensive racemization occurred when the acetylating medium was acetic acid catalyzed by sulfuric acid, whereas with acetic anhydride (uncatalyzed) this reaction proceeded without racemization. Kenyon and Snellgrove[7] also noted an inversion in sign when alkyl vinyl or alkyl ethyl carbinols were converted to their acetates. On the basis of rotatory data, the latter investigators showed that the methyl vinyl and methyl ethyl carbinols of the same sign of rotation are probably related configurationally. In agreement with Kenyon and Snellgrove's[7] rotatory data, hydrogenation of our dextrorotatory methyl vinyl carbinol yielded dextrorotatory methylethylcarbinol.

Levene, Walti and Haller[8] have shown that dextrorotatory methylethylcarbinol possesses the same configuration as dextrorotatory lactic acid, which belongs to the L-series. L-(+)-Methylethylcarbinol is thus related to dextrorotatory 2,3-butylene glycol and the enantiomorphs of the latter are, therefore, L-(+)- and D-(−)- for the dextro- and levorotatory forms, respectively. The following configurational formulas show the reactions which were conducted starting with the L-(+)-glycol



From the above stereochemical formulas, it is evident that L-(−)- methyl vinyl carbinol acetate (III) is the only optically active product possible when one molecule of acetic acid is removed from L-(−)-2,3-butylene glycol diacetate (II). Deacetylation from the 2,3 position produces the isomeric acetate of the 2–3 enol of methyl ethyl ketone, $CH_3—C(OAc)=CH—CH_3$ which contains no asymmetric carbon atom. All of the compounds formulated above can exist in only two optically active forms, D- and L-. For any of them, therefore, the sign of rotation is sufficient to determine which active form is present. In the case of the glycols, or their diacetates, the inactive forms which can also be present are D,L-, *meso-* and a mixture of both. In the deacetylation reaction, the optically active methyl vinyl carbinol acetate formed must have the same configuration as the active glycol originally present, for any D-, L- or *meso*-glycol also present could form only D-, L-methylvinylcarbinol acetate.

Experimental

The glycols were obtained from glucose by the Fermentation Division of this Laboratory. Their isolation from the beers was conducted by the Engineering and Development Division. A complete description of the preparation of the glycols, the acetylation and pyrolysis reactions, and the separation of the bulk of the acetic acid in the pyrolysis liquors, will be included in future communications from this Laboratory on the conversion of 2,3-butylene glycol to butadiene, of which the present investigation is an incidental part.

The physical and analytical values observed for the compounds described below are given in the accompanying table. For convenience in referring to the table, each compound has been assigned a number, starting with the five compounds formulated in the reactions given above for the conversion of dextrorotatory 2,3-butylene glycol (I) to dextrorotatory methyl ethyl carbinol (V). The experiments on racemization, conducted in connection with the possibility of Walden inversion during the acetylation reaction, are treated separately and are not included in the table.

All specific rotations reported refer to the homogeneous liquids, no corrections being made for their densities. In reporting the rotations below, reference to concentration is omitted since this is 100%, unless specified otherwise. A Schmidt and Haensch polarimeter was used, readings reproducible to ±0.01° being readily obtained.

I. Dextrorotatory 2,3-Butylene Glycol.—The glycol was obtained from glucose by the fermentative action of *Aerobacter aerogenes*, as described by Ward, Pettijohn, Lockwood and Coghill,[9] and exhibited a rotation of $[\alpha]^{23}D$ +1.06°. This low value is due to the fact that the organism produces the *meso-* form predominantly, as shown by Fulmer, Underkofler and Bantz.[10] Several attempts to isolate the active enantiomorph, by resolution, have been reported, the highest specific rotations obtained being +5.0° (Böeseken and Cohen[3]) and +6.9° (Chappel[11]). Fulmer, Underkofler and Bantz[10] fermented the dextrorotary glycol ($[\alpha]^{25}D$ +1.0°, produced by the action of *Aerobacter aerogenes*) to acetyl methyl carbinol by means of *Aerobacter suboxydans;* the *meso-* form was preferentially attacked and the unfermented glycol exhibited a specific rotation of +10.15°. Their results indicated that little or none of the levorotatory glycol was produced by *Aerobacter aerogenes*. Since an optically pure isomer of 2,3-butylene glycol has not yet been conclusively obtained, it

(7) J. Kenyon and D. R. Snellgrove, *J. Chem. Soc.*, **127**, 1169 (1925).

(8) P. A. Levene, A. Walti and H. L. Haller, *J. Biol. Chem.*, **71**, 465 (1926).

(9) G. E. Ward, O. G. Pettijohn, L. B. Lockwood and R. D. Coghill, THIS JOURNAL, **66**, 541 (1944).

(10) E. I. Fulmer, L. A. Underkofler and A. C. Bantz, *ibid.*, **65** 1425 (1943).

(11) C. H. Chappel, "A Study of 2,3-Butylene Glycol and its Derivatives," Thesis, Iowa State College, 1935.

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is not possible to calculate the concentration of the active form present in the sample used.

II. Levorotatory 2,3-Butylene Glycol Diacetate.—A 10 molar acetylation of I was conducted as described by Hill and Isaacs,[6] using 25 moles of acetic acid, 16.2 g. of sulfuric acid, and benzene as the water entraining agent. In five hours, water removal from the gravity separator had ceased. To the hot solution 45 g. of $NaOAc \cdot 3H_2O$ was added and after cooling, filtering and distilling, the fraction b. r. 190–192° was obtained.

III. Levorotatory Methylvinylcarbinol Acetate.—One hundred and seventy-five grams of II was pyrolyzed at 410° in a 2″ × 36″ Pyrex tube, packed with stainless steel shavings, at the rate of 0.73 g. per minute. The vapors from the tube entered a column where the butadiene gas was stripped from the condensed pyrolysis liquor, 162 g. of the latter, containing 35.5% acetic acid, being obtained. To 121 g. of the liquor was added 300 ml. of ether, and dry ammonia gas was passed into the solution with cooling, until it was neutral to litmus. After filtering, washing with ether and distilling, the main fraction, b. r. 111.5°–113.5°, weighing 15.7 g., was obtained. After saponification, it gave only a trace of a precipitate with 2,4-dinitrophenylhydrazine, thus indicating the absence of the isomeric acetate of 2-butene-2-ol. A determination of its iodine no. (3 min. Wijs method using mercuric acetate) gave a value of 217; theory, 222.

IV. Dextrorotatory Methylvinylcarbinol.—The diacetate of I (2 lb. moles) was prepared by a method similar to that described above for II. The pyrolysis was conducted at 595° in a stainless steel coil and the intermediate unsaturated acetate fraction, mixed with some by-products, was separated from the bulk of the acetic acid in the pyrolysis liquor. The mixture contained 7.2% acetic acid and 21.0% unsaturated acetates as measured by saponification. Two hundred and ninety-four grams of the mixture was saponified with a 10% calculated excess of aqueous sodium hydroxide by stirring (2 layers) under reflux on a steam-bath for eight hours. On distillation, the fraction b. r. 77–100° was collected, which separated into two layers. The upper layer was exhaustively extracted with water and the combined aqueous fractions were redistilled, the fraction b. r. 80–100° being collected. The latter was saturated with sodium chloride and the upper layer so formed was dried over sodium sulfate. On distillation, the fraction b. r. 96.2–96.5°, weighing 19.4 g., was obtained. It exhibited a rotation of +1.36° in a 2-dcm. tube at 23°. Based on Kenyon and Snellgrove's[7] value of $[\alpha]^{25}D$ +33.7° for the pure enantiomorph of methylvinylcarbinol, it contained 2.0% of the active form.

V. Dextrorotatory Methylethylcarbinol.—To 14.6 g. of IV was added 0.2 g. of freshly prepared PtO_2[12] and hydrogenation was conducted in a Parr apparatus[13] at an initial gage pressure of 45 lb. In one hour absorption had ceased, the theoretical quantity of hydrogen being consumed. The catalyst was filtered and washed with 20 ml. of benzyl alcohol, which facilitated the subsequent distillation of the lower boiling methylethylcarbinol, the main fraction having a b. r. of 99–100°. The carbinol weighed 9.3 g. It exhibited a rotation of +0.48° in a 2-dcm. tube at 23°. Based on Kenyon and Snellgrove's[7] value of $[\alpha]^{20}D$ +13.9° for the pure enantiomorph of methylethylcarbinol, it contained 1.7% of the active form, which is in good agreement with the 2.0% concentration of active methylvinylcarbinol in the sample, IV, hydrogenated.

VI. Inactive Methylvinylcarbinol.—In order to compare the physical constants of IV and X (below) under identical conditions, a sample of Shell Development Company methylvinylcarbinol was redistilled, the fraction of b. r. 96.0–96.5° being used.

VII. Inactive Methylethylcarbinol.—In order to compare the physical constants of V under identical conditions, sample VI was hydrogenated and the inactive methylethylcarbinol was isolated exactly as described above for V.

VIII. Levorotatory 2,3-Butylene Glycol.—The glycol was obtained by the fermentative action of *Bacillus polymyxa*, as described by Ward, Pettijohn, Lockwood and Coghill.[9] It exhibited a specific rotation of $[\alpha]^{23}D$ −12.85° and a b. r. of 179–180°. Levorotatory 2,3-butylene glycol, $[\alpha]^{23}D$ −2.4°, had been obtained previously by Neuberg and Nord[14] by the action of fermenting yeast on diacetyl. By a similar biochemical reduction of acetylmethylcarbinol, Neuberg and Kobel[15] obtained the levorotatory glycol $[\alpha]^{25}D$ −5.51°, b. r. 178–181°. As in the case of I, it is not possible to calculate the concentration of the active form present in the sample used.

IX. Dextrorotatory 2,3-Butylene Glycol Diacetate.—The glycol VIII (2 lb. moles) was acetylated as described above for II, except that acetic anhydride was used to complete the esterification. As may be seen from the saponification equivalents in the table, the anhydride readily converted the glycol monoacetate[5,16] to the diacetate.

X. Levorotatory Methylvinylcarbinol.—From the pyrolysis liquor of IX, the levorotatory methylvinylcarbinol was isolated as described above for IV. It exhibited a rotation of −1.28° in a 1-dcm. tube at 23°. Based on Kenyon and Snellgrove's[7] value of $[\alpha]^{25}D$ −33.7° for the pure enantiomorph, it contained 3.8% of the active form.

Effect of Method of Acetylation on the Racemization.—In considering the possibility of Walden inversion, it was of interest to acetylate one of the glycols and saponify the resulting diacetate, in order to learn whether the original glycol would be regenerated.

A. Acetylation with Acetic Anhydride (Uncatalyzed).—To 90 g. (1 mole) of a sample of 2,3-butylene glycol, which exhibited a rotation of −25.98° in a 2-dcm. tube at 23° ($n^{18}D$ 1.4340; d^{25}_4 0.990) was added 225 g. (2.2 moles) of acetic anhydride. The mixture was heated for one hour at 100° and then distilled, the fraction b. r. 193°–193.5°, 156.9 g., being obtained. It exhibited a rotation of +27.46° in a 2-dcm. tube at 23°, sap. equiv., 87.1, calcd. 87.1; $n^{18}D$ 1.4163; D^{30}_4 1.016.

B. Acetylation with Acetic Acid in Presence of Sulfuric Acid.—Ninety grams of the same sample of glycol described in A was acetylated as described above for II, three hours being required before water removal from the gravity separator had ceased. After neutralization with sodium acetate and distillation, the fraction b. r. 190–191°, 85.6 g., was obtained. It exhibited a rotation of +9.96° in a 2 dcm. tube at 23°; sap. equiv. 86.0, calcd. 87.1; $n^{18}D$ 1.4163; d^{30}_4 1.016.

C. Saponification of the Diacetate Prepared with Acetic Anhydride.—To 17.0 g. of the diacetate described in A was added a solution of 13 ml. of 1:1 sodium hydroxide diluted to 50 ml. with methanol. Approximately 30 ml. of water was added and after cooling to room temperature (fifteen minutes), the solution was diluted with water to 100 ml. It exhibited a rotation of −2.28° in a 2 dcm. tube at 23°. The concentration of glycol liberated on saponification was 8.80% and the specific rotation, therefore, was −12.95°, agreeing with that of the original glycol used, −12.98°. Previous analytical studies showed that under the above conditions the saponification was complete.

D. Saponification of the Diacetate Prepared with Acetic Acid and Sulfuric Acid.—Seventeen grams of the diacetate described in B was treated exactly as described above in C. The solution obtained on saponification exhibited a specific rotation of −4.77° for the regenerated glycol. The extent of racemization during the three-hour HOAc–H_2SO_4 acetylation was, therefore, 63.2%, whereas no racemization had occurred during the uncatalyzed acetic anhydride acetylation.

Discussion

In relating the configuration of the active 2,3-butylene glycols to the methyl ethyl carbinols

(12) R. Adams, V. Voorhees and R. L. Shriner, "Org. Syntheses," Coll. Vol. I, 452 (1932).

(13) R. Adams and V. Voorhees, *ibid.*, 53.

(14) C. Neuberg and F. F. Nord, *Ber.*, **52**, 2248 (1919).

(15) C. Neuberg and M. Kobel, *Biochem. Z.*, **160**, 253 (1925).

(16) S. Winstein and R. E. Buckles, THIS JOURNAL, **64**, 2790 (1942).

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TABLE I

TABLE OF PHYSICAL AND ANALYTICAL DATA FOR COMPOUNDS I TO X

Compound Name	No.	$[\alpha]^{23}D$ observed	Boiling range, °C. Observed (745 mm., uncor.)	Lit.	Refractive index, n_D^T Observed	Lit.
2,3-Butylene glycols	I	+ 1.06	180 –182	[b] 179–182[10]	1.4387 at 18°	[c]
	VIII	−12.85	179 –180	[b] 178–181[14]	1.4340 at 18°	[c]
2,3-Butylene glycol diacetates	II	− 0.60	190 –192	[e]	1.4140 at 25°	[f]
	IX	+ 1.35	192 –194	[e]	1.4158 at 18°	[f]
Methylvinylcarbinol acetate	III	− 1.71	111.5–113.5	111–112[18]	1.4020 at 30°	1.4039 at 20°[18]
Methylvinylcarbinols	IV	+ 0.68	96.2– 96.5	96– 98[7]	1.4106 at 30°	1.4120 at 20°[7]
	VI	[g] 0.00	96.0– 96.5	96– 97[19]	1.4106 at 30°	1.4127 at 20°[18]
	X	− 1.28	96.0– 97.0	96– 98[7]	1.4100 at 30°	1.4120 at 20°[7]
Methylethylcarbinols	V	+ 0.24	99 –100	99[20]	1.3937 at 27°	1.3954 at 20°[7]
	VII	[h] 0.00	99 –100	99.5[17]	1.3935 at 27°	1.3950 at 25°[17]

Compound Name	No.	Density, (DT_4) Observed	Lit.	Saponification equivalent Observed	Calcd.	[a] Micro-combustion %, C Observed	%, C Theory	%, H Observed	%, H Theory
2,3-Butylene glycols	I	0.996 at 30°	[d]	...	...	53.34	53.31	11.33	11.19
	VIII	0.990 at 25°	[d]	...	...	53.38	53.31	11.15	11.19
2,3-B. G. Diacetates	II	1.016 at 30°	[f]	85.9	87.1	55.18	55.16	8.14	8.10
	IX	1.017 at 30°	[f]	86.8	87.1	55.20	55.16	7.96	8.10
M. V. C. Acetate	III	...	...	116	114	63.29	63.18	8.80	8.84
Methylvinylcarbinols	IV	0.832 at 26°	0.836 at 15°[7]	...	...	66.58	66.63	11.10	11.18
	VI	0.831 at 26°	0.832 at 20°[18]	...	...	...	...	...	...
	X	0.830 at 28°	0.816 at 39°[7]	...	...	66.44	66.63	11.21	11.18
Methylethylcarbinols	V	...	...	...	...	64.50	64.82	13.74	13.61
	VII	...	...	...	...	...	...	...	...

[a] Conducted by the Analytical and Physical Chemical Division of this Laboratory. [b] Wilson and Lucas[4] report 176.7°$_{742}$ for the D-, L- and 181.7°$_{742}$ for the *meso*- forms. [c] Huntress and Mulliken[17] report $n^{25}D$ 1.4364 for the D-, L- form. [d] Huntress and Mulliken[17] report D^{20}_4 1.0433 for the D-, L- form. [e] Wilson and Lucas[4] report $70_{5.5}$ for the D-, L- and $66_{5.5}$ for the *meso*- forms. [f] Not reported in the literature. [g] Redistilled Shell Development Company methylvinylcarbinol, inactive. [h] From hydrogenation of VI, inactive.

(see reactions I to V above), the possibility of Walden inversion must be considered. Winstein and Lucas[5] observed that in the stepwise transformation of 2,3-butylene glycol to 2,3-dibromobutane, via 3-acetoxy-2-butanol, 2-acetoxy-3-bromobutane and 3-bromo-2-butanol, Walden inversion does not occur in the acetylation and hydrolysis reactions. Since two asymmetric carbon atoms are involved, in order that the configurations formulated above could be vitiated by Walden inversion, the inversion would have had to occur at both asymmetric centers; for inversion at only one center would produce the inactive *meso*-glycol. The regeneration of levorotatory glycol by successive acetylation and hydrolysis (as in racemization experiments above) shows that in *both* of these reactions there was either *no* inversion or *complete double* Walden inversion. The probability of the latter must be extremely small, and in view of the observations of Winstein and Lucas,[5] it is evident that the configurations assigned above to the active 2,3-butylene glycols are not in error due to Walden inversion.

The methylvinylcarbinols isolated from the pyrolysis liquors exhibited $[\alpha]^{23}D$ +0.68° and −1.28°, as obtained from the dextro- and levorotatory glycols, respectively, whereas the pure enantiomorphs of Kenyon and Snellgrove[7] showed $[\alpha]^{25}D$ ±33.7°. Hydrogenation of the dextrorotatory methylvinylcarbinol yielded methylethylcarbinol, $[\alpha]^{23}D$ +0.24°, whereas Kenyon and Snellgrove[7] report $[\alpha]^{25}D$ ±13.9° for the pure enantiomorphs. Since the values of our specific rotations were relatively low (2-dcm. polarimeter tubes were generally used, so that the observed rotations were actually twice as great as reported), the possibility of optically active impurities being present in the original fermentation glycol preparations must also be considered. If present, however, they would have been carried through the acetylation, pyrolysis, hydrolysis, and hydrogenation reactions, and at each step would have contaminated the product isolated. The analytical and physical data for each of the five compounds involved in this series of reactions agreed well with both the literature and theory. The fact that the methylvinylcarbinols isolated exhibited the same sign of rotation as the glycols from which they were prepared would require, furthermore, that any such impurity be dextrorotatory in one case and levorotatory in the other. The probability that the observed rotations were due to impuritities must, therefore, be extremely small.

The proof of the configuration of the 2,3-

(17) E. H. Huntress and S. P. Mulliken, "Identification of Pure Organic Compounds," J. Wiley and Sons, Inc., New York, N. Y., 1941, pp. 432, 467.
(18) J. Baudrenghien, *Bull. soc. chim. Belg.*, **31**, 160 (1922).
(19) A. Wohl and M. S. Losanitsch, *Ber.*, **41**, 3621 (1908).
(20) R. H. Pickard and J. Kenyon, *J. Chem. Soc.*, **103**, 1923 (1913).

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butylene glycols herein presented is somewhat unique in that reactions involving extensive racemization, namely, esterification and pyrolysis, were employed and, furthermore, the sign of rotation always indicated which active form was present. The symmetry of the glycol molecule containing two asymmetric centers permits the existence of only two active forms, the D- and L-, and on removing one of these centers by dehydration (or deacetylation of the diacetate), the methylvinylcarbinol (or its acetate) so produced also exists in only two active forms, D- or L-. As pointed out above, the active methylvinylcarbinol (or its acetate) must have the same configuration as the active glycol from which it was prepared.

Summary

In studying the conversion of optically active 2,3-butylene glycols to butadiene, the intermediate methylvinylcarbinols were isolated, each exhibiting the same sign of rotation as the glycol from which it was prepared. Hydrogenation to methylethylcarbinol also proceeded without change in sign. Since the configuration of dextrorotatory methylethylcarbinol had already been related to that of dextrorotatory lactic acid, which belongs to the L-series, the configuration of the active 2,3-butylene glycols was, therefore, established as D-(−)- and L-(+)−.

PEORIA, ILLINOIS RECEIVED FEBRUARY 17, 1944

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Orientation in the Biphenyl System. The Preparation of 2- and 4-Aminobiphenyl-4′-sulfonamides[1]

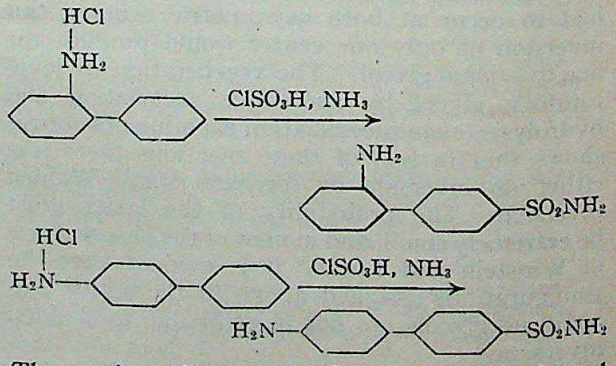
BY A. H. POPKIN AND G. B. MCVEA

Detailed studies[2] on orientation in the biphenyl system have been made in the past and several hypotheses have been proposed to explain the data obtained. These may be summarized as follows: (1) the usual directive influences ascribed to all simple groups when present in the benzene nucleus occur also in the biphenyl group; (2) those groups which normally orient ortho–para usually direct other groups into the same nucleus; conversely, meta-orienting groups direct further substitution into the adjacent ring; (3) the two nuclei of biphenyl act independently of each other.

Certain anomalous behaviors of the acetamido group which normally exhibits an ortho–para-orienting influence have been noted. The nitration of 2-acetamidobiphenyl[3] gave a 50% yield of 2-acetamido-4′-nitrobiphenyl instead of substitution into the five position of the same ring. Also the mononitration of diacetylbenzidine in concentrated sulfuric acid as solvent gave 2-nitrobenzidine instead of the expected 3-nitro-substitution.[4] More recently it was noted that the reaction of 2-acetamidobiphenyl with chlorosulfonic acid also gave substitution in the 4′-position.[5]

Bell[6] explained the anomalous behavior of the acetamido group stating that "this group enters into salt formation with a strong acid thereby being converted into a weakly orienting positive group so that further substitution naturally resembles that of 2-nitrodiphenyl."[7] This conclusion was substantiated by the work of Orton and Bradfield,[8] who showed that the velocity of chlorination of acetanilide was decreased with an increase of the concentration of hydrochloric acid which indicated a gradual shift of the acetamido group from ortho–para-orienting to a meta-orienting characteristic.

The present work confirms further the conclusions arrived at by Bell. The hydrochlorides of 2-aminobiphenyl and 4-aminobiphenyl were each treated with chlorosulfonic acid and ammonia. In each case, substitution was obtained in the 4′-position of the second ring, the products being 2-aminobiphenyl-4′-sulfonamide, 66% yield, and 4-aminobiphenyl-4′-sulfonamide, 88% yield.



The purity of the materials isolated indicated strongly the absence of isomers which might arise from substitution in the five position of the first ring. This proves that the amino group, and by

(1) Presented before the Division of Organic Chemistry, Cleveland meeting of the American Chemical Society, April, 1944.
(2) *E. Chem. Soc.*, 1926–1931.
(3) Scarborough and Waters, *ibid.*, 89 (1927).
(4) Le Fèvre and Turner, *ibid.*, 2041 (1926).
(5) Popkin, THIS JOURNAL, **65**, 2043 (1943).
(6) Bell, *J. Chem. Soc.*, 2770 (1928).
(7) Dadwell and Kenner, *ibid.*, 1102 (1927); Le Fèvre and Turner, *ibid.*, 2043 (1926); Bell and Kenyon, *ibid.*, 2707 (1926).
(8) Orton and Bradfield, 986 (1927).

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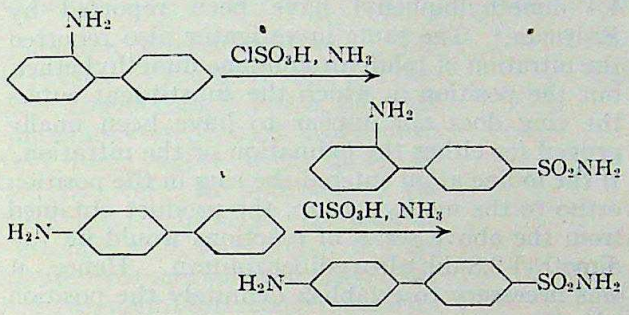
analogy the acetamido group, in combination with a mineral acid as a salt, exhibits a meta-orienting influence.

The reaction of 2-acetamidobiphenyl with chlorosulfonic acid to give 4′-substitution[5] suggested that the corresponding amino compound, being more basic, might react similarly and thereby make available a new and simplified preparation of the sulfonamide. This proved to be true. The reaction of 2-and 4-aminobiphenyls with chlorosulfonic acid and ammonia gave 2-aminobiphenyl-4′-sulfonamide, 55% yield, and 4-aminobiphenyl-4′-sulfonamide, 54% yield.



However, it was surprising to note that the unprotected amino compounds required a more vigorous treatment than either the corresponding acetamido compounds or the hydrochlorides. This was unexpected in the light of the established practice of protecting the amino groups for most substitution reactions.[9]

These reactions are now being applied to aniline, aniline hydrochloride and their various derivatives, and will be reported later.

Experimental

Preparation of 2- and 4-Aminobiphenyl Hydrochlorides.—A solution was made of 200 g. of the corresponding aminobiphenyl in three liters of benzene. Hydrogen chloride gas, generated by dropping concd. sulfuric acid into concd. hydrochloric acid, was bubbled into the solution. The colorless hydrochloride which formed was separated by suction filtration, washed with a liter of benzene and dried at 80°. In this manner, 2- and 4-aminobiphenyl hydrochlorides were prepared in 85–95% yields and substantially free of unconverted amine.

Reaction of 2-Aminobiphenyl Hydrochloride with Chlorosulfonic Acid and Ammonium Hydroxide.—Into a two-liter beaker was placed 1150 g. (650 cc., 9.86 moles) of chlorosulfonic acid. To this was added 410 g., 1.99 moles, of 2-aminobiphenyl hydrochloride during one hour and twenty minutes. The reaction temperature was kept below 10° during the addition. The resulting product was heated during three hours at 60° and then poured slowly and with agitation into 3200 cc. of concd. aqueous ammonium hydroxide. The temperature was kept at 8° during the latter addition. The precipitate was separated by suction filtration, the filter cake reslurried twice with two liters of water and then washed with distilled water until free of chloride and sulfate ions. The solid was dried at 55°; wt. 327 g., 66% yield; m. p. 178–182°. Solution in aqueous alkali and treatment with Norite gave purified 2-aminobiphenyl-4′-sulfonamide, m. p. 186–187°. A mixed m. p. with a sample of known material[5] showed no depression in the m. p.

(9) Smiles and Stewart, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1925, Vol. V, p. 3.

Reaction of 4-Aminobiphenyl Hydrochloride with Chlorosulfonic Acid and Ammonium Hydroxide.—This reaction was conducted in the manner just described using 50 g. of 4-aminobiphenyl hydrochloride. A crude product was obtained; wt. 53.7 g., 88% yield; m. p. 230–250°. Purification from methanol gave m. p. 248–250°. No depression in the melting point was obtained when this was mixed with a sample of known 4-aminobiphenyl-4′-sulfonamide.[10]

Reaction of 2-Aminobiphenyl with Chlorosulfonic Acid and Ammonium Hydroxide.—Into a 250-cc. beaker was placed 105 g. (60 cc., 0.9 mole) of chlorosulfonic acid. To this was added 32.3 g., 0.19 mole, of 2-aminobiphenyl (Monsanto Chemical Co.) during fifteen minutes. The reaction temperature was allowed to rise from 25° to 70° during the addition. The resulting product was heated during one and one-half hours at 90° and then poured slowly and with agitation into 300 cc. of concd. aqueous ammonium hydroxide. The temperature was kept below 20° during the latter addition. The precipitate was separated by suction filtration, the press cake reslurried twice with 50 cc. of water and then washed with distilled water until free of chloride and sulfate ions. The solid was dried at 80°; wt. 26.3 g., 55.4% yield; m. p. 176–182°. Crystallization from ethyl alcohol gave purified 2-aminobiphenyl-4′-sulfonamide, m. p. 186–187°. A mixed m. p. with a sample of known material[5] gave no depression in the m. p.

The above conditions were found to give the optimum yield of the sulfonamide. When 2-aminobiphenyl was heated with chlorosulfonic acid at 60° for three hours, unreacted 2-aminobiphenyl was obtained when the reaction product was poured into ammonium hydroxide. When 2-aminobiphenyl was heated with chlorosulfonic acid at 110° for one hour, only 9.3 g. of the sulfonamide was obtained. When heated for one hour at 100° and added to ammonium hydroxide at 25–50°, 8.2 g. of the sulfonamide resulted.

Reaction of 4-Aminobiphenyl with Chlorosulfonic Acid and Ammonium Hydroxide.—This reaction was conducted with the optimum conditions described above and starting with 129.2 g., 0.76 mole, of 4-aminobiphenyl (Monsanto Chemical Co.) and 420 g. (244 cc., 3.7 moles) of chlorosulfonic acid. A crude product was obtained; wt. 103.1 g., 54% yield, m. p. 233–250°. Purification gave m. p. 252–254°. No depression in the m. p. was obtained when this was mixed with a sample of known 4-aminobiphenyl-4′-sulfonamide.

Preparation of 4-Aminobiphenyl-4′-sulfonamide.—This was prepared from 4-acetamidobiphenyl without isolation of the intermediates 4-acetamidobiphenyl-4′-sulfonyl chloride and 4-acetamidobiphenyl-4′-sulfonamide. The reaction product of 4-acetamidobiphenyl and chlorosulfonic acid was poured upon ice water, the resulting solid treated with aqueous ammonium hydroxide and then with boiling hydrochloric acid. Crude 4-aminobiphenyl-4′-sulfonamide was obtained by treating the hydrochloride with ammonium hydroxide and purification effected by washing with boiling water and crystallization from ethyl alcohol; m. p. 255–256° with slight decomposition. Van Meter, Bianculli and Lowy[10] reported m. p. 261° with slight decomposition for a highly purified sample of the same compound.

Acknowledgment.—The authors are indebted to the General Printing Ink Corporation for permission to publish this work.

Summary

2- and 4-aminobiphenyl-4′-sulfonamides were prepared from 2- and 4-aminobiphenyls and their hydrochlorides by the action of chlorosulfonic acid and ammonia. This substantiates the hypothesis that the acetamido group in biphenyl exercises a meta-orienting influence in the presence

(10) Van Meter, Bianculli and Lowy, THIS JOURNAL, 62, 3146 (1940).

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of a strong acid because of salt formation. The stability of the unprotected amines toward chlorosulfonic acid was unexpected.

NEW YORK, N. Y. RECEIVED FEBRUARY 7, 1944

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Dibenzofuran. XX. 2,3,7,8-Derivatives[1]

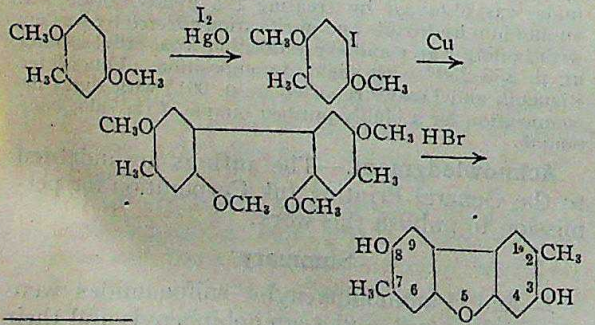
BY HENRY GILMAN, JACK SWISS, H. B. WILLIS AND F. A. YEOMAN

The present work is an extension of studies concerned with the bridging of the 1,9-positions. In an earlier paper,[2] the dibromination of 4,6-dimethoxydibenzofuran was reported. The structure of the resulting dibromo compound has not been definitely established, but it may possibly be 1,9-dibromo-4,6-dimethoxydibenzofuran.

We are now reporting the dibromination of 2,8-dimethoxydibenzofuran. From this reaction there resulted two isomeric dibromodimethoxydibenzofurans, one of m. p. 196–197°, and the other of m. p. 260–261°. The lower-melting isomer has been designated tentatively as 1,9-dibromo-2,8-dimethoxydibenzofuran, since it is known that 1-bromo-2-methoxydibenzofuran has a lower m. p. than the 3-bromo isomer.[3] However, it is possible that the spatial configuration of the dibenzofuran molecule is such that the 1- and 9-positions are in close proximity and simultaneous substitution of both positions by any large group or atom may, consequently, be very difficult. The 1,7-dibromo isomer is, therefore, a possibility not to be excluded from consideration.

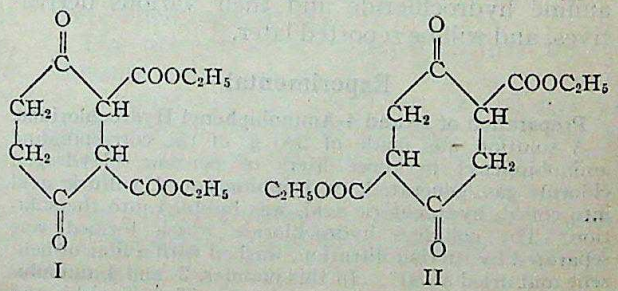
The higher-melting isomer is now shown to be 3,7-dibromo-2,8-dimethoxydibenzofuran. This structure was established by conversion to 3,7-dimethyl-2,8-dihydroxydibenzofuran and comparison of this compound with an authentic sample prepared by a synthesis involving ring closure.

The series of transformations resulting in the formation of 3,7-dimethyl-2,8-dihydroxydibenzofuran through ring closure is schematically represented below.



The iodination of toluhydroquinone dimethyl ether and the Ullmann coupling of the resulting iodo compound to give 2,2′,5,5′-tetramethoxy-4,4′-dimethylbiphenyl have been reported by Erdtman.[4] The same investigator also reported the nitration of toluhydroquinone dimethyl ether, but the position in which the substituent enters the ring does not appear to have been finally proved for either the iodination or the nitration.[5] If the iodine atom entered the ring in the position ortho to the methyl group, the product obtained from the above series of reactions would be 1,9-dimethyl-2,8-dihydroxydibenzofuran. Hence, it was necessary to establish definitely the position of iodination.

Nef[6] has reported the synthesis of 2,5-dimethoxyterephthalic acid and of its diethyl ester from ethyl succinylsuccinate. The latter compound was first prepared by Hermann[7] who believed it to have the structure (I) and oxidized it to the corresponding benzene derivative. Ebert, however, has shown that the symmetrical structure (II) is the correct one.[8]



Accordingly, the iodination product of toluhydroquinone dimethyl ether was converted to 2,5-dimethoxyterephthalic acid by the following series of reactions.

The iodo compound was first converted to the corresponding nitrile by the method of Koelsch.[9]

(1) Paper XIX: Gilman, Swiss and Cheney, THIS JOURNAL, **62**, 1963 (1940). The present address of Jack Swiss is Research Laboratories, Westinghouse Electric and Manufacturing Co., East Pittsburgh, Pa., and that of H. B. Willis is Fine Chemicals Division, Gelatine Products Co., Detroit, Michigan.

(2) Gilman and Cheney, THIS JOURNAL, **61**, 3149 (1939).

(3) Gilman and P. R. Van Ess, *ibid.*, **61**, 1365 (1939).

(4) Erdtman, *Proc. Roy. Soc.* (London), **A143**, 191 (1933).

(5) In a private communication, Dr. Erdtman stated, "I don't think the structure of this compound (5-iodotoluhydroquinone dimethyl ether) has been rigorously proved, but it follows, I believe, conclusively from the analogous reactivity of toluquinol and hydroxyquinol." The present authors have been unable to find any record of an investigation of this type having been carried out on toluhydroquinone or hydroxyhydroquinone. We are grateful to Dr. Erdtman for a sample of the 5-iodotoluhydroquinone dimethyl ether prepared by him. The material proved identical with the iodination product prepared in this Laboratory.

(6) Nef, *Ann.*, **258**, 297 (1890).

(7) Hermann, *ibid.*, **211**, 306 (1882).

(8) Ebert, *ibid.*, **229**, 45 (1885).

(9) Koelsch, THIS JOURNAL, **58**, 1328 (1936).

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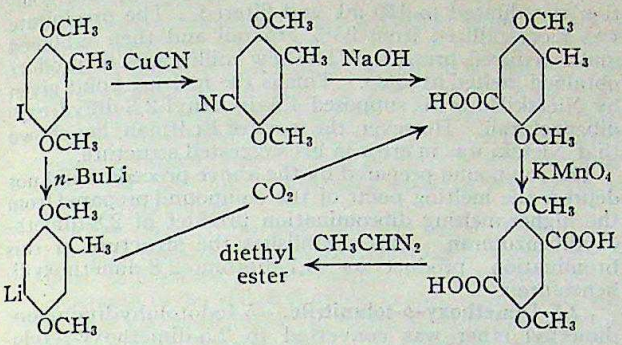
The resulting nitrile was hydrolyzed to give 2,5-dimethoxy-*p*-toluic acid which was oxidized to



2,5-dimethoxyterephthalic acid. The diethyl ester of the final acid was prepared. The melting points of both the 2,5-dimethoxyterephthalic acid and its diethyl ester agree with those reported by Nef. In addition to the method just mentioned, 2,5-dimethoxy-*p*-toluic acid was prepared from 5-iodotoluhydroquinone dimethyl ether by halogen–metal interconversion with *n*-butyllithium followed by carbonation.

Conversion of 3,7-dibromo-2,8-dimethoxydibenzofuran to 3,7-dicarboxy-2,8-dimethoxydibenzofuran and preparation of the dimethyl ester of this acid have already been reported.[10]

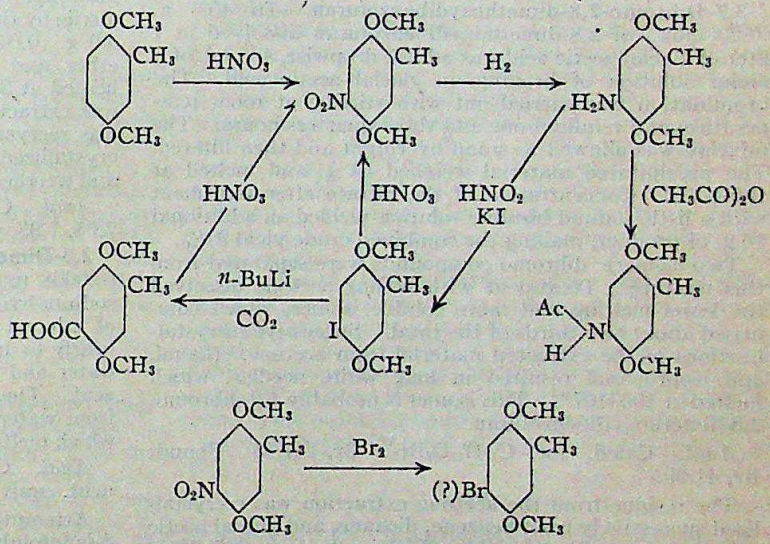
A number of attempts was made to prepare a compound from which 1,9-dimethyl-2,8-dihydroxydibenzofuran might be synthesized by ring closure. Such a compound could be prepared from toluhydroquinone dimethyl ether by introduction of a halogen atom into the 3-position.

First, the structure of the nitration product of toluhydroquinone dimethyl ether was established as being 5-nitrotoluhydroquinone dimethyl ether, in agreement with Erdtman's assumption, by reduction to the amine and conversion to the 5-iodo compound whose structure has been demonstrated.

Since the nitro group is a meta director, halogenation of 5-nitrotoluhydroquinone dimethyl ether might be expected to introduce the halogen atom into the 3-position. The nitro group could then be removed by stannous chloride reduction followed by diazotization. Bromination of the nitro compound proved difficult and the product obtained from the reaction was found to contain bromine, but no nitrogen. This substance has not been further investigated, but it seems likely that the nitro group was replaced by a bromine atom. Attempts at iodination of 5-nitrotoluhydroquinone dimethyl ether were unsuccessful.[11]

An additional substituent introduced into 2,5-dimethoxy-*p*-toluic acid might also be expected to enter the position ortho to the methyl group, since the carboxyl group is a meta directing group. Nitration of 2,5-dimethoxy-*p*-toluic acid, however, resulted in replacement of the carboxyl group by the nitro group. Attempts at iodination of the same acid met with no success.

Nitration of 5-iodotoluhydroquinone dimethyl ether resulted in replacement of the iodine atom by a nitro group. A diagrammatic representation of the work done in attempting to synthesize an intermediate for the preparation of 1,9-dimethyl-2,8-dihydroxydibenzofuran appears below.



A striking feature of this series of reactions is the rather unusual exchange of groups occurring in the 5-position. The marked contrast between the reactivity of this position and that of the other two unsubstituted positions on the ring is difficult to explain on the basis of the normally rather weak directing influence of the methyl group, and yet all three positions bear the same relation to the two methoxyl groups.

Experimental

2,8-Dimethoxydibenzofuran.—An intimate mixture of 100 g. (0.307 mole) of 2,8-dibromodibenzofuran (m. p. 185–189°), 200 g. of technical, flake sodium hydroxide (76% NaOH), and 24 g. of copper–bronze powder was poured onto a mat of 100 g. of copper turnings in a 600 ml. copper beaker, and 100 ml. of copper sulfate solution containing 30 g. of $CuSO_4 \cdot 5H_2O$ was added. The mixture was heated at 235–240° for twelve hours in an electrically heated bomb.[12]

The contents of the beaker were extracted with 300 ml. portions of boiling water until acidification of the filtrate gave no further precipitate. The combined filtrates were made acid to congo red with hydrochloric acid, and the light tan product was filtered. The dried product weighed 67 g. and melted at 230–235°. The theoretical yield is 62 g., but the crude product contained occluded sodium chloride.

To 237.5 g. of crude 2,8-dihydroxydibenzofuran, prepared as described above and dissolved in a liter of water

(10) Gilman, Swislowsky, and Brown, This Journal, 62, 348 (1940).

(11) Unpublished studies by F. A. Yeoman.

(12) The authors are grateful to Dr. F. E. Brown for the use of a steel bomb.

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containing 103 g. of sodium hydroxide, was added 280 ml. of dimethyl sulfate, dropwise with stirring. The mixture was stirred two hours and then stirred and refluxed three hours. Excess dimethyl sulfate was destroyed by addition of 30 g. of sodium hydroxide. The yield of crude 2,8-dimethoxydibenzofuran was 221 g. (81%). This was distilled (b. p., 187° (5 mm.)) to give, after crystallization from 95% ethanol, 89 g. of white plates melting at 88–89°. Concentration of the mother liquor, and extraction of the residue in the Claisen flask yielded an additional 35 g. of impure material which gave on distillation and recrystallization 24 g. of pure product. The total yield of pure 2,8-dimethoxydibenzofuran was 113 g. (45.5% based on the weight of 2,8-dibromodibenzofuran required for its preparation).

Anal. Calcd. for $C_{14}H_{12}O_3$: C, 73.61; H, 5.30. Found: C, 73.65; H, 5.47.

3,7-Dibromo-2,8-dimethoxydibenzofuran.—To 45.6 g. (0.20 mole) of 2,8-dimethoxydibenzofuran dissolved in 1 liter of glacial acetic acid was added, dropwise, 400 ml. of a molar solution of bromine in glacial acetic acid. The bromination was carried out with stirring at room temperature and required one and three-quarters hours. The mixture was allowed to stand overnight and then filtered. The precipitated material weighed 54 g. and melted at 180–220°. Concentration of the filtrate after treatment with a little sodium bisulfite solution yielded an additional 16 g. of product, making the combined crude yield 91%.

Two isomeric dibromo compounds were separated from this mixture. Treatment with boiling acetone dissolved the lower-melting and more soluble isomer, which comprised about two-thirds of the total. Successive recrystallizations of the extracted material from acetone, ethanol, and isopropanol resulted in long white needles, which melted at 196–197°. This isomer is probably 1,9-dibromo-2,8-dimethoxydibenzofuran.

Anal. Calcd. for $C_{14}H_{10}O_3Br_2$: Br, 41.45. Found: Br, 41.90.

The residue from the acetone extraction was recrystallized successively from benzene, dioxane, and glacial acetic acid to give white needles which melted at 260–261°. This compound is 3,7-dibromo-2,8-dimethoxydibenzofuran.

Anal. Calcd. for $C_{14}H_{10}O_3Br_2$: Br, 41.45. Found: Br, 40.90.

Conversion of 3,7-Dibromo-2,8-dimethoxydibenzofuran to 3,7-Dimethyl-2,8-dimethoxydibenzofuran.—*n*-Butyllithium, prepared from 2 g. of lithium and 7 ml. of *n*-butyl bromide in 37 ml. of ether, was added to 4.6 g. (0.0119 mole) of 3,7-dibromo-2,8-dimethoxydibenzofuran in 75 ml. of benzene, and the mixture was refluxed with stirring for 30 minutes. The mixture was cooled for five minutes and 5 ml. of dimethyl sulfate in 10 ml. of ether was added dropwise. Stirring was continued for four hours.

Upon working up the product there was obtained 1.5 g. (49%) of a compound which melted at 140° after recrystallization from ethanol. A second recrystallization from the same solvent raised the melting point to 144–144.5°.

Preparation of 3,7-Dimethyl-2,8-dihydroxydibenzofuran.—To 0.1 g. (0.00039 mole) of 3,7-dimethyl-2,8-dimethoxydibenzofuran was added 2 ml. of glacial acetic acid and 2.5 ml. of constant boiling hydrobromic acid. The mixture was refluxed for seventeen hours in an apparatus fitted with ground-glass joints and then poured into 45 ml. of water. The crude dihydroxy compound which precipitated melted at 225–227°. This material was treated with Norite in boiling alcohol and then recrystallized from dilute alcohol. Light yellow plates, which sintered at 228° and melted at 231–232°, were obtained.

2,2′,5,5′-Tetramethoxy-4,4′-dimethylbiphenyl.—This compound was prepared in essential accordance with the procedure of Erdtman[4] from 3 g. of copper and 3 g. (0.0108 mole) of 5-iodotoluhydroquinone dimethyl ether. The yield was 50% of white crystals that melted at 134°. In a second, larger run the yield was raised to 84%.

Demethylation of 2,2′,5,5′-tetramethoxy-4,4′-dimethylbiphenyl.—A mixture of 4.5 g. (0.0149 mole) of 2,2′,5,5′-tetramethoxy-4,4′-dimethylbiphenyl, 20 ml. of glacial acetic acid, and 25 ml. of 42% hydrobromic acid was refluxed twenty hours in an all-glass apparatus. The solution was diluted to 450 ml. and filtered. The precipitate was recrystallized from 95% ethanol and then sublimed under reduced pressure. The few milligrams of product obtained melted at 232°. This is the melting point given by Nietzki[13] for his supposed 4,6-dimethyl-2,8-dihydroxydibenzofuran. However, the work of Erdtman[4] has shown that Nietzki was in error in his suggested structure.

The compound prepared by the above procedure did not depress the melting point of the compound prepared from the higher-melting dibromination product of 2,8-dimethoxydibenzofuran. This establishes the structure of this bromination product as 3,7-dibromo-2,8-dimethoxydibenzofuran.

2,5-Dimethoxy-*p*-tolunitrile.—5-Iodotoluhydroquinone dimethyl ether was converted to 2,5-dimethoxy-*p*-tolunitrile by the method of Koelsch.[9] An intimate mixture of 3.0 g. (0.0108 mole) of 5-iodotoluhydroquinone dimethyl ether and 2.12 g. of anhydrous cuprous cyanide was heated at 240° for four hours. The solid mass remaining was extracted with acetone and the yellow solid obtained was recrystallized from dilute ethanol. The pure nitrile crystallized in yellow needles which melted at 130–131° and weighed 1.4 g. (73%).

Anal. Calcd. for $C_{10}H_{11}O_2N$: N, 7.91. Found: N, 7.95, 7.98.

2,5-Dimethoxy-*p*-toluic Acid.—A solution of 1.2 g. (0.0068 mole) of 2,5-dimethoxy-*p*-tolunitrile in 5.8 g. of sodium hydroxide in a mixture of 5 ml. of water and 35 ml. of ethanol was refluxed ten hours and then evaporated nearly to dryness. The residue was extracted with boiling water and the cooled extract acidified with hydrochloric acid. The precipitate was filtered off and recrystallized from water. The pure acid crystallized in white needles which melted at 125–126° and weighed 0.55 g. (41%).

Anal. Calcd. for $C_{10}H_{12}O_4$: neut. equiv., 196. Found: neut. equiv., 197, 195.

Attempts at preparation of the Grignard reagent from 5-iodotoluhydroquinone dimethyl ether were unsuccessful.

A halogen–metal interconversion on the iodo compound using *n*-butyllithium was successful. To the *n*-butyllithium prepared from 0.20 g. (0.0285 mole) of lithium and 1.52 ml. (0.0144 mole) of *n*-butyl bromide in 30 ml. of ether was added with stirring a solution of 2.0 g. (0.0072 mole) of 5-iodotoluhydroquinone dimethyl ether in 20 ml. of ether. The mixture was stirred five minutes at room temperature and then carbonated. The crude acid obtained melted at 124–125° and weighed 0.57 g. Upon recrystallization from water, 0.50 g. of acid melting at 125–126° was obtained, representing a yield of 35%. The acid thus prepared did not depress the melting point of the acid prepared by hydrolysis of the nitrile.

Oxidation of 2,5-Dimethoxy-*p*-toluic Acid.—To a boiling solution of 1.0 g. (0.0051 mole) of 2,5-dimethoxy-*p*-toluic acid in 80 ml. of water was added a solution of 1.6 g. of potassium permanganate in 40 ml. of water. The permanganate was reduced almost instantaneously. A further 0.5 g. of potassium permanganate was added and the solution refluxed for fifteen minutes, at which time decolorization of the permanganate was again complete. The mixture was filtered hot, concentrated to 50 ml., and acidified with hydrochloric acid. The crude product resulting melted at 210–239°, and weighed 0.47 g., a crude yield of 40%.

Purification was difficult, but finally crystallization from a large volume of water yielded 30 mg. of pure 2,5-dimethoxyterephthalic acid of m. p. 265–265.5° in agreement with the melting point reported by Nef.[6]

Anal. Calcd. for $C_{10}H_{10}O_6$: neut. equiv., 113. Found: neut. equiv., 114.

A small amount (about 8 mg.) of 2,5-dimethoxyterephthalic acid was esterified by treatment with diazoethane in ether solution. The crude diethyl ester melted

(13) Nietzki, *Ber.*, **11**, 1278 (1878).

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at 91–96°. Two recrystallizations from ethanol raised the melting point to 101–102° in agreement with that reported by Nef.

5-Aminotoluhydroquinone Dimethyl Ether.—In a glass hydrogenation vessel was placed a solution of 9.0 g. (0.0456 mole) of 5-nitrotoluhydroquinone dimethyl ether in the minimum amount of hot ethanol. One gram of activated Raney nickel catalyst was added. The mixture was hydrogenated at a hydrogen pressure maintained between 30 and 45 pounds gage pressure at a temperature of 100° for one hour. Constant shaking was maintained during this period.

After the mixture had been thoroughly cooled and the pressure released, it was filtered quickly to remove catalyst. A colorless filtrate resulted. The solution was concentrated under reduced pressure and, when nearly all the alcohol had been removed, white needles which melted at 108.5–109.5° precipitated. The amine darkened very rapidly upon exposure to air and, consequently, no attempt was made to purify it for analysis.

To the flask containing the crude 5-aminotoluhydroquinone dimethyl ether was added 10 ml. of acetic anhydride. The light yellow solution which resulted upon gentle heating was transferred to a small Erlenmeyer flask and refluxed one hour. Dilution and cooling resulted in a white, granular precipitate which was filtered off and recrystallized several times from an ethanol–water mixture. The pure 5-acetaminotoluhydroquinone dimethyl ether, which crystallized in white needles, weighed 5.1 g., and melted at 160–162°. This is a yield of 53% based upon the amount of 5-nitrotoluhydroquinone dimethyl ether originally reduced.

Anal. Calcd. for $C_{11}H_{15}O_3N$: N, 6.69. Found: N, 6.72, 6.75.

Conversion of 5-Aminotoluhydroquinone Dimethyl Ether to 5-Iodotoluhydroquinone Dimethyl Ether.—The 5-aminotoluhydroquinone dimethyl ether resulting from the reduction of 10.0 g. (0.0507 mole) of 5-nitrotoluhydroquinone dimethyl ether was transferred quickly to a one liter Erlenmeyer flask flushed out with nitrogen. A solution of 11 ml. of concentrated hydrochloric acid in 38 ml. of water was added and the resulting solution was cooled to 0°. To the chilled amine hydrochloride solution was added slowly with stirring a solution of 2.6 g. of sodium nitrite in 11 ml. of water. On slow addition of a solution of 6.4 g. of potassium iodide in 12 ml. of water to the above mixture, a yellow precipitate formed. Upon boiling, the color of the precipitate darkened through red to black. Attempts at crystallization of this material were unsuccessful, but sublimation at reduced pressure yielded a light tan solid which melted at 79–81°. Recrystallization from alcohol raised the melting point to 84–85° and removed virtually all the color. The pure product did not depress the melting point of an authentic sample of 5-iodotoluhydroquinone dimethyl ether.

Bromination of 5-Nitrotoluhydroquinone Dimethyl Ether.—To a solution of 3.94 g. (0.02 mole) of 5-nitrotoluhydroquinone dimethyl ether in 25 ml. of carbon tetrachloride was added 3.2 g. (0.02 mole) of bromine. A trace of iron was added as a catalyst and the solution was refluxed for several hours. When all the bromine had reacted, the mixture was washed with sodium thiosulfate solution and the carbon tetrachloride was distilled off. The yield was 2.4 g. of crude product. Recrystallization from ethanol gave 1.5 g. of pure product which melted at 168°. This compound contained bromine but no nitrogen.

The corresponding diacetoxy compound was prepared by hydrolysis of the above compound with hydrobromic acid in glacial acetic acid followed by acetylization with acetic anhydride. The diacetoxy derivative melted at 253–254°. These compounds were not analyzed or further investigated.

Nitration of 2,5-Dimethoxy-*p*-toluic Acid.—To a solution of 3.0 g. (0.0153 mole) of 2,5-dimethoxy-*p*-toluic acid in 25 ml. of glacial acetic acid was added slowly with stirring 5.0 ml. of concentrated nitric acid. The mixture was warmed to 45° for ten minutes and then cooled and diluted with water. An amorphous yellow precipitate which melted at 114–117° formed. Two recrystallizations from alcohol produced 2.5 g. (83%) of yellow plates melting at 118–119°. A mixed melting point with an authentic sample of 5-nitrotoluhydroquinone dimethyl ether showed no depression.

Nitration of 5-Iodotoluhydroquinone Dimethyl Ether.—A nitration was carried out on 3.0 g. (0.0107 mole) of 5-iodotoluhydroquinone dimethyl ether by the same procedure as that applied to 2,5-dimethoxy-*p*-toluic acid. Iodine vapors were given off during the course of the reaction. When the mixture was worked up, 1.7 g. (80%) of pure 5-nitrotoluhydroquinone dimethyl ether was obtained, as shown by a mixed m. p. with an authentic sample.

Summary

Several 2,3,7,8-substituted derivatives of dibenzofuran have been prepared. Their structures have been demonstrated through a biphenyl ring closure.

The structures of the 5-iodotoluhydroquinone dimethyl ether and the 5-nitrotoluhydroquinone dimethyl ether reported by Erdtman have been established.

An unusual series of reactions involving exchange of groups substituted in the 5-position of toluhydroquinone dimethyl ether is reported.

Ames, Iowa Received February 12, 1944

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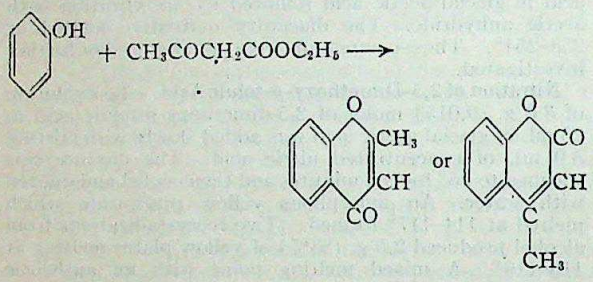
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Formation of a Chromone by the von Pechmann Condensation of Ethyl Acetoacetate with 4-Chloro-3,5-dimethylphenol

BY ROGER ADAMS AND J. W. MECORNEY

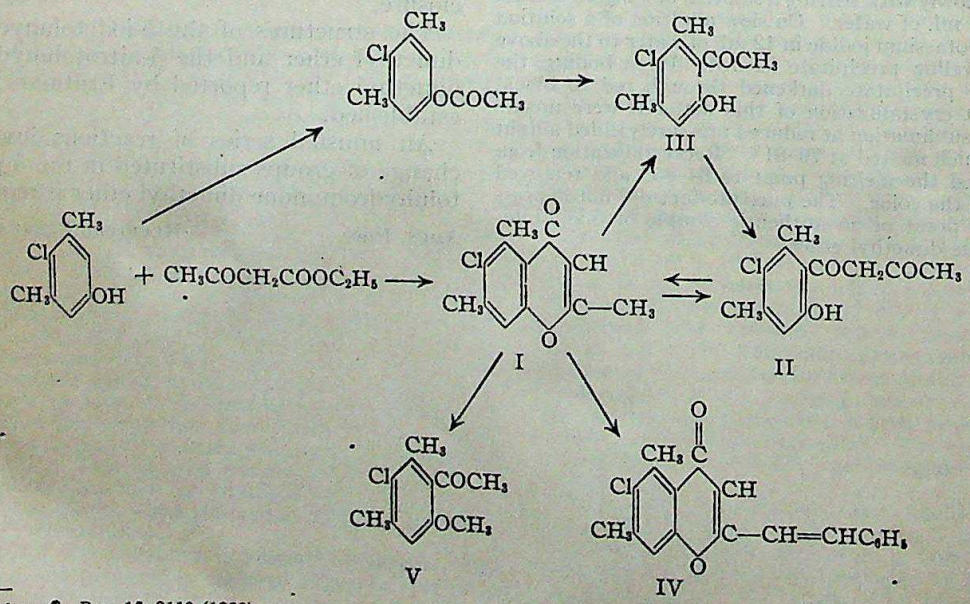
The condensation of ethyl acetoacetate or its substitution products with phenols proceeds under the influence of various reagents to give either chromones or coumarins.



Experience has shown that the von Pechmann[1] reaction, namely, that which involves the use of concentrated sulfuric acid as a condensing agent, leads almost invariably to the coumarin. The report of Jacobson and Ghosh[2] that chromones had been synthesized by the von Pechmann procedure was shown to be incorrect by later investigators[3] who demonstrated that coumarins actually had been obtained. Dey and Laksminarayanan[4] isolated merely the coumarin from the crude condensation product of ethyl acetoacetate and β-naphthol. From the same crude reaction product they were able by the action of benzaldehyde and sodium ethoxide to isolate a small yield of a styryl derivative of 1,4-β,α-naphthopyrone, indicating that some chromone was present. Chakravarti[5] states that with this exception there is no other case in which the presence of a chromone has even been detected when sulfuric acid was used as a condensing agent.

The requirements in another research of a coumarin derived from 4-chloro-3,5-dimethylphenol led to experiments on the application of the von Pechmann reaction first to 3,5-dimethylphenol as a type compound and then to 4-chloro-3,5-dimethylphenol. The synthesis with 3,5-dimethylphenol proceeded smoothly to a coumarin as previously reported,[6] but the chloro derivative yielded a pure product which was not a coumarin and was, therefore, assumed to be a chromone. Investigation has confirmed these facts. It does appear therefore that the von Pechmann condensation may lead to coumarins when the phenols are properly substituted.

The proof of the structure of the chromone (I) from 4-chloro-3,5-dimethylphenol, ethyl acetoacetate and sulfuric acid was established by (1) hydrolysis to a 1,3-diketone (II) which was synthesized by the unequivocal method of condensation of 5-chloro-4,6-dimethyl-2-hydroxyacetophenone (III) with ethyl acetate and which by the action of acid reverts to the chromone; (2) condensation with benzaldehyde to a styryl derivative (IV); (3) hydrolysis to a hydroxy ketone (III) or hy-



(1) Von Pechmann, *Ber.*, **16**, 2119 (1883).

(2) Jacobson and Ghosh, *J. Chem. Soc.*, **107**, 424, 959, 1051 (1915); Ghosh, *ibid.*, **109**, 105 (1916).

(3) Baker and Robinson, *ibid.*, **127**, 1981 (1925); Baker, *ibid.*, **127**, 2349 (1925).

(4) Dey and Laksminarayanan, *J. Ind. Chem. Soc.*, **9**, 149 (1932).

(5) Chakravarti, *ibid.*, **12**, 536 (1935).

(6) Clayton, *J. Chem. Soc.*, **93**, 2016 (1908).

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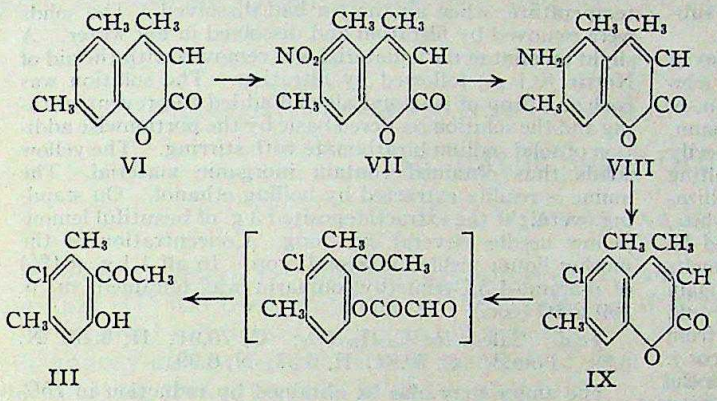
drolysis followed by methylation to a methoxy ketone (V).

In order to obtain the desired chlorinated coumarin, the coumarin (VI) from 3,5-dimethylphenol and ethyl acetoacetate was nitrated to a mononitro compound (VII) which was reduced to the amine (VIII) and this was diazotized and treated with hydrochloric acid to replace the amino group with chlorine (IX).



The structure of the coumarin was confirmed by ozonization followed by treatment with alkali. 5 - Chloro - 4,6 - dimethyl - 2 - hydroxyacetophenone was obtained, which serves to identify the original compound as a coumarin and at the same time to establish the position of the chlorine atom.

Experimental

6-Chloro-2,5,7-trimethylchromone (I).—To a mixture of 50 g. of 4-chloro-3,5-dimethylphenol (1 mol. equiv.) and 42 g. of freshly distilled ethyl acetoacetate (1 mol. equiv.), was added 300 cc. of concentrated sulfuric acid. The solution was warmed on a steam-bath for one-half hour and then allowed to stand at room temperature for one week. Fine needles separated from the reaction mixture on cooling and were redissolved by occasional warming. A large quantity of solid material was obtained by adding the solution to 3 kg. of crushed ice and allowing to warm to room temperature. The crude solid was removed by filtration, thoroughly washed with water, and after two crystallizations from aqueous ethanol, 25 g. (35%) of flat white rods 1–2 cm. long was obtained; m. p. 145–146° (cor.). The mother liquors contained considerable amounts of oily material which was not investigated further. Previous runs with a twenty-four hour reaction time gave lower yields (7–20%).

Anal. Calcd. for $C_{12}H_{11}ClO_2$: C, 64.73; H, 4.98; Cl, 15.92. Found: C, 64.96 (64.97); H, 4.81; Cl, 15.80.

6-Chloro-5,7-dimethyl-2-β-styrylchromone (IV).—This styryl derivative is readily formed by the condensation of the chromone with benzaldehyde in the presence of alcoholic sodium ethoxide following the general procedure of Heilbron, Barnes and Morton[7]; fluffy, flocculent crystals from absolute ethanol; m. p. 186–186.5° (cor.); yield, quantitative.

Anal. Calcd. for $C_{19}H_{15}ClO_2$: C, 73.43; H, 4.87; Cl, 11.41. Found: C, 73.61; H, 4.74; Cl, 11.56.

4-Chloro-3,5-dimethyl-6-acetylacetophenol (II).—A solution of 5 g. of 6-chloro-2,5,7-trimethylchromone and 5 g. of potassium hydroxide pellets in 50 cc. of absolute ethanol was refluxed with stirring for one-half hour. The solution which had turned a claret red, was added to crushed ice and gave a clear solution. Cold, dilute hydrochloric acid was added dropwise and a yellow oil separated which solidified slowly. The crude solid was dissolved in 5% aqueous sodium hydroxide and warmed on the steam-bath for one minute. Norite (0.1 g.) was added and the solution was filtered. Upon careful addition of cold, dilute hydrochloric acid a solid was obtained which could be crystallized from toluene as fine, white needles, m. p. 148–150° (cor.), yield 2.5 g. (45%).

Anal. Calcd. for $C_{12}H_{13}ClO_3$: C, 59.88; H, 5.44; Cl, 14.73. Found: C, 60.06; H, 5.59; Cl, 14.70.

It is insoluble in 5% sodium bicarbonate solution, but readily soluble in 5% aqueous sodium hydroxide solution. Aqueous suspensions, as well as ethanolic and acetonic solutions, gave no color with ferric chloride. A transient coloration could be obtained in the following way. Five cubic centimeters of glacial acetic acid is heated to boiling and a drop of 3% ferric chloride solution added. Upon addition of 50 mg. of the 1,3-diketone, an intense red color is obtained which disappears rapidly upon stirring.

The 1,3-diketone could be readily converted to the chromone by warming 0.2 g. in glacial acetic acid to which a drop of dilute hydrochloric acid had been added.[8] Water is added to the reaction mixture and the crystals removed by filtration, m. p. 145–146° (cor.); yield, quantitative. A mixed m. p. with 6-chloro-2,5,7-trimethylchromone (I) prepared above showed no depression

5-Chloro-4,6-dimethyl-2-hydroxyacetophenone (III).—A mixture of 2 g. of the chromone, 1.2 g. of sodium hydroxide and 13 cc. of water was refluxed vigorously for five hours. The reaction mixture was added to crushed ice and acidified with concentrated sulfuric acid. The solid was collected by filtration and crystallized from dilute aqueous methanol; long white needles, m. p. 89.5–90° (cor.).

Anal. Calcd. for $C_{10}H_{11}ClO_2$: C, 60.46; H, 5.58. Found: C, 60.39; H, 5.76.

It is insoluble in 5% aqueous sodium bicarbonate but readily soluble in 5% aqueous sodium hydroxide.

5-Chloro-4,6-dimethyl-2-methoxyacetophenone (V).—A mixture of 10 g. of the chromone, 6 g. of sodium hydroxide and 65 cc. of water was refluxed with stirring for five hours, the chromone dissolving in about two hours. In the course of one hour, 26 cc. of dimethyl sulfate was added dropwise, the solution kept basic by portionwise addition of 20% aqueous sodium hydroxide. In all, 50 cc. of alkali was added. An insoluble oil soon separated from the reaction mixture. A further 50 cc. of 20% alkali was added and the heating and stirring continued for one hour. The solution was added to crushed ice and the oil which separated solidified readily. The solid was taken up in hot methanol and the solution was concentrated. Upon standing overnight at room temperature, large white rhombohedral crystals were obtained, m. p. 76–77° (cor.); yield, 5 g. (52%). von Auwers, Muerbe and Sauerwein[9] report m. p. 76–77°. The melting point of a mixture with authentic material showed no depression.

Anal. Calcd. for $C_{11}H_{13}ClO_2$: C, 62.12; H, 6.16. Found: C, 62.53; H, 6.32.

4-Chloro-3,5-dimethylphenyl Acetate.—A mixture of 15 g. of 4-chloro-3,5-dimethylphenol, 16 cc. of acetic anhydride and two drops of concentrated sulfuric acid was warmed on the steam-bath for five hours, then poured onto crushed ice. The acetate separated as an oil which solidified on standing. The crude acetate is suitable for the Fries rearrangement without further purification. It can be crystallized from petroleum ether (b. p. 60–110°), m. p. 48° (cor.); yield 19 g. (93%).[10]

(7) Heilbron, Barnes and Morton, *J. Chem. Soc.*, **123**, 2559 (1923).

(8) Wittig, *Ber.*, **57**, 88 (1924).

(9) von Auwers, Muerbe and Sauerwein, *Fortschr. Chem. Physik physik. Chem.*, **18**, 33 (1924).

(10) Klarmann, Shternov and Gates, THIS JOURNAL, **55**, 2576 (1933).

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5-Chloro-4,6-dimethyl-2-hydroxyacetophenone (III).—To a well-stirred melt of 4-chloro-3,5-dimethylphenyl acetate warmed to 50°, was added 12.5 g. of anhydrous aluminum chloride. The mixture became quite viscous and stirring had to be discontinued. The temperature of the bath was raised to and held at 155° for forty-five minutes. After cooling, the solids were decomposed and triturated with ice and dilute hydrochloric acid. The compound can be purified by steam distillation. The solids thus collected contained some unchanged acetate and were freed by washing with cold dilute alkali. Upon acidification, the solid was collected and crystallized from petroleum ether (b. p. 60–110°). It is a white, flaky substance, m. p. 106–110° (cor.), yield 7 g. (41%).[9,10]

The substance was found to show the characteristics of dimorphs. von Auwers, Muerbe and Sauerwein,[9] who prepared this compound by a different route, report m. p. 106–109° crystallizing from petroleum ether. Klarmann, Shternov and Gates[10] report m. p. 89.7° but do not specify the solvent used for crystallization. The higher-melting form could be converted to the lower by two crystallizations from aqueous ethanol or methanol: long, white, well defined needles, m. p. 89–90° (cor.). It should be pointed out that although the lower modification melts quite sharply at 89–90° (cor.) the liquid does not remain clear until 110° (cor.). The lower-melting form could also be converted to the higher, by one crystallization from petroleum ether (b. p. 60–110°), m. p. 106–110° (cor.). That no unexpected migration of groups took place in the course of the Fries rearrangement was shown by conversion to the methyl ether with dimethyl sulfate, m. p. 76–77° (cor.).[9] The possibility that the lower form might be a hydrate was excluded on the basis of the fact that its melting point remained 89–90° (cor.) both before and after drying for analysis.

4-Chloro-3,5-dimethyl-6-acetylacetophenol (II).—To 3 g. of 5-chloro-4,6-dimethyl-2-hydroxyacetophenone, m. p. 106–110° (cor.) in 16 g. of ethyl acetate, was added 1.2 g. of clean finely-chopped sodium.[8] An immediate reaction took place with the liberation of hydrogen and the insoluble sodium phenolate precipitated. Upon gentle warming a lively reaction set in and the mixture was allowed to stand overnight. The reddish-brown solution was decanted from a small amount of tarry matter and added to water acidified with dilute acetic acid. An orange oil separated which solidified when scratched with a stirring rod. After two crystallizations from toluene, small white needles were obtained, m. p. 148–150° (cor.). A mixed m. p. with the 1,3-diketone isolated by the mild alcoholic hydrolysis of the chromone was not depressed; yield, 2 g. (55%).

6-Chloro-2,5,7-trimethylchromone (I).—The 1,3-diketone thus prepared could also be converted to the chromone by warming in glacial acetic acid to which a drop of dilute hydrochloric acid had been added, m. p. 145–146° (cor.). The mixed m. p. of this material with the chromone prepared by the von Pechmann reaction gave no depression.

4,5,7-Trimethylcoumarin (VI).—Following the procedure described by Clayton,[6] 50 g. of 3,5-dimethylphenol and 55 g. of freshly distilled ethyl acetoacetate were condensed in the presence of 300 cc. of concentrated sulfuric acid; yield, 25 g. (32%) of 4,5,7-trimethylcoumarin, m. p. 181° (cor.). Clayton[6] reports m. p. 175–176°.

6-Nitro-4,5,7-trimethylcoumarin (VII).—This substance was prepared by the method of Jordan and Thorpe.[11] To 30 g. of 4,5,7-trimethylcoumarin dissolved in 300 cc. of concentrated sulfuric acid cooled to −10° by means of a salt–ice-bath, was added with stirring 46 cc. of a nitrating mixture comprised of three parts by volume of sulfuric acid to one part of nitric acid (sp. gr. 1.42) in the course of nine hours. If at any time the temperature reached −5° the addition was interrupted and the reaction mixture was cooled. After an additional hour the solution was allowed to warm to room temperature in the course of forty-five minutes, and added to crushed ice. The solid was collected, washed with water and crystallized from glacial acetic acid. The first crop of fine, white needles weighed 21 g. The mother liquor can be worked up by further crystallization to yield additional material. In all 26 g. (80%) of nitrocoumarin, m. p. 209–211° (cor.) was obtained. Jordan and Thorpe[11] report m. p. 208°. If the rate of addition is increased materially or the temperature allowed to exceed 0°, the yield is much lower.

6-Amino-4,5,7-trimethylcoumarin (VIII).—To 7.5 g. of 6-nitro-4,5,7-trimethylcoumarin was added 8 g. of tin, 7.5 g. of stannous chloride, 75 cc. of concentrated hydrochloric acid and 20 cc. of ethanol. After standing overnight the contents were shaken mechanically for six hours at room temperature, when all the tin had dissolved. The solids were removed by filtration and dissolved in hot water. A slight amount of dark material was removed with the aid of Norite (0.1 g.) followed by filtration. The solution was cooled, a drop of iso-amyl alcohol added to prevent frothing and the solution rendered basic by the portionwise addition of solid sodium bicarbonate with stirring. The yellow solids thus obtained contain inorganic material. The amine is readily extracted by boiling ethanol. On standing overnight the extract deposited 3 g. of beautiful lemon-yellow needles several cm. long. Concentration of the mother liquor yielded a second crop. In all 4.1 g. (64%) of 6-amino-4,5,7-trimethylcoumarin was obtained, m. p. 199–200° (cor.).

Anal. Calcd. for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.45; N, 6.89. Found: C, 70.84; H, 6.57; N, 6.99.

The amine may also be obtained by reduction in 75% acetic acid with iron powder. The method is somewhat more laborious and the yield unreliable (25–70%).

6-Chloro-4,5,7-trimethylcoumarin (IX).—To 300 cc. of water and 35 cc. of concentrated hydrochloric acid heated to boiling was added 9.5 g. of 6-amino-4,5,7-trimethylcoumarin. The clear solution was then cooled rapidly to 0° with vigorous stirring, whereupon the amine hydrochloride separated as a light lavender solid in a finely divided state. In the course of one hour and fifteen minutes, 3.52 g. of reagent quality sodium nitrite dissolved in 45 cc. of water was added from a dropping funnel until the diazotized solution gave an immediate blue color with starch iodide paper. The clear, cold diazonium solution was then added to 15 g. of freshly prepared cuprous chloride dissolved in 60 cc. of concentrated hydrochloric acid cooled to 5° with vigorous stirring. Immediate evolution of nitrogen took place and a white solid separated. After one hour the stirring was discontinued and the contents were allowed to stand overnight. Crystallization from ethanol gave 8.7 g. (83%) of the chlorocoumarin. The material thus obtained has a light orange hue. Repeated crystallization from ethanol gave a colorless product, m. p. 194–195.5° (cor.).

Anal. Calcd. for $C_{12}H_{11}ClO_2$: C, 64.73; H, 4.98; Cl, 15.92. Found: C, 64.81; H, 5.15; Cl, 15.73.

Ozonization of 6-Chloro-4,5,7-trimethylcoumarin (IX).—A solution of 0.5 g. of 6-chloro-4,5,7-trimethylcoumarin in 75 cc. of ethyl acetate–methanol mixture 1:1, was subjected to a stream of ozone, 2.5% by volume, at the rate of 100 cc. per minute for three hours. The ozonide was decomposed with 20 cc. of water and the solvent removed on the steam-bath with an air blast. The intermediate glyoxalate was not isolated. The resulting oil was taken up in aqueous methanol, 0.5 g. of sodium hydroxide added and the solution refluxed for two hours. Upon acidification a dark oil separated and was removed by extraction with ether. The ethereal solution was extracted with dilute aqueous sodium hydroxide, acidified and reëxtracted with ether. Upon removal of the ether with an air blast, an oil resulted that was extracted twice with 10 cc. of petroleum ether (b. p. 60–110°). The extract was concentrated and upon standing overnight at 0° deposited about 50 mg. of 5-chloro-4,6-dimethyl-2-hydroxyacetophenone. The higher melting modification, m. p. 106–110°, was obtained.

(11) Jordan and Thorpe, *J. Chem. Soc.*, **107**, 387 (1915).

Summary

1. It has been demonstrated that the von

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Pechmann condensation of ethyl acetoacetate and phenols does not always yield coumarins as previously reported.

2. Although sulfuric acid causes the condensation of 3,5-dimethylphenol and ethyl acetoacetate to a coumarin, this same reagent results in the formation of a chromone from 4-chloro-3,5-dimethylphenol and ethyl acetoacetate.

3. The structure of the chromone was established by various hydrolytic reactions and by condensation with benzaldehyde.

4. The coumarin expected in the initial condensation was synthesized by nitration of 4,5,7-trimethylcoumarin, followed by reduction and replacement of the amino group by chlorine. The proof that the product was a coumarin and that the chlorine was in the 6-position was determined by ozonolysis to 5-chloro-4,6-dimethyl-2-hydroxyacetophenone.

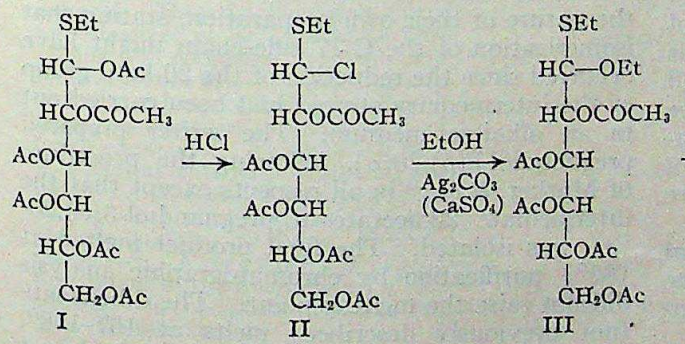
URBANA, ILLINOIS RECEIVED MARCH 2, 1944

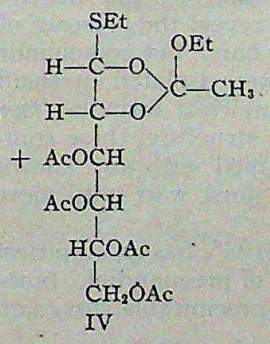
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

An Acyclic Sugar Orthoacetate

BY M. L. WOLFROM AND D. I. WEISBLAT

1-Chloro-1-thioethoxy-*aldehydo*-D-galactose pentaacetate (II) has been prepared by the action of a dry ethereal solution of hydrogen chloride upon 1-thioethoxy-*aldehydo*-D-galactose hexaacetate (I).[1] On repeating this procedure in larger quantities, a crude preparation of II was treated with ethanol and silver carbonate. The main reaction product was III, designated D-galactose diethyl monothioacetal pentaacetate and previously synthesized[2] in a similar manner from pure II, prepared by the action of a mixture of acetyl chloride and phosphorus oxychloride upon D-galactose diethyl mercaptal pentaacetate. In addition there was obtained in low yield a product IV, to which is assigned an orthoacetate structure.





The orthoacetate structure of IV, designated 1-thioethoxy-*aldehydo*-D-galactose ethyl 1,2-orthoacetate tetraacetate, is based upon the fact that one acetyl group in the compound was resistant to alkaline hydrolysis but was removable by acid hydrolysis. This fact, among others, has been employed in establishing the orthoacetate structure[3] in the cyclic sugar derivatives. In formula IV, the placement of the sulfur atom and the size of the ring are probable but arbitrary. To our knowledge, this is the first recorded occurrence of an orthoacetate structure in an acyclic sugar derivative.

Experimental

1-Thioethoxy-*aldehydo*-D-galactose Ethyl 1,2-Orthoacetate Tetraacetate.—Crude unrecrystallized 1-chloro-1-thioethoxy-*aldehydo*-D-galactose pentaacetate (m. p. 95–98°, 45 g.), prepared from 1-thioethoxy-*aldehydo*-D-galactose hexaacetate as previously described[1] and thoroughly washed with an ether–petroleum ether (1:1) mixture, was added to a suspension of 25 g. of Drierite (anhydrous calcium sulfate) and 60 g. of silver carbonate in 250 cc. of absolute ethanol. The reaction was then allowed to run at room temperature, under mechanical stirring and protection from atmospheric moisture, for approximately sixteen hours. The inorganic salts were removed by filtration through a bed of Super-cel (Johns-Manville) and the clear filtrate was made just opalescent with water. One crop of crystals was deposited on cooling to ice-box temperature; a second and third crop of crystals were obtained by treating the successive filtrates in a like manner. The first two crops (15–16 g.) were recrystallized from six parts of hot absolute ethanol; m. p. 103–105°, spec. rot. +50° (25°, *c* 4, abs. $CHCl_3$, D line). This product was therefore identified (mixed m. p. with an authentic sample unchanged) as D-galactose diethyl monothioacetal pentaacetate for which the following constants are recorded:[2] m. p. 104–105°, spec. rot. +50° (20°, *c* 3.5, abs. $CHCl_3$, D line). The third crop (6–8 g.) had a melting point of 85–95°. Pure material was obtained after five recrystallizations from four parts of hot methanol; yield 1.5–2.0 g., m. p. 125–126° (mixed m. p. with D-galactose diethyl monothioacetal pentaacetate of m. p. 104–105°, 93°), spec. rot. +54° (24°, *c* 4, abs. $CHCl_3$, D line).

The substance crystallized in transparent, elongated prisms and exhibited properties and solubilities similar to the isomeric D-galactose diethyl monothioacetal pentaacetate, except that it was more sensitive to acidity.

Anal. Calcd. for $C_{10}H_{17}O_6S(CH_3CO)_5$: C, 49.99; H, 6.71; S, 6.67; CH_3CO (4 equiv.), 8.33 cc. 0.1 *N* NaOH per 100 mg.; CH_3CO (5 equiv.), 10.41 cc. Found: C, 49.92; H, 6.73; S, 6.86; CH_3CO (alkaline hydrolysis, Kunz and Hudson[4] method), 8.39 cc.; CH_3CO (acid

(1) M. L. Wolfrom, D. I. Weisblat and A. R. Hanze, THIS JOURNAL, **62**, 3246 (1940).

(2) M. L. Wolfrom and D. I. Weisblat, *ibid.*, **62**, 878 (1940).

(3) K. Freudenberg and E. Braun, *Naturwissenschaften*, **18**, 393 (1930); E. Braun, *Ber.*, **63B**, 1972 (1930); H. G. Bott, W. N. Haworth and E. L. Hirst, *J. Chem. Soc.* 1395 (1930).

(4) A. Kunz and C. S. Hudson, THIS JOURNAL, **48**, 1982 (1926).

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hydrolysis, Freudenberg and Harder[5] method), 10.52 cc.

Summary

1. There is reported the synthesis, in crystalline form, of the first acyclic sugar orthoacetate (IV), designated 1-thioethoxy-*aldehydo*-D-galactose ethyl 1,2-orthoacetate tetraacetate.

(5) K. Freudenberg and M. Harder, *Ann.*, **433**, 230 (1923).

COLUMBUS, OHIO RECEIVED FEBRUARY 21, 1944

[CONTRIBUTION FROM THE PHYSIOLOGICAL LABORATORIES, CLARK UNIVERSITY]

A Study of the Neutral, Non-Saponifiable Fraction of Ox Bile[1]

BY W. H. PEARLMAN[1a]

A theory[2] postulating a biological conversion of cholesterol to the bile acids has recently received experimental support in an investigation[3] carried out with the aid of deuterium. One might expect to find metabolic products intermediate between cholesterol and the bile acids in bile since it contains these steroids in large amount. Studies of the comparative biochemistry of the bile have already furnished clues as to the nature of the hypothetical intermediates. The bile of elasmobranchs[2] contains a polyhydric alcohol, scymnol ($C_{27}H_{46}O_5$) which is related to cholesterol; it can be readily degraded in the laboratory to cholic acid.[4,5] Other alcohols of an alleged steroid nature have been isolated from the bile of frogs[6] and toads[7,8]; of these, pentahydroxybufostane ($C_{28}H_{50}O_5$) can be oxidized *in vitro* to cholic acid.[7] A mechanism for the biological oxidation of the side-chain of steroids with 27 and 28 carbon atoms has been suggested by Kazuno.[7]

An exploratory examination of the neutral fraction of ox bile failed to reveal the presence of scymnol, etc. On the other hand, five compounds (other than cholesterol[9]) were isolated in small amount. Although the empirical formulas (see Table I) point to a steroid structure, these compounds could not be identified with any known steroids. Structural proof must wait until more material is available.

Compound B, m. p. 192–193°, has an empirical formula identical with that of pregnandiol. Since Compound B is digitonin-precipitable, pregnandiol-3(β),20(α) was suspected to be the isomer in question. This steroid had been prepared by Butenandt and Müller[14] and they reported a melting point of 189–190.5° uncor. Marker, *et al.*,[15] had previously prepared the isomer from pregnandiol but their preparation melted at 182°. This discrepancy in melting points was noted by Butenandt and Müller; they raised a doubt regarding the nature of their own preparation, stating that isomerization of the C-17 side-chain might have occurred since the reduction of the 20-keto group of the intermediary steroid had been carried out in an alkaline medium. The writer prepared pregnandiol-3(β),20(α), following the procedure of Marker, *et al.*,[15] in all respects except that the intermediate 20-acetate of pregnandiol-3(α),20(α), was isolated. The final product melted at 182°; purification by chromatographic analysis did not raise the melting point. The dibenzoate (not previously described) melts at 167–168°. Since the dibenzoate of Compound B melts at 234–235°, it is clear that Compound B cannot be identical with pregnandiol-3(β),20(α). Compound B thus remains unidentified for the time being; it is probably an (*allo*) pregnane derivative containing a 3(β)-hydroxyl group.

TABLE I

COMPOUNDS (OTHER THAN CHOLESTEROL) ISOLATED FROM THE NEUTRAL, NON-SAPONIFIABLE FRACTION OF OX BILE

Compd.	M. p.,[12] °C.	Tentative empirical formula	Derivatives: Type	Derivatives: M. p.,[12] °C.
A	300	$C_{27}H_{40}O_3$	Monoacetate	216–217
			Monobenzoate	155–157
B	192–193	$C_{21}H_{36}O_2$	Dibenzoate	234–235
C	255–257	$C_{25\text{-}26}H_{40\text{-}42}O_4$	Monoacetate	187
D	232–233	$C_{24}H_{40}O_3$[13]	Monoacetate	111
E	202	$C_{24}H_{42}O_4$	Diacetate	142.5

Compound C contains either 25 or 26 carbon atoms. This is an unusual number for naturally occurring steroids but it might be mentioned that a C-26 acid has been obtained from bile.[6]

The ever-recurrent question of artifact formation deserves mention in this report but, since the

(1) Aided by a grant from G. D. Searle and Company.

(1a) Present Address: Department of Biology, Princeton University, Princeton, N. J.

(2) L. F. Fieser, "The Chemistry of Natural Compounds Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1937.

(3) K. Bloch, B. N. Berg and D. Rittenberg, *J. Biol. Chem.*, **149**, 511 (1943).

(4) H. Asikari, *J. Biochem.* (Japan), **29**, 319 (1939).

(5) W. Bergmann and Wm. T. Pace, THIS JOURNAL, **65**, 477 (1943).

(6) Y. Kurauti and T. Kazuno, *Z. physiol. Chem.*, **262**, 53 (1939).

(7) T. Kazuno, *ibid.*, **266**, 11 (1940).

(8) H. Makino, *ibid.*, **220**, 49 (1933).

(9) No attempt was made to isolate dihydrocholesterol which Schoenheimer, *et al.*,[10] have shown to be present to the extent of 1–2% in cholesterol from various organs; Pertzborn[11] reports 3.6% dihydrocholesterol in ox bile.

(10) R. Schoenheimer, H. V. Behring and R. Hummel, *ibid.*, **192**, 93 (1930).

(11) R. Pertzborn, *Z. ges. exptl. Med.*, **101**, 350 (1937).

(12) All m. p.'s in this paper are corrected.

(13) Empirical formula deduced from analytical data on acetate.

(14) A. Butenandt and G. Müller, *Ber.*, **71**, 191 (1938).

(15) R. E. Marker, O. Kamm, E. L. Wittle, T. S. Oakwood, E. J. Lawson and J. F. Laucius, THIS JOURNAL, **59**, 2291 (1937).

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steroid structure of Compounds A-E is not yet established, any discussion as to the possible origin of these from either cholesterol or the bile acids during the course of isolation would be altogether premature.

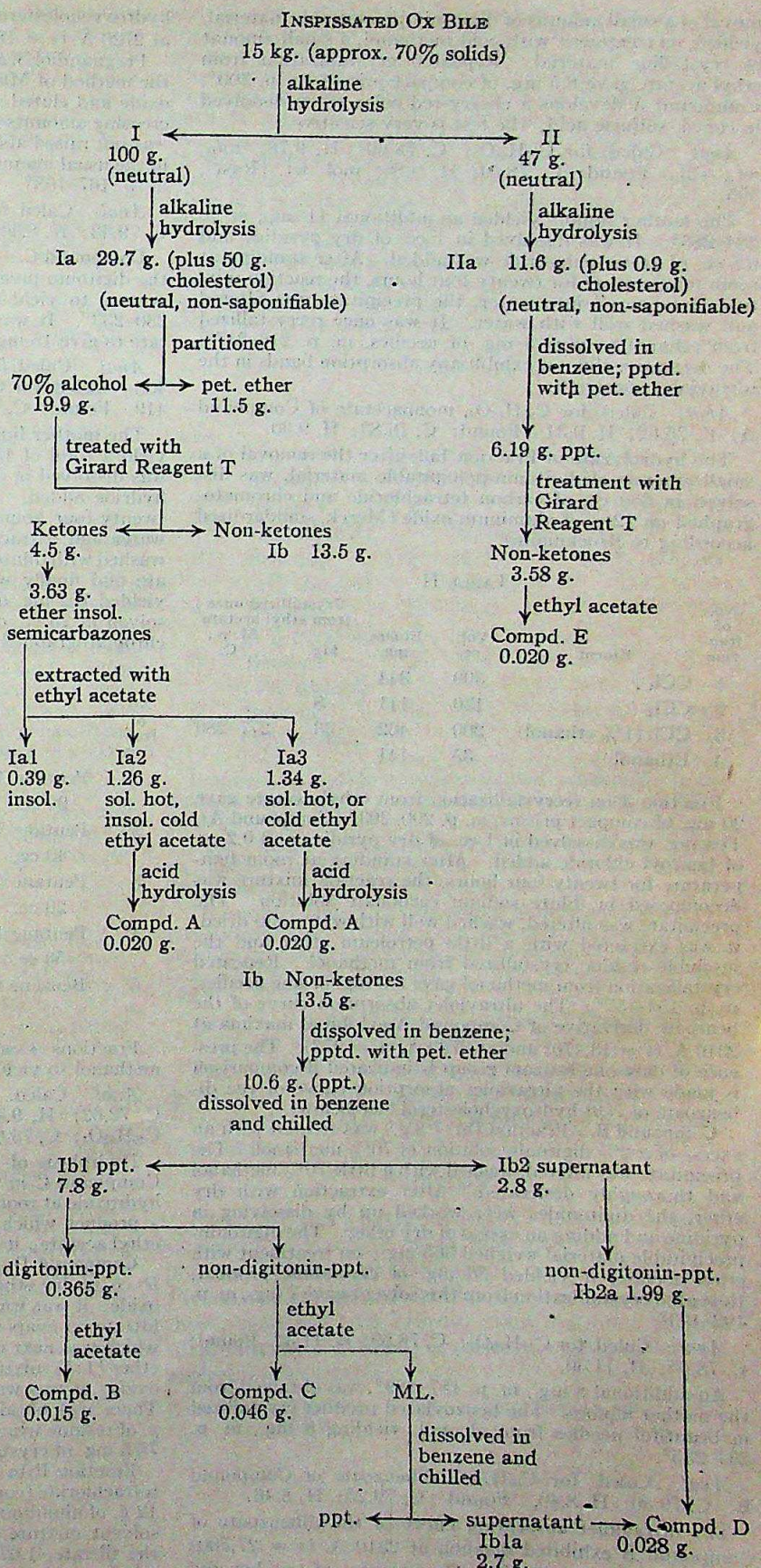
This investigation was undertaken at the kind invitation of Professor Gregory Pincus. The author is grateful to Miss Mary Ruth Jones for technical assistance.

Experimental

The Non-saponifiable Fraction of Ox Bile.—Fifteen kilograms of inspissated ox bile, containing approximately 70% solids, was hydrolyzed for eighteen to twenty hours at 104° in 27% solution with 6% sodium hydroxide. Addition of hydrochloric acid to the hydrolyzate gave a precipitate of crude bile acids which was extracted with ethyl acetate. The extract was evaporated, the residue dissolved in dilute alkali and extracted with ether. The ether extract on evaporation weighed 100 g. (Fraction I). The crude bile acids were crystallized from alcohol. The mother liquor was evaporated and the residue crystallized from 55% acetic acid. The mother liquor was evaporated, the residue dissolved in dilute alkali, and extracted with ether. The ether extract on evaporation weighed 47 g. (Fraction II).[16]

Fractions I and II still contained considerable amounts of saponifiable material. These fractions were therefore dissolved in 90% methanol containing 5% potassium hydroxide and refluxed for one hour. The hydrolyzate of Fraction I crystallized on cooling to room temperature, yielding 50 g. of crude cholesterol; an additional 29.7 g. of neutral material (Fraction Ia) was obtained. Fraction II likewise yielded 11.6 g. of neutral material (Fraction IIa) in addition to 0.9 g. of crude cholesterol. A very much abbreviated description of the fractionation of the neutral, non-saponifiable material follows (see flow sheet).

Compound A.—Fraction Ia (29.7 g.) was partitioned between 70% alcohol and low boiling petroleum ether (30–60°). The 70% alcohol fraction (19.9 g.) was treated with Girard reagent T[19] to give 4.5 g. of ketones, from which was obtained 3.63 g. of ether-insoluble semicarbazones. Treatment of the latter with boiling ethyl acetate yielded three fractions. Fraction Ia1 (0.39 g.) was insoluble in hot or cold ethyl acetate. Fraction Ia2 (1.26 g.) was soluble in hot ethyl acetate but insoluble in the cold and Fraction Ia3 (1.34 g.) was soluble in hot or cold ethyl acetate. These fractions were hydrolyzed with acid under mild conditions. The hydrolyzate of Fraction Ia1 failed to yield any crystalline products. The hydrolyzate of Fraction Ia2, after the re-



(16) The processing was carried out in the laboratories of G. D. Searle and Company; the author is especially indebted to Dr. R. T. Dillon.

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moval of a small amount of digitonin-precipitable material, yielded, on treatment with cold methanol, a small amount of crystalline material. Repeated crystallization from ethyl acetate gave 8.5 mg. of compact prisms, m. p. 300°. Compound A develops a cherry-red color when dissolved in concd. sulfuric acid; the test is very sensitive.

Anal. Calcd. for $C_{27}H_{40}O_3$: C, 78.60; H, 9.78; mol. wt., 413. Found: C, 78.64; H, 9.86; mol. wt. (Rast), 395.

The mother liquors yielded an additional 11 mg., m. p. 284–286°. It was dissolved in 1 cc. of dry pyridine and 0.5 cc. of acetic anhydride was added. After standing at room temperature for twenty-four hours, the reaction mixture was poured into water, the precipitate was filtered and washed well with water. It was once recrystallized from ethanol to give 5 mg. of needles, m. p. 216–217°. The derivative did not exhibit any absorption bands in the ultraviolet spectrum.

Anal. Calcd. for $C_{29}H_{42}O_4$, monoacetate of Compound A: C, 76.62; H, 9.31. Found: C, 76.83; H, 9.30.

The hydrolyzate of Fraction Ia3, after the removal of a small amount of digitonin-precipitable material, was dissolved in 250 cc. of carbon tetrachloride and chromatographed on 12 g. of aluminum oxide (Merck, standardized according to Brockmann).

TABLE II

No. of fraction	Eluent	Vol., cc.	Eluate, mg.	Crystallized once from ethyl acetate Mg.	Crystallized once from ethyl acetate M. p., °C.
1	CCl_4	300	344		
2	CCl_4	130	111	8	
3	CCl_4 (1% ethanol)	200	462	33	277–280
4	Ethanol	35	141		

Fraction 3 on recrystallization from ethyl acetate gave 20 mg. of compact prisms, m. p. 290–293° (Compound A). Ten mg. was dissolved in 1 cc. of dry pyridine and 0.2 cc. of benzoyl chloride added. After standing at room temperature for twenty-four hours, the reaction mixture was decomposed in dilute sodium carbonate solution. The precipitate was filtered, washed well with water and dried; it was extracted with a little petroleum ether and the insoluble residue crystallized from methanol. Repeated crystallization from methanol gave 3.5 mg. of fine needles, m. p. 155–157°. The ultraviolet absorption curve of the benzoate derivative of Compound A exhibited maxima at 2310 A. (ϵ = 13,470) and at 2720 Å. (ϵ = 973). The presence of only one benzoyl group is indicated if comparison is made with the ultraviolet absorption curve of the dibenzoate of 7(β)-hydroxycholesterol (see below).

Compound B.—Fraction Ibl (7.8 g.) was treated with an excess of a 2% digitonin solution in 70% methanol. The precipitate was filtered, washed with a little 70% methanol and thoroughly desiccated. After extraction with dry ether, the digitonides were worked up by dissolving in pyridine and adding an excess of dry ether. The digitonin-precipitable material weighed 365 mg.; on treatment with ethyl acetate, it yielded 56 mg. of crystalline product. Repeated crystallization from this solvent gave 7 mg., m. p. 192–193°.

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.33. Found: C, 78.65; H, 11.30.

An additional 8 mg., m. p. 187–189°, was obtained from the mother liquors. The benzoylated product crystallized in beautiful needles from alcohol, yielding 8 mg., m. p. 234–235°.

Anal. Calcd. for $C_{35}H_{44}O_4$, dibenzoate of Compound B: C, 79.50; H, 8.40. Found: C, 79.25; H, 8.46.

The ultraviolet absorption curve of the dibenzoate of Compound B exhibited maxima at 2310 A. (ϵ = 27,700) and at 2720 Å. (ϵ = 1985). The presence of two benzoyl groups is thus indicated if comparison is made with the ultraviolet absorption curve of the dibenzoate of 7(β)-hydroxycholesterol[17] [maxima at 2310 Å. (ϵ = 30,000) and at 2720 Å. (ϵ = 1857)].

Pregnandiol-3(β),20(α) which had been prepared by the method of Marker, *et al.*,[15] was adsorbed on aluminum oxide and eluted with carbon tetrachloride containing increasing amounts of ethanol. The m. p. of the preparation was not raised above 182°. The product was benzoylated in the usual manner. It crystallized from alcohol as plates, m. p. 167–168°.

Anal. Calcd. for $C_{35}H_{44}O_4$: C, 79.50; H, 8.40. Found: C, 79.43; H, 8.30.

Compound C.—Fraction Ibl (7.8 g.), after the removal of the digitonin-precipitable material, was treated with ethyl acetate to yield 65 mg. of a crystalline product, m. p. 230–233°. It was crystallized repeatedly from ethyl acetate to give 15 mg. of long white needles, m. p. 255–257°.

Anal. Calcd. for $C_{25}H_{40}O_4$: C, 74.21; H, 9.96; mol. wt., 405. Calcd. for $C_{26}H_{42}O_4$: C, 74.61; H, 10.11; mol. wt., 419. Found: C, 74.47; H, 10.18; mol. wt. (Rast), 386.

The mother liquors of Compound C were worked up to yield a total of 151 mg. of crude crystalline material. It was dissolved in 5 cc. of pyridine and 2.5 cc. of acetic anhydride added. After standing at room temperature for twenty-four hours, the reaction mixture was poured into water and extracted with ether. The ether extract was washed with dilute hydrochloric acid, dilute sodium carbonate and finally with water; evaporation of the extract yielded 102 mg. of a colorless glassy product. It was dissolved in 25 cc. of a pentane:benzene (4:1) mixture and chromatographed on 7 g. of aluminum oxide.

TABLE III

No. of fraction	Eluent	Eluate, mg.	Crystallized once from methanol Mg.	Crystallized once from methanol M. p., °C.
1	Pentane:benzene (4:1) 90 cc.	2.7 (oil)		
2	Pentane:benzene (1:1) 40 cc.	25.5 (oil)	5.6	225–228
3	Pentane:benzene (1:1) 20 cc.	14.9 (oil)	5.9	176–178
4	Pentane:benzene (1:1) 50 cc.	23.8 (cryst.)	9.5	185–186
5	Benzene 95 cc.	38.2 (cryst.)	33.2	181–183

Fractions 4 and 5 were repeatedly crystallized from methanol to yield, in all, 31 mg. of needles, m. p. 187°.

Anal. Calcd. for $C_{27}H_{42}O_5$, monoacetate of $C_{25}H_{40}O_4$: C, 72.62; H, 9.47. Calcd. for $C_{28}H_{44}O_5$, monoacetate of $C_{26}H_{42}O_4$: C, 73.00; H, 9.64. Found: C, 72.69; H, 9.70.

Hydrolysis of a specimen of the acetate derivative of Compound C in 90% methanol containing 5% potassium hydroxide at room temperature for twenty-four hours gave a product which crystallized in long white needles from ethyl acetate; it melted at 260°.

Compound D.—Fraction Ib2a (1.99 g.) was dissolved in 50 cc. of dry ether and filtered through 12 g. of aluminum oxide; it was washed with 20 cc. of dry ether. The ether filtrate on evaporation gave 1.23 g. of a glass-like residue which was next dissolved in 35 cc. of an ether–petroleum ether (1:1) mixture and filtered through 12 g. of aluminum oxide; it was washed with 65 cc. of the solvent mixture. There was obtained on evaporation of the filtrate, 0.94 g. of residue which on treatment with ethyl acetate yielded 75.5 mg. of crystalline material, m. p. 198–217°.

Fraction Ib1a (2.7 g.) was dissolved in 40 cc. of carbon tetrachloride (containing 3% ethanol) and filtered through 12 g. of aluminum oxide; it was washed with 10 cc. of the solvent mixture. There was obtained on evaporation of the filtrate, 1.67 g. of residue which on treatment with ethyl acetate gave 155 mg. of crystalline material, m. p.

(17) Kindly furnished by Prof. O. Wintersteiner.

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180–185°. It was recrystallized twice from ethyl acetate to give 70 mg., m. p. 190–195°; this product appeared to be a complex crystalline mixture. It was combined with the 75.5 mg. from Fraction Ib2a, which appeared to be of a similar nature and acetylated in the usual manner. There was obtained in all 166 mg. of acetylated material which was dissolved in 50 cc. of carbon tetrachloride and chromatographed over 12 g. of aluminum oxide.

TABLE IV

No. of fraction	Eluent	Vol., cc.	Eluate, mg.	Crystallized once from methanol Mg.	M. p., °C.
1	CCl_4	60	7		
2	CCl_4	40	64	45	110–111
3	CCl_4	40	10	5	180–185
4	CCl_4	40	3		
5	Ethanol	40	80	38	150–160

Fraction 5 was a crystalline mixture which could not be resolved. Fraction 2, on repeated crystallization from methanol, yielded 28 mg. of needles, m. p. 111°; $[\alpha]^{18}D$ +72° (*c* 0.806 in absolute ethanol).

Anal. Calcd. for $C_{26}H_{42}O_4$: C, 74.61; H, 10.11; mol. wt., 419. Found: C, 74.36; H, 10.09; mol. wt., 408 (by titration of acetyl groups).

To 16.1 mg. (0.0385 ml.) of the acetate derivative, there was added 15 cc. of methanol and an excess of aqueous standard alkali. The solution was refluxed for four hours and then permitted to stand for forty-eight hours at room temperature. Back titration with standard acid solution indicated that 0.0394 milliequivalent of alkali had been neutralized, after deducting the value of the blank. Refluxing for an additional three hours did not cause any further neutralization of alkali. The hydrolyzate yielded a product which on crystallization from methanol gave 7 mg. of plates, m. p. 229–231°. Recrystallization from the same solvent gave 2 mg., melting sharply at 232–233° (Compound D). The empirical formula of Compound D is assumed to be $C_{24}H_{40}O_3$ since its acetate derivative appears to contain but one acetyl group.

TABLE V

No. of fraction	Eluent	Eluate, mg.	Hydrolyzate[18] mg.	Crystallized once from aqueous methanol Mg.	M. p., °C.
1	Pentane: benzene (3:1) 105 cc.	293	263	6 (prisms)	202–207
2	Pentane: benzene (3:1) 25 cc.				
	Pentane: benzene (1:1) 90 cc.	79.7	70	29.5 (needles)	184–191
3	Benzene 50 cc.	79.6	68	24 (needles)	188–190

Compound E.—Fraction IIa (11.6 g.) was taken up in a little benzene and an excess of petroleum ether added. The precipitate (6.19 g.) was treated with Girard reagent T[19] to yield 3.58 g. of non-ketones. Treatment with ethyl acetate gave 448 mg. of crystals, m. p. 192–200°; these were difficultly soluble in ethyl acetate, acetone, benzene and chloroform but moderately soluble in ethanol. Recrystallization twice from ethanol gave 99 mg. of compact prisms, m. p. 204–206°; $[\alpha]^{26}D$ +37° (*c* 0.979 in ethanol). The material was recovered and crystallized repeatedly from alcohol but the melting point of each new crop rose until 11 mg. was obtained which melted at 216–218°. The original crystalline fraction was obviously a mixture. It was recovered (total, 433 mg.) and acetylated in the usual manner. The acetates (569 mg.) were dissolved in 40 cc. of a pentane: benzene (3:1) mixture and chromatographed over 10 g. of aluminum oxide (Table V).

The hydrolyzates of Fractions 2 and 3 were combined (total-138 mg.) and extracted with small portions of hot benzene, using in all 35 cc. of benzene. A residue of 51.5 mg. remained. The benzene extract was chromatographed over 7.5 g. of aluminum oxide.

TABLE VI

No. of fraction	Eluent	Vol., cc.	Eluate, mg.	Crystallized once from aqueous methanol Mg.	M. p., °C.
1	Benzene	175	trace		
2	Benzene (4% ethanol)	25	34.4 (semicryst.)	14.0	195–196
3	Benzene (4% ethanol)	25	23.1 (cryst.)	14.9	198–199
4	Benzene (4% ethanol)	25	4.4 (oil)		
5	Benzene (4% ethanol)	25	0.8		
6	Benzene (8% ethanol)	50	21	10.7	210–215

Fractions 2 and 3 were crystallized repeatedly from aqueous methanol to give 8.5 mg. of needles, m. p. 202° (Compound E).

Anal. Calcd. for $C_{24}H_{42}O_4$: C, 73.04; H, 10.72; mol. wt., 395. Found: C, 72.66; H, 10.51; mol. wt. (Rast), 380, 395.

The mother liquors of Compound E were worked up to give an additional 11.6 mg., m. p. 199–200°. It was acetylated in the usual manner to give on repeated crystallization from aqueous methanol, 4.7 mg. of needles, m. p. 142.5°.

Anal. Calcd. for $C_{28}H_{46}O_6$, diacetate of Compound E: C, 70.25; H, 9.69. Found: C, 70.36; H, 9.56.

The carbon and hydrogen analyses and the molecular weight (Rast) determinations were performed by Mr. Wm. Saschek at Columbia University.

Summary

An exploratory examination of the neutral, non-saponifiable fraction of ox bile yielded five compounds (other than cholesterol) in small amount. Tentative empirical formulas were established for these, pointing to a steroid constitution. Structural elucidation must, however, wait until more material is available.

WORCESTER, MASS. RECEIVED DECEMBER 22, 1943

(18) Hydrolyzed in 90% methanol containing 5% potassium hydroxide at room temperature for twenty-four hours.

(19) A. Girard and G. Sandulesco, *Helv. Chim. Acta*, **19**, 1095 (1936).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

The Reaction of Diazomethane with α-Cyanocrotonic Acid[1]

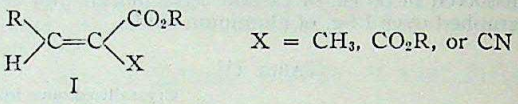
BY WILLIAM G. YOUNG, LAWRENCE J. ANDREWS, SEYMOUR L. LINDENBAUM AND STANLEY J. CRISTOL

Among several methods considered for the preparation of the methyl ester of α-cyanocrotonic acid was the reaction of the acid with diazomethane. It was hoped that the diazomethane would methylate the carboxyl group much faster than it would attack the ethylenic linkage.[2] However, the product isolated had considerably different properties from those of methyl α-cyanocrotonate prepared by treatment of the silver salt of α-cyanocrotonic acid with methyl iodide or by the acid catalyzed esterification with methanol.

An investigation of the structure of the product of the reaction with diazomethane indicated that the compound isolated was methyl isopropylidenecyanoacetate. The presence of the isopropylidene linkage was demonstrated by the fact that the compound liberated acetone on heating with aqueous sodium hydroxide. This unsaturated compound, like others of its type,[3] was resistant to ozonization; and no acetone could be isolated when the product of its reaction with ozone was hydrolyzed. On the other hand, methyl α-cyanocrotonate gave small amounts of acetaldehyde both when it was ozonized and when it was heated with dilute alkali. The structure of the diazomethane reaction product was definitely established by a comparison of its absorption spectrum and melting point with those of a sample of methyl isopropylidenecyanoacetate prepared by condensing acetone with methyl cyanoacetate.[4]

It previously has been shown that diazomethane reacts with the olefin bond of α,β-unsaturated esters[5] or ketones[6] producing a pyrazoline which loses nitrogen on heating, usually to form a mixture of a substituted cyclopropane and the β-methyl analog of the original olefin. Presumably the reaction of diazomethane with α-cyanocrotonic acid first gives a methyl ester which then reacts with a second molecule of diazomethane forming a pyrazoline. An attempt was made to isolate this pyrazoline intermediate by treatment of methyl α-cyanocrotonate with an ether solution of diazomethane, but the mixture gave off nitrogen at room temperature, and the only product isolated was methyl isopropylidenecyanoacetate.

It is interesting to note that in reactions of diazomethane with compounds of the type I the carbon atom of diazomethane attaches to the β-carbon of the ethylenic linkage. This is no doubt associated with the existence of resonance forms



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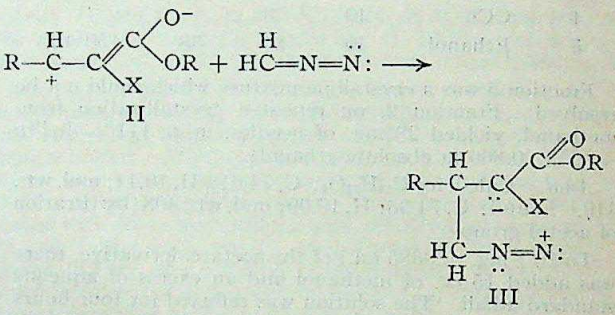
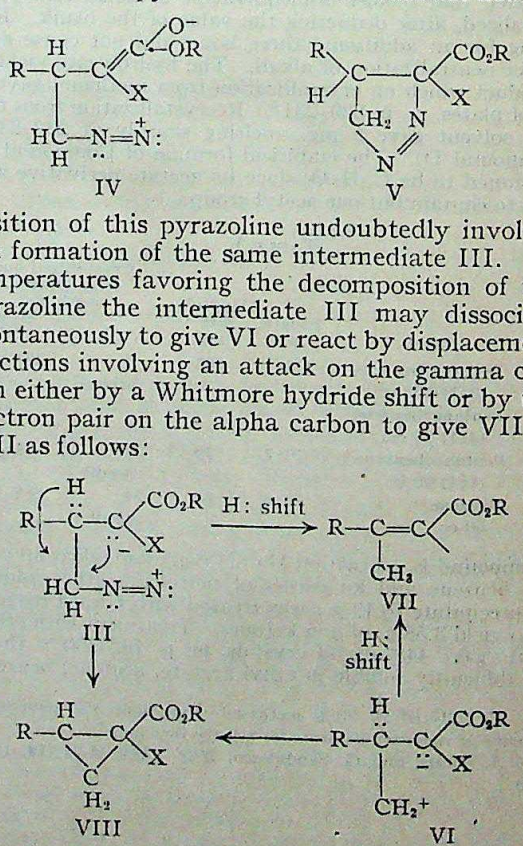
of the type II which may allow the β-carbon atom to enter into an electrophilic attack on the carbon–nitrogen double bond of diazomethane to give the intermediate III which is stabilized by resonance



II III

with the form IV. This normally leads to the production of the pyrazoline V. The thermal decomposition of this pyrazoline undoubtedly involves the formation of the same intermediate III. At temperatures favoring the decomposition of the pyrazoline the intermediate III may dissociate spontaneously to give VI or react by displacement reactions involving an attack on the gamma carbon either by a Whitmore hydride shift or by the electron pair on the alpha carbon to give VII or VIII as follows:



IV V III VII VIII VI

If X is a cyano or carboalkoxy[5] group, the only product isolated is VII; while if X is a methyl[5] group both VII and VIII are obtained. When X is a cyano or carboalkoxy group the intermediates III and VI have a decreased electron density on

(1) This work was made possible by a research grant from Sharp and Dohme, Inc.

(2) Fieser, "Experiments in Organic Chemistry," Second edition, D. C. Heath and Company, Boston, Mass., 1941, p. 375.

(3) Scheiber and Meisel, *Ber.*, **48**, 238 (1915).

(4) Cope, THIS JOURNAL, **59**, 2327 (1937).

(5) Auwers and König, *Ann.*, **496**, 252 (1932).

(6) Smith and Pings, *J. Org. Chem.*, **2**, 23 (1937).

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the α-carbon atom due to increased resonance involving these groups. Consequently the hydride shift should be favored.

Experimental Part

α-Cyanocrotonic Acid.—Fifty grams (0.58 mole) of cyanoacetic acid,[7] 34 g. (0.77 mole) of acetaldehyde and 1.4 ml. of piperidine were placed in that order in a 125-ml. pressure bottle and the mixture was heated at 60–70° for ten hours. The product was cooled and excess acetaldehyde was removed under reduced pressure. The hygroscopic crude yellow crystalline product was filtered under a rubber dam. The weight of crude product was 36 g. For ordinary synthetic work the acid was purified by two recrystallizations from a carbon tetrachloride–ether solution using decolorizing carbon. To obtain an analytically pure sample a small quantity of the crude acid was recrystallized several times from carbon tetrachloride until the product no longer oiled out but crystallized from the solvent. The properties of a pure sample were: m. p. 96–99°.[8] *Anal.* Calcd. for $C_5H_5O_2N$: C, 54.06; H, 4.54; neut. eq., 111.1. Found: C, 53.84; H, 4.69; neut. eq., 113.2.

Methyl α-Cyanocrotonate.—The dried silver salt prepared from 11.1 g. (0.1 mole) of α-cyanocrotonic acid was refluxed and stirred for twenty-four hours with a solution of 21.3 g. (0.15 mole) of methyl iodide in 100 ml. of ether. The ether solution of the product was filtered from the silver residue. After removal of the ether the product was distilled under reduced pressure. Six grams of methyl α-cyanocrotonate having the following properties was obtained: b. p. 75.5–76.8° (4–5 mm.); m. p. 20.0–22.0°; $n^{25}D$ 1.4571; d^{25}_4 1.0687; M_D calcd. 30.85; M_D obs. 31.89; exalt., +1.04; absorption maximum in 95% ethanol 220 mμ (ε 8400). *Anal.* Calcd. for $C_6H_7O_2N$: C, 57.59; H, 5.64. Found: C, 57.71; H, 6.04.

This ester was also prepared by heating (80–95°) a mixture of 11 g. (0.1 mole) of α-cyanocrotonic acid, 80 ml. of anhydrous methanol and 0.4 ml. of concentrated sulfuric acid in a pressure bottle for ten hours. Excess methanol was removed under reduced pressure, and 150 ml. of water was added to the residue. The mixture was extracted several times with ether. The ether solution was washed with water and aqueous sodium carbonate, dried and distilled. The properties of the methyl α-cyanocrotonate (3.3 g.) thus obtained were essentially those given for the ester prepared from the silver salt of the acid.

The Reaction of α-Cyanocrotonic Acid with Diazomethane.—Seven hundred ml. of an ether solution containing about 5 g. of diazomethane, prepared from 25 ml. of ethyl N-nitroso-N-methylcarbamate,[9] was treated with 11.6 g. of α-cyanocrotonic acid. Vigorous evolution of nitrogen took place, and the solution lost its yellow color. After the solution had stood for several hours, the ether was removed and the residue distilled under reduced pressure. The distillate (6.7 g.) had properties which were within experimental error identical with those of methyl isopropylidenecyanoacetate prepared according to Cope.[4] These properties and those of the sample prepared by the method of Cope (in parentheses) were: b. p. 90–91° (5 mm.) (88–90° (5 mm.)); m. p. 19.5–21.0° (21.5–22°) (mixed m. p. of the two samples 21.0–22.0°); $n^{25}D$ 1.4728 (1.4726); d^{25}_4 1.0605 (1.0632); M_D calcd. 35.45; M_D obs. 36.89; exalt., +1.44; absorption maximum in 95% ethanol 230 mμ, ε 11100 ($\lambda_{max.}$ 230 mμ, ε 10900). *Anal.* (diazomethane reaction product) Calcd. for $C_7H_9O_2N$: C, 60.42; H, 6.52. Found: C, 60.16, 59.74; H, 7.02, 6.57.

The Reaction of Methyl α-Cyanocrotonate with Diazomethane.—To an ice-cold solution of 1.9 g. of diazomethane in 500 ml. of ether was added a solution of 5 g. (0.04 mole) of methyl α-cyanocrotonate in 25 ml. of ether. The yellow color of the diazomethane immediately decreased in intensity. As the ether solution warmed to room temperature, nitrogen bubbled off vigorously and the solution became almost colorless. Three grams of methyl isopropylidenecyanoacetate, having the same physical properties as those previously given, was obtained after removing the ether and distilling the product.

The Reaction of Methyl α-Cyanocrotonate and Methyl Isopropylidenecyanoacetate with Dilute Aqueous Alkali.—Each ester (0.75 g.) was heated at 90° in a modified Claisen flask with 10 ml. of 3 *N* sodium hydroxide solution until the ester had completely dissolved. The bath temperature was then raised, and 2 ml. of distillate was collected in an ice-cooled receiver. A few drops of the distillate was tested for acetone by the use of sodium nitroprusside.[10] The product from methyl α-cyanocrotonate gave a negative test, while those from the methyl isopropylidenecyanoacetate samples gave a positive test. The remainder of the distillate was treated with a solution of 2,4-dinitrophenylhydrazine in acidified ethanol. The isopropylidene type ester gave 0.12 g. of acetone 2,4-dinitrophenylhydrazone (m. p. after one recrystallization from ethanol and mixed m. p. with an authentic sample 125.5–127.5°). The ethylidene type ester gave 0.038 g. of acetaldehyde 2,4-dinitrophenylhydrazone which after two recrystallizations from ethanol melted from 160.5–162.5° (mixed m. p. with an authentic sample 160.5–164.5°) with some softening below these temperatures.

Ozonization of Methyl α-Cyanocrotonate.—A solution of 1.0 g. (0.008 mole) of the ester in 6 ml. of methylene chloride was ozonized at dry-ice temperature for one hour. After removal of the solvent the ozonide was decomposed under reducing conditions,[11] and the aqueous solution of the product was tested with methone reagent for formaldehyde and acetaldehyde.[12] No formaldehyde derivative was obtained, but a small quantity of the methone derivative of acetaldehyde was isolated. After one recrystallization from ethanol this gave a m. p. and mixed m. p. with an authentic sample of 142–144°.

When methyl isopropylidenecyanoacetate was submitted to this ozonization procedure, no aldehyde or acetone could be detected after reductive decomposition procedures were applied.

The authors are indebted to Mr. J. W. Ralls for the combustion analyses reported.

Summary

The reaction of diazomethane with α-cyanocrotonic acid produces methyl isopropylidenecyanoacetate rather than methyl α-cyanocrotonate. The reaction is presumed to occur through the formation of a pyrazoline as an intermediate, and a mechanism for the decomposition of this pyrazoline has been proposed.

LOS ANGELES, CALIFORNIA RECEIVED JANUARY 25, 1944

(7) Purified by the method of Weissberger and Porter, THIS JOURNAL, **65**, 52 (1943).

(8) The method described for preparing the acid is a modification of those of Auwers, *Ber.*, **56B**, 1172 (1923), who gave a m. p. of 80°, and of Fiquet, *Bull. soc. chim.*, [3] **7**, 767 (1892), who gave a m. p. of 92°.

(9) Pechmann, *Ber.*, **28**, 855 (1895).

(10) Huntress and Mulliken, "Identification of Pure Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1941, p. 374.

(11) Whitmore and Church, THIS JOURNAL, **54**, 3710 (1932).

(12) Kimel and Cope, *ibid.*, **65**, 1992 (1943).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ILLINOIS INSTITUTE OF TECHNOLOGY]

The Debromination of Pentaerythrityl Bromide by Zinc. Isolation of Spiropentane[1]

BY M. J. MURRAY AND EUGENE H. STEVENSON

When Gustavson[2] first debrominated pentaerythrityl bromide he assigned to the reduction product the structure vinyltrimethylene. Zelinsky,[3] however, concluded that the spirocyclane (spiropentane) configuration would more nearly account for the chemical reactions and for the synthesis of the compound. Shortly thereafter Philipov[4] was convinced that the reduction product was a mixture of methylenecyclobutane and methylcyclobutene. In 1923 Ingold[5] stated that "the simplest possible *spiro*-compound has never yet been isolated or even transiently formed as an unstable intermediate product." Rogowski,[6] however, in 1939, interpreted the results of an electron diffraction study on the reduction product as proving spiropentane to be the correct formula. Whitmore and Williams[7] painstakingly fractionated a large quantity of the reduction product and proved by ozonolysis that it consisted of a mixture of 2-methyl-1-butene and methylenecyclobutane. The ratio found was about one of the former to eleven of the latter. No evidence could be obtained for the presence of any other compound. Bauer and Beach[7] made an electron diffraction study of the high-boiling fraction obtained by Whitmore and Williams and concluded that it could not possibly be spiropentane and that the methylenecyclobutane structure was the correct one.[8]

The present work began with a Raman spectroscopic investigation of the product obtained when pentaerythrityl bromide was reduced by zinc in aqueous methanol. Two Raman lines which could be assigned neither to the main product, methylenecyclobutane (I), nor to 2-methyl-1-butene (II) showed that a third compound (III) was present. Modified conditions of reduction resulted in the formation of a much larger proportion of the third component and made possible its isolation. A preliminary study of the compound lends considerable support to the opinion that it is the long-sought spiropentane.

Discussion

The spectroscopic results obtained in this work are listed in Table I. For purposes of comparison the spectra of 2-methyl-1-butene and cyclobutanone were taken from the literature.

The high-boiling fraction (41.6–41.9°) of the product obtained from the reduction in aqueous methanol shows a strong, polarized Raman line near 960 cm.$^{-1}$. This line is present also in the spectra of cyclobutanone and methylcyclobutane and is characteristic of the cyclobutane ring. Cyclobutanone has very nearly the same symmetry, mass, and force constants as would be present in methylenecyclobutane, and there is excellent correspondence in a majority of the lines of this ketone with those of the high-boiling fraction of the reduction product.

In ordinary, unconjugated ketones the carbonyl frequency is near 1720 cm.$^{-1}$. The value of 1774 cm.$^{-1}$ found by Kohlrausch and Skrabal for cyclobutanone indicates that the carbonyl is attached to a ring that is not strain free. Similarly, the spectrum of the high-boiling fraction has an olefinic frequency at 1679 cm.$^{-1}$, an unusually high value for an unsymmetrical disubstituted ethylene which normally has this vibration near 1650 cm.$^{-1}$. This is excellent evidence that the olefin is exocyclic. Furthermore, if the olefinic linkage were within the strained ring itself (methylcyclobutene), it would be expected to exhibit a much lower frequency—probably near 1600 cm.$^{-1}$.[9] On the basis of these considerations the authors feel that the spectrum of the high-boiling fraction is thoroughly consistent with the methylenecyclobutane structure.

After eliminating the lines due to methylenecyclobutane from the spectrum obtained for the low-boiling fraction, the remaining lines, with two exceptions, are found to be the more prominent lines in the spectrum of 2-methyl-1-butene. This gives spectroscopic confirmation to the chemical evidence of Whitmore and Williams on the occurrence of this compound. The absence of any trace of line at 1338 cm.$^{-1}$ precludes the possibility that any significant amount of 2-methyl-2-butene exists in the mixture. The appearance of the substantial line at 1033 cm.$^{-1}$ and of the somewhat weaker line at 581 cm.$^{-1}$, however, proves that a third component is present. The quantity of the third compound cannot be estimated with any degree of certainty until the scattering ability of the substance is known, but it seems rather likely that the crude reduction product may contain between 1 and 5% of the compound.

A careful study of the Raman spectra of the crude reduction product and of various fractions obtained in its distillation revealed that the com-

(1) For a communication regarding this work see Murray and Stevenson, THIS JOURNAL, 66, 314 (1944)

(2) Gustavson, *J. prakt. Chem.*, [2] 54, 97 (1896).

(3) Zelinsky, *Ber.*, 46, 160 (1913).

(4) Philipov, *J. prakt. Chem.*, [2] 93, 163 (1916).

(5) Ingold, *J. Chem. Soc.*, 123, 1710 (1923).

(6) Rogowski, *Ber.*, 72, 2021 (1939).

(7) See footnote to an article by Bauer and Beach, THIS JOURNAL, 64, 1142 (1942).

(8) In a recent article Shand, Schomaker and Fischer (*ibid.*, 66, 636 (1944)) also conclude that the main product of the reduction is methylenecyclobutane.

(9) The two methylcyclobutenes would exhibit different olefinic frequencies; the one having the methyl group attached to the doubly bound carbon would have the slightly higher value.

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TABLE I

RAMAN SPECTRA OF THE DEBROMINATION PRODUCTS OF PENTAERYTHRITYL BROMIDE COMPARED WITH THE SPECTRA OF RELATED COMPOUNDS

2-Methyl-1-butene[a]		Low-boiling fraction		Methylenecyclobutane			Cyclobutanone[c]		Methylcyclobutane[d]		III (Spiropentane)	
$\Delta\nu$ cm.$^{-1}$	I	$\Delta\nu$ cm.$^{-1}$	Ib	$\Delta\nu$ cm.$^{-1}$	Ib		$\Delta\nu$ cm.$^{-1}$	I	$\Delta\nu$ cm.$^{-1}$	Ib	$\Delta\nu$ cm.$^{-1}$	Ib
252	0											
		354	17	354	23	0.8			320	1	305	4
393	2b	371	15	373	13		403	3	416	0.4		
433	2b	428	w				458	6				
485	1											
530	1											
											581	16
		581	6						603	1.4		
		659	12	657	20	0.3	674	4			613	4
709	1								743	5.0		
773	5	770	12						772	0.5	779	4
		871	16	873	14	0.9			872	4	872	30
890	2	904	18	907	20	0.8	898	5b	914	12		
964	1	955	65	957	72	0.2	957	8	962	14		
1020	1b	1033	14				1013	00?	1066	1	1033	50
1091	3	1082	1						1100	4		
							1141	00?	1159	1	1150	1
		1193	7	1191	11	0.9	1196	2	1217	2		
									1256	1		
									1339	1		
1390	0	1390	16	1391	20	0.7	1398	4b	1377	w	1397	5
1413	3	1415	w									
1433	3	1429	28	1428	20	0.8	1442	00?	1447	8	1426	10
1654	5	1651	21									
		1679	36	1673	48	0.3	1774	3				
				2826	4				2724	0.3	2836	0.4
2856	3	2861	2	2861	4		2882	0	2861	34		
											2891	w
2893	5b	2901	68	2902	60	0.2			2907	73		
2917	4	2921	74	2921	75		2929	12b				
2942	4	2954	73	2952	88	0.4			2958	100		
2971	2	2987	100	2986	100	0.4	2970	6b				
2984	3										2991	100
		3076	18	3072	18	0.8	2994	2			3065	30

[a] Thompson and Sherrill, THIS JOURNAL, **58**, 746 (1936). [b] Intensity measured on a Gaertner microdensitometer. Values of ρ for methylene cyclobutane were also measured on this instrument. Lines listed as w were too weak for intensity measurements. [c] Kohlrausch and Skrabal, *Z. Elekt.*, **43**, 282 (1937). [d] The sample used was not fractionated. It contained some III, hence lines known to belong to that compound have been deleted.

pound responsible for the 1033 and 581 cm.$^{-1}$ lines should boil within a few degrees of 37°. This observation sharply narrowed the list of compounds to be considered. A number of other compounds were eliminated because of the absence of Raman lines in certain positions. For example, the lack of a line in the 2100–2200 cm.$^{-1}$ region proved that the compound was not an acetylene. Still other substances were eliminated because they were known not to exhibit Raman lines at 1033 and 581 cm.$^{-1}$. In this way it was possible tentatively to conclude that III was no compound whose properties were known to the authors. (Methylcyclobutane was eliminated only after its spectrum was obtained—see Table I.)

At this point the authors were convinced that there was excellent chance that III was spiropentane.

In the isolation of the new compound there appeared to be two possible procedures. One was the tedious concentration, either by chemical means or by fractional distillation, of the small amount of the substance in the crude reduction product which was obtained when aqueous methanol was employed as solvent. The other was the use of different conditions for the debromination. Fortunately the latter method proved successful and the authors were able, by carrying out the reduction by zinc in molten acetamide[10,11,12] containing sodium iodide and sodium carbonate, to obtain a product consisting of about 40% of the new compound.

Spectroscopically this method of reduction was

(10) Hass, McBee, Hinds and Gluesenkamp, *Ind. Eng. Chem.*, **28**, 1178 (1936).

(11) McBee, Hass and Tarrant, Abstracts of the 97th meeting, 1939, Am. Chem. Soc., Organic Section, p. 29. (1939).

(12) Whitmore, Popkin, Bernstein and Wilkins, THIS JOURNAL, **63**, 124 (1941).

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shown to yield the same volatile products as did the debromination in aqueous methanol.

While separation of the components of the crude mixture by fractionation should be possible in an efficient column, the amount of hydrocarbon mixture available at the moment (18 g.) was not sufficient for this purpose.

Distinct enrichment of III was accomplished easily by repeated extraction with cool, almost saturated, aqueous silver nitrate. The hydrocarbon recovered by heating the separated silver nitrate layer showed spectroscopically that practically no III was absorbed in the extraction. Further purification was carried out by extraction with almost saturated silver perchlorate.

There are certain definite advantages to the use of silver ions for the separation of an olefin from other organic compounds, whenever the extraction is a possible one. The coördinating action of silver ion on olefins is so mild as to cause no detectable rearrangement,[13] a fact which is in direct contrast to the results often obtained with sulfuric acid. Bromine and alkaline permanganate give new products that require separation, and in the latter case the solid manganese dioxide creates experimental difficulties. Finally the silver nitrate method of extraction allows one to recover the olefin merely by warming the solution for low molecular weight substances or by diluting for high-boiling compounds.

On the other hand, the formation of the silver ion-olefin complex is an equilibrium process[13] which makes it increasingly difficult to extract the olefin as its concentration in the organic layer becomes smaller. Furthermore, the ease of coördination differs markedly with various olefins. In the present case it was found to be much easier to extract from III a larger amount of methylenecyclobutane than the somewhat smaller amount of 2-methyl-1-butene. It was necessary to complete the purification process by reaction of the olefin with bromine. Analysis showed the compound to be C_5H_8. The Raman spectrum of the final sample is listed in Table I.

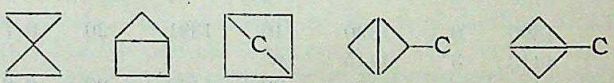
Throughout the early stages of purification of III the hydrocarbon mixture always had the sharp, characteristic odor of low molecular weight, unsaturated compounds. The odor remained practically unchanged until the final extractions with concentrated silver perchlorate solution. The organic layer then had an odor similar to that of chloroform.

It was felt at first that the observed boiling point of the new compound, 38.3–38.5°, was too high for spiropentane. However, Dr. H. I. Bernstein called the authors' attention to the fact that the boiling point of 1,1-dimethylcyclopropane is about 10° higher than that of neopentane. Closure of the second ring would undoubtedly increase the boiling point considerably.

(13) Winstein and Lucas (THIS JOURNAL, 60, 836 (1938)) found that neither *cis*- nor *trans*-2-butene underwent isomerization in the aqueous solution.

The value of the highly polarized frequency, 1033 cm.$^{-1}$, is nearer to that for a cyclobutane ring (960 cm.$^{-1}$) than that for a cyclopropane ring (1200 cm.$^{-1}$). That spiropentane should show an abnormal cyclopropane ring frequency is definitely not out of order. First, the addition of a second ring in the gem position would give rings with strain characteristics quite different from the one ring system; and, second, the almost pure inner vibration obtained for those hydrocarbons with one ring would probably be replaced by a more highly coupled vibration involving both rings more intimately. This may be considered similar to an effect observed in the Raman spectra of olefins. The C=C vibration is always represented in the spectrum by a prominent line near 1600 cm.$^{-1}$ except when another double bond carbon is attached to the first to form an allene. The interaction of the two double bonds in this type of compound is sufficient to move the vibration completely out of the 1600 cm.$^{-1}$ region.

Raman spectra considerations and the nonreactivity with bromine eliminate acetylenes, diolefins and monocyclic olefins and leave of the C_5H_8 isomers only the dicyclic compounds



IV V VI VII VIII

as structural possibilities.

There are at present two reasons why the authors believe structure IV to be the most plausible:

1. In the presence of sodium iodide and sodium carbonate the reduction of 1,3-dihalides in molten acetamide has been found to produce good yields of the normally expected compounds (cyclopropane and derivatives) when the starting products were 1,3-dichloropropane,[10] 1,3-dichlorobutane[11] and 1,3-dibromo-2,2-dimethylpropane.[12] The formation from pentaerythrityl bromide of any condensed ring system other than spiropentane could occur only through an extensive series of rearrangements—a phenomenon which would be expected to occur *less* in acetamide than in aqueous methanol.

2. The carbon–hydrogen Raman lines between 2800 and 3100 cm.$^{-1}$ can be cited as favoring structure IV. Both compounds V and VI have hydrogen attached to cyclobutane rings, whereas IV has the hydrogen combined only with cyclopropane groups. Kohlrausch and Skrabal,[14] who have made a comprehensive study of cyclobutyl and cyclopropyl compounds by means of the Raman effect, found that hydrogen atoms attached to cyclobutane rings produced several intense frequencies near those of aliphatic hydrocarbons; *i. e.*, between 2850 and 3000 cm.$^{-1}$. On the other hand, cyclopropane and those derivatives with hydrogens attached only to three-membered rings (carbocyclic) produce no intense Raman lines in

(14) Kohlrausch and Skrabal, *Monatsh.*, 70, 44, 377 (1937).

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this region much below 3000 cm.$^{-1}$. In the new compound the only intense Raman lines between 2800 and 3100 cm.$^{-1}$ occur at 2991 and 3065 cm.$^{-1}$. Although 2991 cm.$^{-1}$ might belong to a substance having either a cyclobutane or a cyclopropane ring, the former structure would show several intense lines below this figure, whereas only the latter structure could give rise to the 3065 cm.$^{-1}$ frequency. This appears to the authors to be quite conclusive as to the absence of a cyclobutyl and as to the presence of a cyclopropyl compound. The weak lines at 2836 and 2891 cm.$^{-1}$ in the spectrum of the sample studied may be due to a trace of impurity or they may actually belong to the pure compound. Their occurrence, since they are so weak, appears to the authors to be beside the point as far as structural arguments are concerned. Structures VII and VIII are ruled out because each has a methyl group and hence would exhibit strong carbon–hydrogen vibrations between 2850 and 2980 cm.$^{-1}$.

The chemical stability of the new compound is remarkable. Its reaction with bromine at 25° in the dark is negligible. It is not hydrogenated over Raney nickel at room temperature. It appears not to be isomerized at 300° when passed over aluminum oxide. With alkaline permanganate the reaction is very slow, and what reaction there is may be caused by a small amount of impurity.

The Raman effect is a method *par excellence* for the study of a problem of this nature and throughout the investigation close check was kept on the changing composition caused by varying factors. One difficulty, however, should be mentioned. Because of the very great differences in scattering ability of various compounds, error is likely to be made in estimations of the composition of mixtures when unknown compounds are concerned. For example, the scattering power of III is high while that of 2-methyl-1-butene is quite low. Consequently there is a tendency for one to estimate the amounts of the former as too high and of the latter as too low until the spectra of the pure compounds have been obtained under similar conditions.

Experimental

Pentaerythrityl Bromide.[15]—The pentaerythritol used was an Eastman Kodak Company product, m. p. 254°. The only modification made in the procedure given in "Organic Syntheses" for the preparation of the bromide was the substitution of acetone for ethyl alcohol in the extraction of the impure reaction product. When acetone was used it was found that the extraction went at a much faster rate and with a smaller volume of solvent, and yielded a product having a m. p. 160° (not recrystallized) which is the same as that obtained by the use of ethyl alcohol. Furthermore, samples extracted by the two methods upon reduction gave products with identical spectra.

Reduction of Pentaerythrityl Bromide in Aqueous Methanol.—Five hundred sixty grams of the pentaerythrityl bromide was mixed with 380 g. of zinc dust, and 1200 ml. of 50% methyl alcohol was poured over the mixture. The volatile product, 57 g., was caught in a dry-ice trap and then dried over calcium chloride. It was fractionated using an 85-cm. Ewell column. Several fractions were obtained and examined spectroscopically. The only one showing Raman lines for a single compound was the high-boiling fraction, b. p. 41.6–41.9° at 752 mm., d^{20}_4 0.7326, $n^{25}D$ 1.4158.

Reduction of Pentaerythrityl Bromide in Acetamide.—Into a 500-ml. three-necked flask was placed 190 g. of Eastman Kodak Company practical grade acetamide, 10 g. of sodium iodide, 30 g. of sodium carbonate and 90 g. (1.4 mole) of zinc dust. The flask was provided with a mercury-seal mechanical stirrer, a reflux condenser from the top of which a tube led to a dry-ice trap, and a device for slowly adding 90 g. (0.23 mole) of solid pentaerythrityl bromide. The flask was heated in an oil-bath at 170–180°. Each addition of the bromide resulted in the evolution of fumes. Carbon dioxide, which formed in the reaction from the sodium carbonate, escaped from the exit tube of the trap. Nine grams of crude material was caught in the dry-ice trap. The Raman spectrum of this material after straight distillation showed the 1033 line to be more intense than the 957 cm.$^{-1}$ line of the methylenecyclobutane. Several lines of 2-methyl-1-butene were also present.

Purification of the Non-olefinic Constituent.—The separation of the olefinic constituents of the mixture from the compound showing the 1033 cm.$^{-1}$ Raman line was accomplished largely by the use of silver salts. Loss of the highly volatile hydrocarbon during extraction was avoided by use of a cylindrical separatory funnel constructed of 18 mm. glass tubing and having a stopcock attached to each end. The positions of the aqueous and hydrocarbon layers were noted for each extraction in order to determine when the process had reached the point of diminishing returns. The contents of the tube were cooled under the tap.

In this apparatus 18 g. of the hydrocarbon mixture was extracted ten times with 5-ml. portions of nearly saturated aqueous silver nitrate. The volume of the hydrocarbon layer decreased 47%. Then followed four extractions with 5-ml. portions of almost saturated aqueous silver perchlorate. Precautions were, of course, taken in the use of the perchlorate solutions, but no vigorous reaction was noted in any case. In the first and second extractions with perchlorate three layers were obtained. The top was the hydrocarbon, the middle probably contained the greater amount of the olefin, and the bottom contained most of the water. The middle layer showed some slight discoloration, but the other two layers remained water-white. The third and fourth extractions gave only two layers each. In spite of several transfers of material, two fractionations for determining constancy of boiling point, and the removal of samples for chemical and spectroscopic tests, the amount of hydrocarbon remaining at this point was 5 g. It appeared by bromination to contain about 6% olefins.

The hydrocarbon layer was then washed thoroughly with water and dried over calcium chloride. It was cooled in an ice–hydrochloric acid-bath, and bromine was added dropwise with stirring until a very faint color of bromine persisted. This color did not noticeably decrease in half an hour. The slight excess of bromine was removed by blowing a trace of olefin vapor from a capillary pipet into the solution. Distillation was through a six inch (length) column packed with glass helices. The main fraction, 38.3–38.5°, was collected at 750 mm.; $n^{20}D$ 1.4117; d^{20}_4 0.755; mol. ref. calcd. for spiropentane, 22.32; found, 22.43. *Anal.*[16] Calcd. for C_5H_8: C, 88.17; H, 11.83. Found: C, 87.91; H, 11.53. The amount finally isolated was only about 1 g. but this was partly because a number of preliminary tests were made with small amounts of the sample before final purification with bromine and partly because of loss in the column which was not equipped with control of reflux ratio.

Stability of the Hydrocarbon.—The method of purification indicates the stability of the product toward bromine. In another experiment several drops (capillary) of the

(15) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 476.

(16) Thanks are due Dr. T. S. Ma, Univ. of Chicago, for a painstaking analysis of this highly volatile liquid.

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hydrocarbon were added to carbon tetrachloride containing a little bromine. In three days at room temperature in the dark there was but little change in the color of the solution.

A few drops (capillary) of the hydrocarbon when shaken with a very dilute aqueous permanganate solution caused no noticeable color change in fifteen minutes. When alkali was added a very slow reaction took place. At the present time it is not certain whether this might be caused by a small amount of impurity or whether it represented a *bona fide* oxidation of the hydrocarbon.

A mixture of methylenecyclobutane, 2-methyl-1-butene and the compound in question was added to cold concentrated sulfuric acid. After dilution and distillation the Raman spectrum showed the presence of both the 1033 and the 581 cm.$^{-1}$ lines.

Passage of a mixture of methylenecyclobutane and the compound thought to be spiropentane over aluminum oxide at 300° resulted in isomerization of almost all of the methylenecyclobutane to isoprene but did not noticeably affect the intensity of the 1033 cm.$^{-1}$ Raman line in the treated sample.

Methylcyclobutane.—Five grams of methylenecyclobutane (containing a small amount of the compound having a Raman line at 1033 cm.$^{-1}$) was hydrogenated over Raney nickel at atmospheric pressure and at room temperature. The Raman spectrum of the material was taken after a straight distillation into the Raman tube without any attempt at fractionation.

Recovery of Olefins.—The combined silver nitrate layers were heated on a water-bath and the olefins collected in a dry-ice trap. A Raman spectrum of the sample showed only lines for methylenecyclobutane and for 2-methyl-1-butene. There was no more than a faint trace of line at 1033 cm.$^{-1}$, the position of the strong Raman-active frequency of III. This, coupled with the fact that treatment of the hydrocarbon layer with silver salts failed after several extractions to dissolve appreciable material from the organic layer, showed that III was practically unaffected by this reagent.

Hg 4358 Å. was used for exciting the Raman spectra. Exposure times were of the order of four hours and the slit width was 0.08 mm. The experimental details of obtaining the spectra are given elsewhere.[17]

Summary

1. Reduction of pentaerythrityl bromide by zinc in aqueous methanol yields a mixture of methylenecyclobutane, 2-methyl-1-butene and a small amount of a third component with Raman lines at 1033 and 581 cm.$^{-1}$.

2. Reduction of pentaerythrityl bromide by zinc in molten acetamide in the presence of sodium carbonate and sodium iodide yields a mixture containing a relatively large amount of the new compound, together with methylenecyclobutane and 2-methyl-1-butene.

3. The new compound was isolated by removal of the olefins with aqueous solutions of silver salts and with bromine.

4. The method of synthesis as well as the Raman spectrum of the substance leads to the belief that the compound is spiropentane.

(17) Cleveland, Murray, Haney and Shackelford, *J. Chem. Phys.*, **8**, 153 (1940); Cleveland and Murray, *ibid.*, **7**, 396 (1939).

CHICAGO, ILLINOIS RECEIVED FEBRUARY 7, 1944

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF UNIVERSAL OIL PRODUCTS COMPANY]

Reaction of Benzene with Butadiene in the Presence of Sulfuric Acid and Hydrogen Fluoride Catalysts

BY V. N. IPATIEFF, HERMAN PINES AND R. E. SCHAAD

The large number of theoretically possible reaction products, some of which may have important applications in the synthesis of valuable materials, prompted us to study the reaction between benzene and butadiene.

We have found that benzene reacts with butadiene in the presence of sulfuric acid or hydrogen fluoride. In order to favor reaction with benzene and to decrease polymerization of butadiene, it was considered advisable to use a large excess of benzene. Under these conditions one mole of butadiene reacted with an average of approximately 1.5 moles of benzene in the presence of sulfuric acid and with 1.2 moles of benzene in the presence of hydrogen fluoride.

The hydrocarbon of lowest boiling point obtained from this reaction was 1,2-diphenylbutane, which was formed by the interaction of two molecules of benzene with one molecule of butadiene. The proof of the structure of this compound was based on the comparison of its physical constants, infrared absorption spectrum, and the melting points and mixed melting points of the acetamino derivative with those of synthetically prepared (liquid) 1,1-, 1,2- and 1,3-diphenylbutanes. The primary product of the reaction was probably 1-phenylbutene-2 formed by the 1,4-addition of benzene to butadiene-1,3 in the presence of the investigated catalysts. Under these conditions phenylbutene then reacted with another molecule of benzene to form the diphenylbutane obtained.

Experimental Part

Reaction of Benzene with Butadiene in the Presence of Sulfuric Acid.—Benzene (156 g.) and 96% sulfuric acid (50.2 g.) were stirred at 0–5° in a 500-cc. flask of the type described[1] by us and 20.0 g. of butadiene (98% pure) was introduced to the stirred mixture as gas from a weighed aluminum bomb during 1.25 hours. The butadiene was added through an opening in the reflux condenser in order that it would be diluted before coming in contact with the sulfuric acid. After the addition of butadiene was completed, the stirring was continued for 0.25 hour while the temperature of the reaction mixture was maintained at 0–5°.

The dark brown product of the reaction consisted of 178 g. of an upper hydrocarbon layer and 46 g. of a lower acid layer. The upper layer, neutralized by sodium hydroxide solution, was steam-distilled to remove the excess of benzene (82 g.). The higher boiling material when distilled

(1) Ipatieff and Pines, *J. Org. Chem.*, **1**, 473 (1936).

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under reduced pressure yielded 13 g. of a hydrocarbon fraction boiling at 152–154° at 16 mm. pressure, and a remainder (81 g.) of higher boiling products. The lower boiling product, after redistillation over sodium, had the properties compared in Table I with the same properties determined on a similar product formed in the presence of hydrogen fluoride and on three synthetically prepared liquid diphenylbutanes.

TABLE I

PROPERTIES OF DIPHENYLBUTANES AND OF THEIR ACETAMINO DERIVATIVES

Diphenylbutane	From reaction in presence of H_2SO_4	HF	1,1-	1,2-[b]	1,3-
B. p. °C.	148	124[d]	145	141	291
B. p. mm.	12	4	16	12	760
$n^{20}D$	1.5545	1.5538	1.5664	1.5513	1.5525
d^{20}_4	0.9761	0.9711	0.9928	0.9707	0.9722
Analyses[a] C, %	91.23	91.84	91.65	91.22	91.03
Analyses[a] H, %	8.72	8.43	7.98	9.00	8.73
Acetamino derivative[2] M. p., °C.	219	...	201–203	227	194
Acetamino derivative[2] Mixed m. p. with product from present reaction	...	...	195	223	165–170
Analyses, % N[c]	8.86	...	....	8.90	8.47

[a] Calculated: C, 91.37; H, 8.63. [b] Infrared absorption indicates that the product is only 90% pure. [c] Calculated: N_2, 8.64. [d] Infrared absorption spectra agreed with that of 1,2-diphenylbutane.

Reaction of Benzene with Butadiene in the Presence of Hydrogen Fluoride.—This reaction was carried out in a stainless steel autoclave provided with a motor-driven stirrer. The autoclave was charged with 408 g. of benzene (5.25 moles) and 311 grams of hydrogen fluoride (15.5 moles) and cooled to 5°. The contents of the autoclave were stirred and a mixture consisting of 312 g. (4 moles) of benzene and 135 g. (2.5 moles) of butadiene was added from a pressure charger during 3.75 hours. The temperature during the reaction rose to 20° and the pressure was the vapor pressure of the mixture. After all the mixture of butadiene and benzene had been added to the reaction mixture, the hydrogen fluoride was released to a potassium hydroxide scrubber, and the autoclave was heated to 50° to remove the greater part of the hydrogen fluoride dissolved in the hydrocarbons. The autoclave was then cooled, and the reaction mixture removed and treated with potassium hydroxide solution. The reaction product formed an emulsion from which the excess of benzene was removed by steam distillation. High boiling products which remained were separated from the alkaline aqueous layer by extraction with *n*-pentane. The extracted material was washed with water, dried, and vacuum distilled. The fractions so separated had the boiling points and refractive indices shown in Fig. 1.

All of the butadiene entered into reaction. The molar ratio of benzene to butadiene which reacted was 1.2:1. About 50% by weight of the reaction product was diphenylbutane. The higher boiling fraction consisted of a complex mixture among which were products of the interaction of 2 moles of benzene with 2 or 3 moles of butadiene as evidenced by the carbon and hydrogen analyses shown in Table II.

TABLE II

PRODUCTS FORMED FROM BENZENE AND BUTADIENE IN THE PRESENCE OF HYDROGEN FLUORIDE

Fraction no.	3–7	16	21
B. p., °C., at 760 mm.	280–285	358–374	418–419
Found, % C	91.84	91.08	90.49
Found, % H	8.43	9.12	9.47
Calcd., % C	91.37	90.85	90.50
Calcd., % H	8.63	9.15	9.50
Formula	$C_{16}H_{18}$	$C_{20}H_{24}$	$C_{24}H_{30}$

(2) V. N. Ipatieff and L. Schmerling, THIS JOURNAL, **59**, 1056 1937); **60**. 1476 (1938).

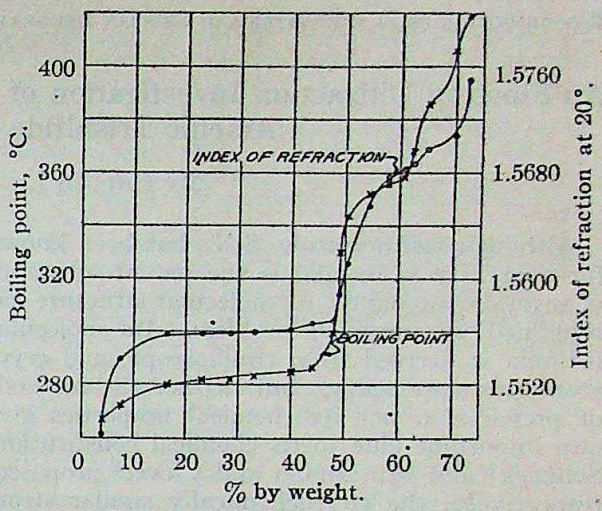

Fig. 1.—Boiling range and index of refraction of the reaction products from benzene and butadiene in the presence of hydrogen fluoride.

Synthesis of Normally Liquid Diphenylbutanes.—The method used for the preparation of diphenylbutanes, illustrated in Table III, consisted in coupling a ketone with a Grignard reagent to form a carbinol which was dehydrated to an olefin by passage over activated alumina at 350°. The olefin was diluted with an equal volume of pentane and hydrogenated at 50° in an Ipatieff rotating autoclave in the presence of a nickel catalyst under 100 atmospheres initial pressure of hydrogen. By this procedure only the olefinic double bond was hydrogenated while the aromatic ring remained unchanged.

TABLE III

SYNTHESIS OF NORMALLY LIQUID DIPHENYLBUTANES

Starting materials			
Ketone	$C_6H_5COC_6H_5$	$C_6H_5CH_2COC_6H_5$	$CH_3COC_6H_5$
Grignard reagent	*n*-C_3H_7MgBr	C_2H_5MgBr	$C_6H_5C_2H_4MgBr$
Diphenylbutane synthesized			
Isomer	1,1-	1,2-	1,3-
Yield, %	65–70	87	75

Acknowledgments.—We are indebted to Dr. W. S. Gallaway for the comparisons of the infrared absorption spectra and to Dr. T. S. Ma of the University of Chicago for the micro determination of carbon, hydrogen, and nitrogen.

Summary

Reaction of butadiene with benzene in the presence of sulfuric acid and hydrogen fluoride catalysts was studied.

1,2-Diphenylbutane was identified as one of the products of the reaction.

The respective yields of 1,2-diphenylbutane obtained from the reaction of butadiene with benzene catalyzed by sulfuric acid and hydrogen fluoride were 14% and 59% on the basis of the benzene which reacted.

RIVERSIDE, ILLINOIS RECEIVED DECEMBER 3, 1943

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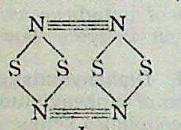
[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY, No. 954]

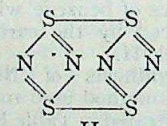
An Electron Diffraction Investigation of Sulfur Nitride, Arsenic Disulfide (Realgar), Arsenic Trisulfide (Orpiment) and Sulfur

BY CHIA-SI LU AND JERRY DONOHUE

Although sulfur nitride, S_4N_4, has been known for over fifty years and is the parent substance of several compounds, its molecular structure has remained an unsolved problem. Its molecular formula is derived from ebullioscopic and cryoscopic measurements; but neither the methods of preparation nor its chemical properties give any important clue to its chemical constitution. Schenck[1] and Muthmann and Clever[2] proposed, respectively, the stereochemically similar structural formulas I and II, which are rather improbable because of the four rings and the small distances. Later Ruff and Geisel[3] proposed the formulas III and IV. They gave preference to the latter formula, which was also supported by



I



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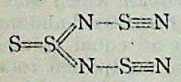
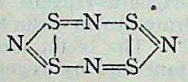
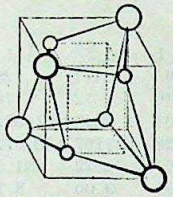


III

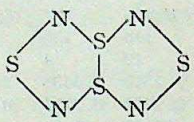


IV

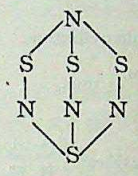
Meuwsen.[4] None of these formulas seems to account for the chemical properties of sulfur nitride satisfactorily. In 1931 Jaeger and Zanstra,[5] on the basis of their x-ray investigation of the crystals of sulfur nitride, reported that the molecules had the configuration of two interpenetrating concentric bisphenoids (tetragonal bisphenoids) of sulfur and nitrogen atoms (formula V). The N-S bond length of their model was only about 1.2 Å., which seems to be far too short. Their results are rendered more doubtful, inasmuch as they regarded the crystals as being orthorhombic, by the fact that the crystals have been shown to possess only monoclinic symmetry by means of both goniometric and x-ray methods[6,7] but usually twin themselves to exhibit orthorhombic symmetry. In 1936 Arnold, Hugill and Hutson[8] proposed formula VI, which would involve resonance among several bond structures. They also considered formula VII, which would easily



V



VI



VII

account for the formation of the thiotrithiazyl ion[9] $(N_3S_4)^+$ from sulfur nitride but would not readily account for the other reactions. Formula VI was supported by Phalnikar and Bhide,[10] although their argument on the basis of their dipole moment measurements is not at all convincing.

The molecular structure of arsenic disulfide (realgar) has been another unsolved problem in structural chemistry. The possibility of isomorphous structures of sulfur nitride and realgar was first suggested by Szarvasy and Messinger.[11] They determined the vapor densities of realgar at several temperatures, and found that the measured vapor density would correspond to As_4S_4 at temperatures below 550° but dissociation into As_2S_2 molecules became appreciable at higher temperatures. They proposed a structure similar to I for the As_4S_4 molecule except with single bonds between the arsenic atoms instead of the triple bonds. Recently Buerger[12] determined the dimensions of the unit cell in the realgar crystal and compared them with those in the crystal of sulfur nitride,[7] and suggested that the difference in the length of the monoclinic *b*-axis might be attributed to the difference in the sizes of the arsenic and nitrogen atoms. However, no complete structure investigation for either substance has been reported in the literature.

Burt[13] reported in 1910 that sulfur nitride can be sublimed readily *in vacuo* at as low a temperature as 100°. Realgar also sublimes readily *in vacuo* at temperatures below its melting point (307°); and excellent realgar crystals can be grown in this way.[14] We have therefore undertaken an electron diffraction investigation of these

(1) R. Schenck, *Ann.*, **290**, 171 (1896).

(2) W. Muthmann and A. Clever, quoted in ref. 8. Their paper in *Z. anorg. Chem.*, **13**, 200 (1896), however, does not mention the formula II.

(3) O. Ruff and E. Geisel, *Ber.*, **37**, 1573 (1904).

(4) A. Meuwsen, *ibid.*, **62**, 1959 (1929); **64**, 2301, 2311 (1931).

(5) F. M. Jaeger and J. E. Zanstra, *Proc. K. Acad. Wetensch. Amsterdam*, **34**, 782 (1931).

(6) E. Artini, *Z. Krist.*, **42**, 68 (1907); G. F. H. Smith, *Min. Mag.*, **16**, 97 (1911).

(7) M. J. Buerger, *Am. Min.*, **21**, 575 (1936). His results are quoted as follows: $a_0 = 8.74$ Å., $b_0 = 7.14$ Å., $c_0 = 8.645$ Å., $\beta = 92°21'$; $C_{2h}^5 - P2_1/n$; $Z = 4$ (S_4N_4).

(8) M. H. M. Arnold, J. A. C. Hugill and J. M. Hutson, *J. Chem. Soc.*, 1645 (1936).

(9) W. Muthmann and E. Seitter, *Ber.*, **30**, 627 (1897).

(10) N. L. Phalnikar and B. V. Bhide, *Current Science*, **8**, 473 (1939).

(11) E. Szarvasy and C. Messinger, *Ber.*, **30**, 1343 (1897).

(12) M. J. Buerger, *Am. Min.*, **20**, 36 (1935). His results are quoted as follows: $a_0 = 9.27$ Å., $b_0 = 13.50$ Å., $c_0 = 6.56$ Å., $\beta = 106°37'$; $C_{2h}^5 - P2_1/n$; $Z = 4$ (As_4S_4).

(13) F. P. Burt, *J. Chem. Soc.*, **97**, 1171 (1910).

(14) A. Schuller, *Z. Krist.*, **27**, 97 (1897).

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two substances in the vapor state. In the course of our investigation we began to feel the desirability of examining arsenic trisulfide (orpiment) and sulfur by means of similar experimental techniques. In the case of orpiment, which exhibits rather large birefringence in the crystal, it might be expected that the crystal structure would be different from that of arsenolite,[15] which consists of As_4O_6 molecules. However, orpiment can be distilled unchanged,[16] although it does not sublime as readily as realgar.[14] It is thus of interest to find out whether it could have the As_4O_6 structure in the vapor state.[17] In the case of sulfur a puckered ring structure has been established in the rhombic crystals[18] as well as in the vapor.[19] Since the electron diffraction photographs of Howe and Lark-Horovitz[19] apparently were not taken to show features beyond $q = 30$ ($q = 40/\lambda \sin \theta/2$), their patterns are not capable of giving as complete information with regard to the size, configuration, and rigidity of the ring as we have been able to obtain.

We have accidentally taken some excellent photographs of arsenic trioxide, which apparently contaminated a sample of stockroom-grade "pure" arsenic trisulfide. Five more features could be seen and measured than those reported by Hampson and Stosick.[20] Our final parameters are as follows: As—O = 1.78 ± 0.02 Å., As—As = 3.20 ± 0.02 Å. and ∠ As—O—As = 128 ± 2° (∠O—As—O = 99 ± 2°). These agree very well with the values of Hampson and Stosick:[20] namely, As—O = 1.80 ± 0.02 Å., As—As = 3.20 ± 0.03 Å. and ∠ As—O—As = 126 ± 3°. It should be noted that both the As—O bond length and the oxygen bond angle indicate large amounts of double bond character in the As—O bonds arising from the unshared electrons on the oxygen atoms.

Experimental.—The sample of sulfur nitride used in this investigation was prepared by the method described by Arnold, Hugill and Hutson.[8] The sample was recrystallized twice from chloroform. It burned quietly in air and left no residue on sublimation *in vacuo*. The samples of realgar and orpiment were purchased from a mineralogical supply service in Pasadena. According to Mr. Grieger of this supply service, the sources of these mineral specimens are: realgar, White Caps mine, Manhattan, Nevada; orpiment, Mercur, Utah. Both specimens are of very high quality. The realgar was purified by sublimation *in vacuo* at a temperature of *ca.* 300°. Orpiment would not sublime so readily; hence it was fused *in vacuo* to a glassy mass at a temperature of 300–400° to remove both arsenic trioxide and realgar, and was then pulverized. The powdered sample had a dark yellow color. Another sample of arsenic trisulfide was prepared artificially by precipitation by hydrogen sulfide from a solution of arsenic trichloride in hydrochloric acid. The sample of sulfur was obtained from the chemical stockroom. It was apparently of very high purity, and it left practically no residue on sublimation *in vacuo*.

The electron diffraction apparatus used for this investigation has been described by Brockway.[21] The camera distance used was about 11 cm. The wave length of the electrons (*ca.* 0.06 Å.) was determined against zinc oxide smoke[22] ($a_0 = 3.2426$ Å., $c_0 = 5.1948$ Å.) with a camera of about 40 cm. distance.

The metal high-temperature nozzle of Brockway and Palmer[23] was found to be unsuitable for sulfur nitride and realgar. With this nozzle no photographs could be obtained below a certain heating current; while at higher heating current only photographs of decomposition or reaction products resulted. A glass high-temperature nozzle of very simple design was made to meet this difficulty and was used throughout this investigation. It consists of a small sample tube (diameter 6 mm.; length 2.5 cm.) with a male ground joint, and a capillary chimney (O. D. 6 mm.; I. D. 2 mm.; length 2.5 cm.) with a female ground joint on one end and a constricted bore of 0.5 mm. diameter on the other. Each of these two parts is wound with a few turns of no. 26 nichrome wire. Of the four substances studied (aside from arsenic trioxide), sulfur nitride required the lowest heating current and orpiment the highest. No attempt was made to measure the temperature of the vapor in the nozzle; evidently it was never as high as the softening point of Pyrex glass. A diagram of the nozzle is shown in Fig. 1.

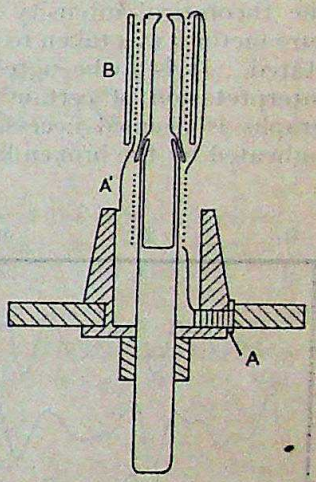

Fig. 1.—Diagram of the high temperature nozzle: A,A', leads for heating coil; B, glass shield for upper part of chimney. In actual practice the entire chimney was wrapped in asbestos.

The photographs were examined on a viewing box, and, for the outer rings, two or more good, heavy photographs were superimposed and examined on a Triplett and Barton viewing lamp of adjustable illumination aperture and intensity. Measurements of the diffraction features were made on a comparator in the usual manner. All the intensity patterns could be observed up to or beyond $q = 80$. The photographs were all corrected for film expansion by measuring two fiducial distances on the film.

Interpretation.—Both the radial distribution method[24] and the correlation method[25] were used in interpreting the photographs. The radial distribution functions were calculated from the visual intensity curves by means of the following equation

(15) R. M. Bozorth, THIS JOURNAL, **45**, 1621 (1923); K. E. Almin and A. Westgren, *Arkiv Kemi, Mineral. Geol.*, **15B**, No. 22 (1942), abstracted in *Chem. Abs.*, **36**, 5688 (1942).

(16) E. Mitscherlich, *Ges. Wiss. Göttingen*, **12**, 137 (1834), quoted in Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," Vol. IX, Longmans, London, 1929.

(17) Szarvasy and Messinger (ref. 10) reported that their vapor density measurements on orpiment indicated appreciable dissociation at 1000°. They did not mention, however, whether it was from As_2S_3 or from As_4S_6 that orpiment dissociated.

(18) B. E. Warren and J. T. Burwell, *J. Chem. Phys.*, **3**, 6 (1935).

(19) J. D. Howe and K. Lark-Horovitz, *Phys. Rev.*, **51**, 380A (1937).

(20) G. C. Hampson and A. J. Stosick, THIS JOURNAL, **60**, 1814 (1938).

(21) L. O. Brockway, *Rev. Mod. Phys.*, **8**, 231 (1936).

(22) C. S. Lu and E. W. Malmberg, *Rev. Sci. Instr.*, **14**, 271 (1943).

(23) L. O. Brockway and K. J. Palmer, THIS JOURNAL, **59**, 2181 (1937).

(24) L. Pauling and L. O. Brockway, *ibid.*, **57**, 2684 (1935); R. Spurr and V. Schomaker, *ibid.*, **64**, 2693 (1942).

(25) L. Pauling and L. O. Brockway, *J. Chem. Phys.*, **2**, 867 (1934).

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$$rD(r) = \sum_{q=1}^{q_{max}} I(q)e^{-aq^2} \sin\left(\frac{\pi}{10} qr\right)$$

where a was so determined that e^{-aq^2} was 1/10 or 1/20 at $q = 90$. The unobservable first feature of the visual curve (dotted part) was introduced arbitrarily. (In the case of sulfur, this first feature was taken from the theoretical intensity curves, *cf.* Fig. 2.) On the other hand, for the correlation treatment the simplified theoretical scattering formula,[24] was used to calculate

$$I^{\circ}(q) = \sum_{i,j}{}' \frac{Z_i Z_j}{r_{ij}} e^{-b_{ij}q^2} \sin\left(\frac{\pi}{10} r_{ij}q\right)$$

the theoretical intensity curves. The temperature factor b was taken to be zero unless otherwise stated. It is to be noted that sometimes a reinterpretation of certain features of the photographs is deemed necessary. Such a change is indicated by the broken lines on the visual curve.

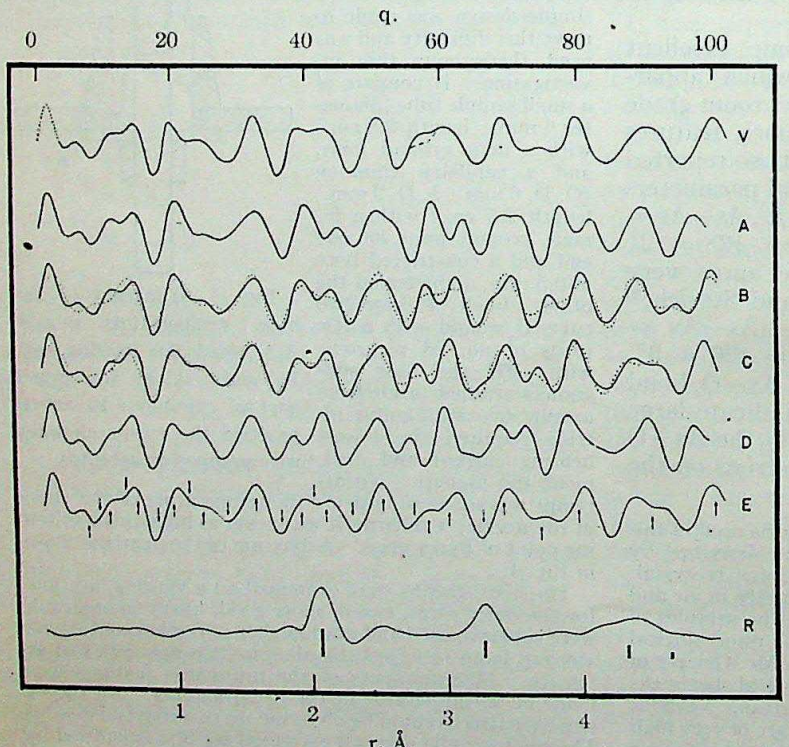

Fig. 2.—Electron diffraction curves for sulfur, S_8

	S.S, Å.	<S.S.S	Remarks
A	2.07	100°	
B	2.07	103°	
C	2.07	106°	
D	2.07	109°	
E	2.07	104°50′	Temperature factor (b = 0.0009) for two longer terms

We shall describe our results obtained in this investigation in the following order: sulfur, orpiment, sulfur nitride and realgar.

Sulfur.—The electron diffraction pattern of the sulfur molecule S_8 is depicted in curve V of Fig. 2. The radial distribution function R calculated for this visual curve gives two sharp peaks at 2.07 and 3.28 Å. and a broad peak at 4.3–4.4 Å. From these we obtain S.S = 2.07 ± 0.02 Å. and ∠ S–S–S = 105 ± 2°. The broad peak should then arise from the longer S–S terms, which, for a regular puckered eight-ring, would be 4.34 and 4.67 Å., with weights *ca.* 2:1. Several configurations derivable from a regular puckered ring by systematic distortions, such as the "tub" form, the "chair" form, the "cradle" form and the "butterfly" form (Fig. 3), have been shown to be incompatible with the radial distribution peak at 4.3–4.4 Å. Therefore the fraction of sulfur molecules having these configurations in the vapor phase must be small.

Four theoretical intensity curves A–D were calculated for regular puckered ring models with S–S = 2.07 Å. and ∠ S–S–S = 100°, 103°, 106° and 109°, respectively. In order to estimate the thermal vibration of the ring two more theoretical curves (dotted curves) including only the two shortest terms were calculated for the models B and C. Qualitative comparison reveals at once that there is a rather large thermal vibration associated with the puckered ring structure. (We estimate from the curves B and C that $\sqrt{\overline{\delta r^2}} \cong 0.15$ Å. for the two longer S–S terms. Curve E calculated with S–S = 2.07 Å., ∠S–S–S = 104°50′, and this amplitude of vibration (corresponding to b = 0.0009) for the two long terms is seen to agree very well with the visual curve.) Quantitative comparison of the observed and the calculated features is given in Table I.

Both the electron diffraction values of Howe and Lark-Horovitz[19] (S–S = 2.08 ± 0.02 Å.) and the x-ray values of Warren and Burwell[18] (S–S = 2.12 Å., ∠ S–S–S = 105°) for the sulfur molecule agree satisfactorily with our present results.

Orpiment.—The fused orpiment and the precipitated arsenic trisulfide gave identical electron diffraction patterns, which are depicted in curve V of Fig. 4. The radial distribution function R calculated for this visual intensity curve gives a sharp peak at 2.25 Å. and a peak at 3.46 Å. with a broad shoulder on the outside. The first peak (2.25 ± 0.02 Å.) corresponds to a single-bond As–S distance.[26] No

(26) See L. Pauling, "The Nature of the Chemical Bond," second edition, Cornell University Press, Ithaca, New York, 1940.

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TABLE I

SULFUR

Min.	Max.	$q_{obs.}$	q_E	$q_E/q_{obs.}$
	1	6.87	5.6	(0.815)
2		8.51	7.6	(.893)
	2	10.05	10.5	(1.045)
3		12.41	11.5	(0.927)
	3	14.29	13.6	(.952)
4		17.27	16.7	(.967)
	4	19.68	20.1	(1.021)
5		22.05	21.8	0.989
	5	24.08	24.3	1.009
6		27.65	27.7	1.002
	6	32.08	31.8	0.991
7		35.77	35.6	.995
	7	38.75	39.0	1.006
8		40.63	41.0	1.009
	8	42.40	43.0	1.014
9		46.26	46.6	1.007
	9	50.89	50.5	0.992
10		55.54	54.2	.976
	10	57.46	57.5	1.001
11			48.8	
	11	60.47	61.7	1.020
12		65.60	65.4	0.997
	12	68.64	69.2	1.008
13			73.0	
	13	74.10	74.3	1.003
14			76.6	
	14	79.60	80.2	1.008
	15	90.3	88.0	(0.975)
	16	99.6	99.2	0.996
		Average		1.001
		Average deviation		0.008

plausible model, however, can be constructed for As_2S_3 such that the As—S bonds would be expected to be essentially single bonds and such that the peaks in the radial distribution function are satisfactorily accounted for. Hence, it is likely that the orpiment molecule in the vapor phase is As_4S_6 and has the As_4O_6 structure. For As_4S_6 with this structure, with As—S = 2.25 Å. and ∠ As—S—As = 100°, we would expect a large As—As peak at 3.45 Å., a small S—S peak at 3.77 Å. (which possibly falls in the shoulder of the As—As peak), a large As—S peak at 4.25 Å., and a negligibly small S—S peak at 5.33 Å. Theoretical intensity curves calculated for this model with As—S = 2.25 Å. and ∠ As—S—As = 97°, 100°, and 103°, respectively, are shown in curves A—C of Fig. 4. In order to estimate the thermal effect on such a rigid model, we calculated two more theoretical curves (dotted curves) including only the three shorter terms for the models B and C. From a qualitative comparison of the curves B and C with the visual curve it is easily seen that if As_4S_6 molecules do exist in the vapor phase they cannot be as rigid as the As_4O_6 molecules. This loss of rigidity is probably due to the high temperature used in our investigation.

Curve D was calculated for an As_4S_6 model with

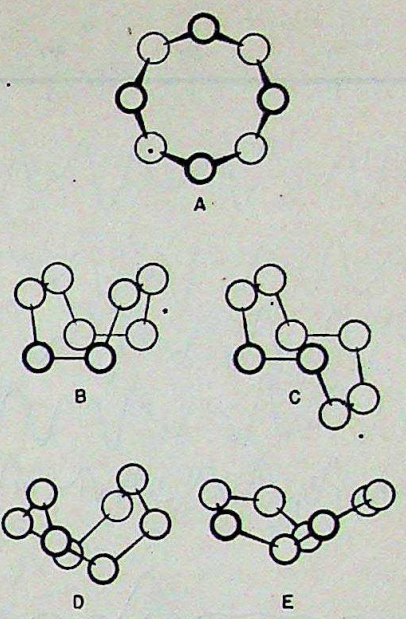

Fig. 3.—Some configurations of the eight ring: A, regular puckered ring (S_8 molecule); B, "tub" form; C, "chair" form; D, "cradle" form; E, "butterfly" form.

As—S = 2.25 Å. and ∠ As—S—As = 101° and a temperature factor (b = 0.0009) for the two longest terms. Quantitative comparison of the

TABLE II

ORPIMENT

Min.	Max.	$q_{obs.}$	q_D	$q_D/q_{obs.}$
	1	6.82	6.5	(0.953)
2		9.80	8.6	(.878)
	2	12.48	11.7	(.938)
3		15.93	15.8	.992
	3	18.78	19.3	1.028
4		22.23	22.3	1.003
	4	24.15	24.3	1.006
5		26.09	26.3	1.008
	5	29.66	29.5	0.995
6		33.22	32.9	.990
	6	35.85	37.0	(1.032)
7		39.55	41.0	(1.037)
	7	41.37	42.5	(1.027)
8		43.55	43.7	1.003
	8	47.10	47.3	1.004
9		51.80	50.8	0.981
	9	54.87	54.3	.990
10			57.0	
	10	59.15	58.5	.989
11		61.71	61.5	.997
	11	64.05	64.5	1.007
12		68.26	68.3	1.001
	12	71.34	71.3	0.999
13		73.28	73.5	1.003
	13	76.95	75.6	0.982
	14	82.71	82.4	.996
	15	89.8	88.8	.989
	16	95.4	93.0	.975
		Average		.997
		Average deviation		.009

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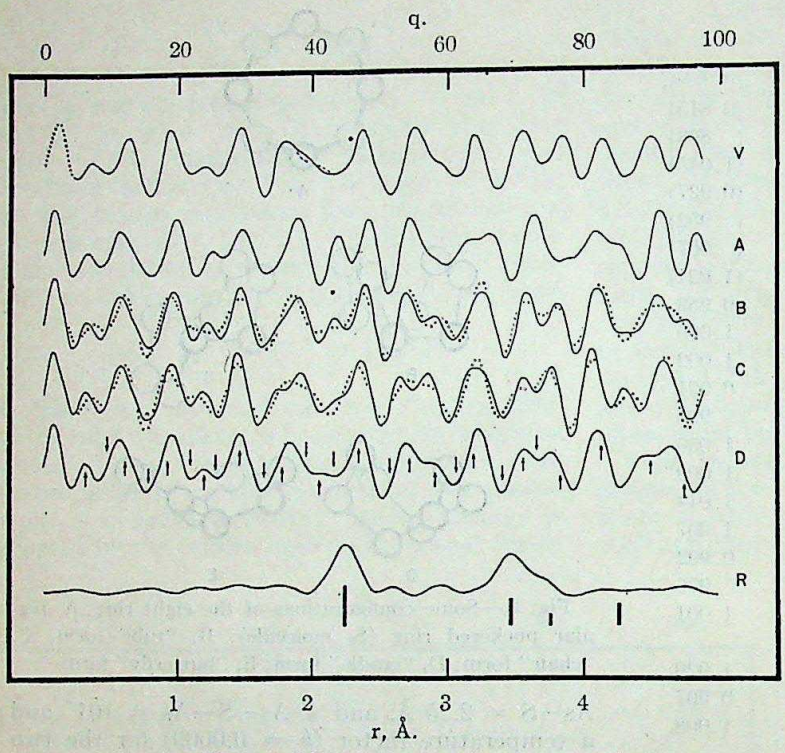

Fig. 4.—Electron diffraction curves for orpiment, As_4S_6:

	As-S, Å	<As-S-As	Remarks
A	2.25	97°	
B	2.25	100°	
C	2.25	103°	
D	2.25	101°	Temperature factor (b = 0.0009) for two longest terms

observed and the calculated features is given in Table II. Our final parameters are as follows: As−S = 2.25 ± 0.02 Å., ∠ As−S−As = 100 ± 2° (∠ S−As−S = 114 ± 2°). The As_4S_6 molecules exhibit large thermal vibration under our experimental conditions.

The orpiment crystal probably bears a similar relationship to As_4S_6 molecules as orthorhombic antimony trioxide (valentinite)[27] does to Sb_4O_6, and possibly even as monoclinic arsenic trioxide (claudetite) does to As_4O_6, although the crystal structure of claudetite is not yet known.

It is interesting to note that Medlin[28] obtained for orpiment the following interatomic distance peaks: 2.24 Å. (somewhat asymmetric), 3.46 Å., and 4.39 Å., from the radial distribution treatment of x-ray powder photographs. Although the close agreement with our radial distribution function is apparently coincidental, this tends to indicate that the bond lengths and bond angles in the orpiment crystal are not subject to severe deformation during the process of volatilization.

Sulfur Nitride.—The electron diffraction pattern of the sulfur nitride molecule S_4N_4 is represented by curve V of Fig. 5. The radial distribution function R calculated for this visual intensity curve gives a sharp peak at 1.62 Å., another equally sharp but somewhat stronger peak at 2.69 Å. with a slight asymmetry on the inside, followed by a small shouldering peak at about 3.1 Å., a small peak at 3.78 Å., and possibly another small but broad peak at about 4.2 Å. The first peak at 1.62 Å. undoubtedly arises from the N−S bonds in the sulfur nitride molecule. Since the length of a single S−N bond is expected to be *ca.* 1.74 Å. while that of a double bond is *ca.* 1.54 Å.,[26] it seems that practically all the S−N bonds in the sulfur nitride molecule would have considerable amounts of double bond character. The second peak at 2.69 Å. might be interpreted as due mostly to the S−S intractions; if this is the case, the bond angle ∠ S−N−S would be close to 112°. Meanwhile, the relative sizes of the first two peaks might have some significance which must be taken into consideration. At any rate, our radial distribution function indicates that the sulfur nitride molecule is rather compact, since no important long distance in the molecule is shown by it.

The height of the first peak and its shape would exclude all models involving either more than one direct bond between the sulfur atoms or more than two N−N bonds. Hence the structural formulas II and IV are very improbable. Formula III, on the other hand, is not likely to be correct since the radial distribution function indicates that there is no important distance longer than 3.1 Å. in the molecule. Jaeger and Zanstra's model (V) is also not acceptable, because even if the N−S bond length and the size of the nitrogen bisphenoid should be made more reasonable, the interatomic distance spectrum of the radial distribution function could not be fitted at all. As a matter of fact, we have not been able to find any satisfactory models consisting of two interpenetrating concentric bisphenoids of nitrogen and sulfur atoms.

Formula VI represents a limiting case of one of the several plausible configurations which can be derived from a regular puckered eight-ring of alternate sulfur and nitrogen atoms by systematic distortions. Calculations were made for two planar models of formula VI with N−S = 1.62 Å. and S−S = 2.08 Å. and 1.88 Å., respectively. The theoretical curves A_1 and A_2 are shown in Fig. 5; and the corresponding interatomic distance spectra are shown under R. Since the

(27) M. J. Buerger and S. B. Hendricks, *Z. Krist.*, **98**, 1 (1937).
(28) W. V. Medlin, THIS JOURNAL, **58**, 1590 (1936).

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inter-ring distances contribute less than one-fifth of the total molecular scattering, the analysis of these two planar models suffices to show that such a configuration, suggested by Arnold, Hugill and Hutson,[8] is not likely, insofar as it is impossible to get a sufficiently important term at about 3.1 Å. The counterpart of such a configuration obtained by the exchange of the sulfur and nitrogen atoms is equally unsatisfactory.

A regular puckered ring model was also investigated. With N−S = 1.62 Å. and ∠S−N−S = 112°, and the angle ∠ N−S−N taken as a variable parameter, satisfactory agreement with the radial distribution function can be obtained (although the relative heights of the peaks are not correct), but only with the unreasonably small value 70° for the sulfur bond angle.

Two other simple "cradle" models, one the counterpart of the other, can be derived from the puckered ring configuration. One consisting of a bisphenoid of nitrogen atoms and a square of sulfur atoms was found to be unlikely by comparison with the radial distribution function and by calculation of a theoretical curve for a model (curve B, Fig. 5) of this type which most nearly agrees with the radial distribution function. The limiting form of this structure, obtained by reducing the N−N distance across the "cradle" to 1.47 Å., the N−N single bond distance,[29] cannot be made to fit the radial distribution function and at best demands unreasonably small nonbonded N−N distances and sulfur bond angles. Essentially the same difficulties are encountered with the less symmetrical model analogous to this which would be taken as the modern realization of formula I. The counterpart of this "cradle" configuration, consisting of a bisphenoid of sulfur atoms and a square of nitrogen atoms, is, on the other hand, a promising configuration. A model with N−S = 1.62 Å., ∠ S−N−S = 112°, and ∠ N−S−N = 106° (the distribution of the sulfur atoms is tetrahedral in this model) gives curve C of Fig. 5; the corresponding interatomic distance spectrum is shown under R. Quantitative comparison of the observed features and those calculated for this model is given in Table III.

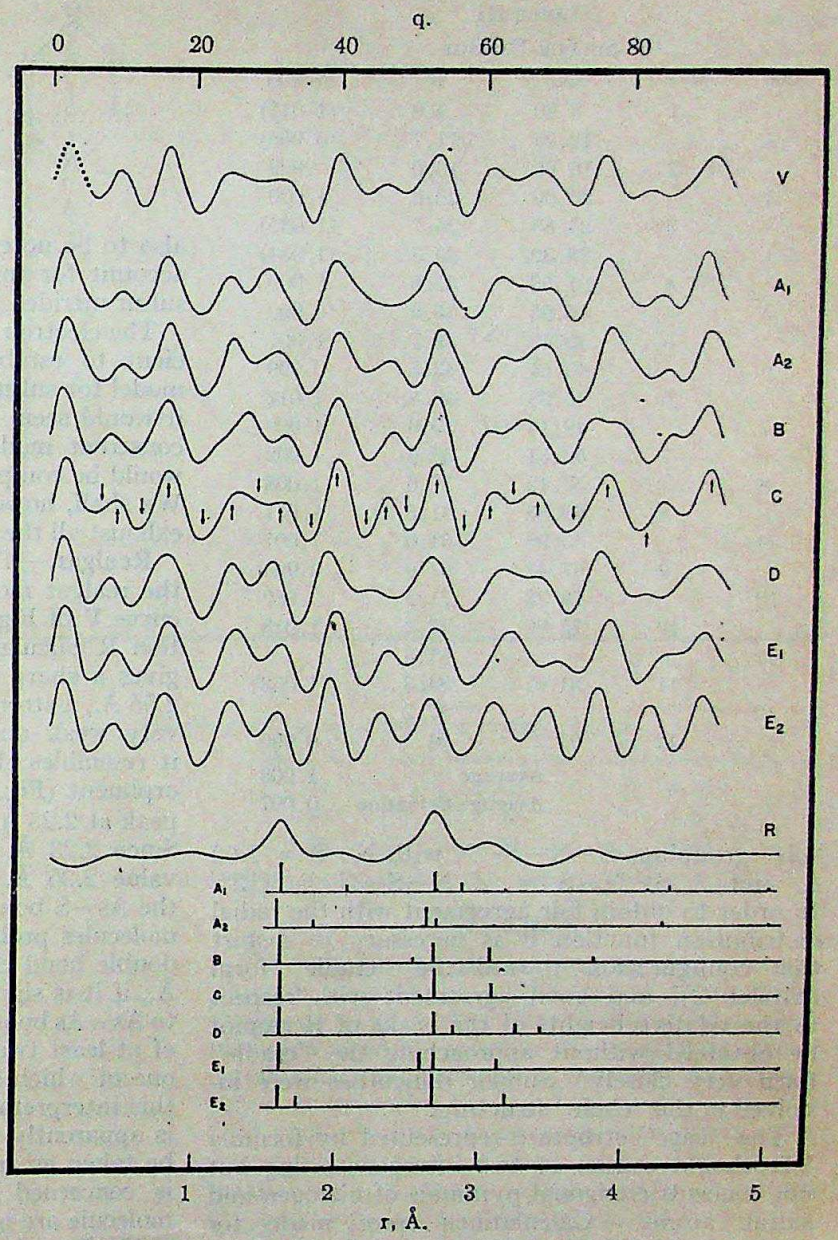

Fig. 5.—Electron diffraction curves for sulfur nitride, S_4N_4:

Configuration

- A_1 formula VI, planar, S–S = 2.08 Å.
- A_2 formula VI, planar, S–S = 1.88 Å.
- B "cradle," bisphenoid of nitrogen atoms, N–N = 2.55 Å.
- C Our proposed structure (*cf.* Fig. 7)
- D "tub" form
- E_1 "cage" form (formula VII), intervening N–S = 1.62 Å.
- E_2 "cage" form (formula VII), intervening N–S = 1.74 Å.

Models of the "chair" and of the "tub" forms derived from the puckered ring configuration were also considered but were found to be unsatisfactory. Curve D of Fig. 5 was calculated for a "tub" model involving four coplanar

(29) V. Schomaker and D. P. Stevenson, THIS JOURNAL, 63, 37 (1941); P. A. Giguère and V. Schomaker, *ibid.*, 65, 2025 (1943).

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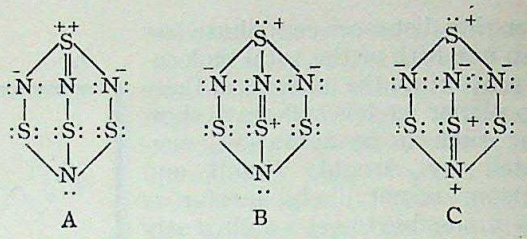
TABLE III

SULFUR NITRIDE

Min.	Max.	$q_{obs.}$	q_C	$q_C/q_{obs.}$
	1	8.90	9.0	(1.011)
2		12.24	11.7	(0.956)
	2	16.02	16.0	.999
3		20.60	20.6	1.000
	3	24.83	25.7	(1.035)
4		28.32	29.3	(1.034)
	4	31.53	31.8	1.009
5		35.95	35.6	0.990
	5	39.42	39.7	1.007
6		43.54	43.5	0.999
	6	46.23	46.8	1.012
7		49.14	49.6	1.009
	7	53.51	53.6	1.002
8		57.12	57.6	1.008
	8	60.85	61.5	1.011
9		63.96	64.0	1.001
	9	67.43	67.0	0.994
10		72.33	71.5	.989
	10	75.92	77.3	1.018
11			81.3	
	11	81.67	84.3	(1.032)
12			87.2	
	12	91.2	91.1	0.999
		Average		1.003
		Average deviation		0.007

"*cis*" groupings S−N−S−N with N−S = 1.62 Å. and ∠ S−N−S = ∠ N−S−N = 112°. In order to obtain fair agreement with the radial distribution function it is necessary to distort this configuration toward the "cradle" form (Model C), and good agreement with respect to the relative heights of the peaks of R cannot be obtained without approaching the "cradle" form very closely. Similar difficulties were involved in the "chair" structure.

The "cage" structure represented by formula VII should consist of two interpenetrating but not concentric trigonal pyramids of nitrogen and sulfur atoms. Calculations were made for models with N−S = 1.62 Å., ∠ S−N−S = ∠ N−S−N = 112° for the two end groups NS_3 and SN_3 and the intervening N−S = 1.62 Å. and 1.74 Å., respectively. The theoretical intensity curves E_1 and E_2 are given in Fig. 5 together with the corresponding interatomic distance spectra. Since five parameters (namely, three distances for the S−N bonds and two pyramidal angles) are required to describe this structure if it has symmetry C_{3v}, it should be possible to construct models with this "cage" configuration in satisfactory agreement with the diffraction pattern. Nevertheless we believe that this configuration may be rejected by consideration of the following plausible bond structures which makes it difficult to understand how the N−S bonds could have such a considerable amount of double bond character as is indicated by the short average bond length 1.62 Å. It is also to be noted that this structure could hardly account for most of the chemical properties of sulfur nitride.



A B C

The electron diffraction data alone are not sufficient to establish with certainty the "cradle" model for sulfur nitride, and, as a matter of fact, it would seem to be not altogether impossible to construct models of other configurations which would be compatible with the diffraction pattern. We shall, however, make no further attempt to exhaust all the possibilities.

Realgar.—The electron diffraction pattern of the realgar molecule As_4S_4 is represented by the curve V of Fig. 6. The radial distribution function R calculated for this visual intensity curve gives a sharp peak at 2.23 Å., a small peak at 2.55 Å., a strong but broad peak at 3.50 Å., and a very weak and broad peak at about 4.75 Å.; it resembles the radial distribution function for orpiment (Fig. 4) to a certain extent. The first peak at 2.23 Å. must arise from the As−S bonds. Since 2.23 Å. is very close to the single bond value 2.25 Å. found in the orpiment molecule, the As−S bonds in the realgar and the orpiment molecules probably have comparable amounts of double bond character. The small peak at 2.55 Å., if it is significant, may be interpreted as due to As−As bonds. The next peak seems to consist of at least two unresolved interatomic distances, one of which is an As−As term. According to this interpretation the bond angle ∠ As−S−As is apparently not greater than 106°. This may be taken as an indication that as far as bonding is concerned the sulfur atoms in the realgar molecule are more like those in dimethyl disulfide (107°)[30] and in sulfur (105°) than like those in sulfur dioxide (120°).[31] It is interesting to note that there is no important long distance in the realgar molecule.

The formulas II–IV suggested for the sulfur nitride molecule could also be formulated for the realgar molecule. None of them, however, could be made to fit the radial distribution function. A regular puckered eight-ring of alternate arsenic and sulfur atoms is also not acceptable. Since the bond angle ∠ As−S−As is small relative to the tetrahedral angle we were unable to construct a satisfactory "cage" model.

On the other hand, a "cradle" configuration consisting of a bisphenoid of arsenic atoms and a

(30) D. P. Stevenson and J. Y. Beach, THIS JOURNAL, **60**, 2872 (1938).

(31) P. C. Cross and L. O. Brockway, *J. Chem. Phys.*, **3**, 821 (1935); V. Schomaker and D. P. Stevenson, THIS JOURNAL, **62**, 1270 (1940).

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square of sulfur atoms (involving rearrangement of bonds in the formula proposed by Szarvasy and Messinger[11]) was found to be plausible. Theoretical intensity curves A–C were calculated for such "cradle" models with As–S = 2.23 Å., As–As = 2.44, 2.49, and 2.55 Å., respectively, and the weighted average value of the longer As–As and As–S terms at about 3.50 Å. These are shown in Fig. 6. Curve B reproduces the qualitative features rather satisfactorily. Quantitative comparison of the observed and the calculated features is given in Table IV. As in the case of sulfur nitride, no attempt is made to exhaust all the possible models of other configurations that are compatible with the diffraction pattern.

Incidentally it is to be noted that Medlin,[28] from the radial distribution treatment of x-ray powder photographs, obtained for realgar the following interatomic distance peaks: 2.16 (somewhat asymmetric), 3.54 and 4.52 Å. The agreement with our finding is not at all disappointing.

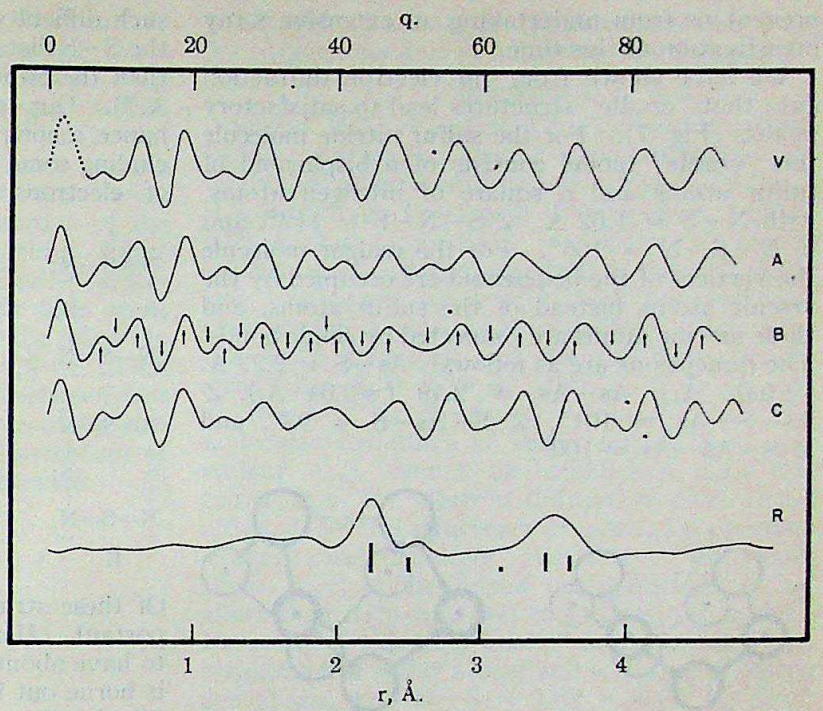

Fig. 6.—Electron diffraction curves for realgar, As_4S_4:

	As-As, Å.	non-bonded As-As, Å.	non-bonded As-S, Å.
A	2.44	3.45	3.58
B	2.49	3.45	3.61
C	2.55	3.43	3.66

All models have configuration as in Fig. 7. bonded As–S = 2.23 Å.

TABLE IV

REALGAR

Min.	Max.	$q_{obs.}$	q_B	$q_B/q_{obs.}$
	1	7.29	7.6	(1.043)
2		9.75	9.4	(0.964)
	2	12.45	12.3	.988
3		15.79	15.6	.988
	3	18.49	18.7	1.011
4		21.94	22.0	1.003
	4	24.13	24.3	1.007
5		26.28	26.5	1.008
	5	29.75	29.5	0.992
6		33.09	32.6	.985
	6	36.15	35.7	.988
7		38.08	38.3	1.006
	7	39.74	40.5	1.019
8		43.47	43.4	0.998
	8	46.91	47.0	1.002
9		52.22	52.5	1.005
	9	56.65	57.1	1.008
10		61.06	60.7	0.994
	10	65.21	65.6	1.006
11		69.05	69.5	1.007
	11	72.69	74.0	1.018
12		77.63	78.9	1.016
	12	82.12	83.1	1.012
13		86.71	86.5	0.998
	13	90.2	90.0	0.998
		Average		1.002
		Average deviation		0.008

Discussion

The structure of the sulfur molecule is essentially the same as that in the crystal, as was to be expected. The large thermal libration of the puckered sulfur molecule is apparently associated with the flexibility of the eight-ring structure. In orpiment the bond angle ∠ As–S–As (100 ± 2°) is found to be much smaller than the corresponding angle ∠ As–O–As (128 ± 2°) in the As_4O_6 molecule. This effectively draws the neighbors to the arsenic atoms closer without perturbing the coördination of the sulfur atoms to an unnecessary extent. The double bond character of the As–S bonds is also diminished.

Our results on the sulfur nitride and realgar molecules are gratifying insofar as these help to make another step forward in the solution of these two unsolved problems in structural chemistry. These structures cannot yet be established with certainty, although several of the structures proposed by previous workers are definitely eliminated. We believe that a detailed analysis of the crystal structures of sulfur nitride and realgar, which should be simplified by our present results, will lead to the ultimate solution of these two problems. (The ease of sublimation of these substances and their solubility in several organic solvents indicate that the crystals are molecular. It seems likely that the structures in vapor and crystal are similar.) Wartime duties, however,

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prevent us from undertaking an extensive x-ray investigation at this time.

We have shown from our electron diffraction data that "cradle" structures lead to satisfactory models (Fig. 7). For the sulfur nitride molecule this "cradle" model consists of a bisphenoid of sulfur atoms and a square of nitrogen atoms, with N−S = 1.62 Å., ∠ S−N−S = 112°, and ∠ N−S−N = 106°. For the realgar molecule the vertices of the bisphenoid are occupied by the arsenic atoms instead of the sulfur atoms, and these arsenic atoms are connected by single bonds. The dimensions are as follows: As−S = 2.23 Å. (±0.02 Å.), As−As = 2.49 (±0.04 Å.), ∠ As−S−As = 101°, ∠ S−As−S = 93°, and ∠ S−As−As = 100°.

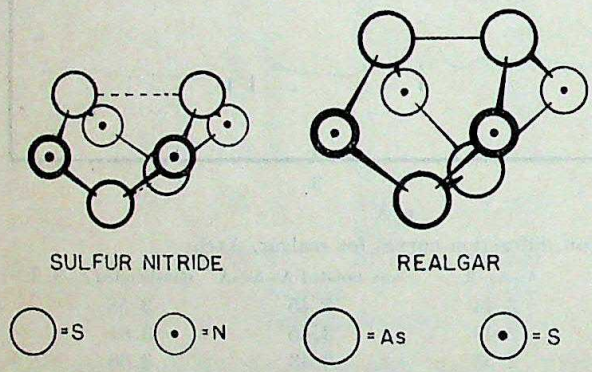
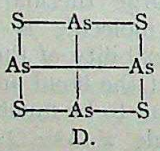


Fig. 7.—The molecular structures proposed for realgar and sulfur nitride.

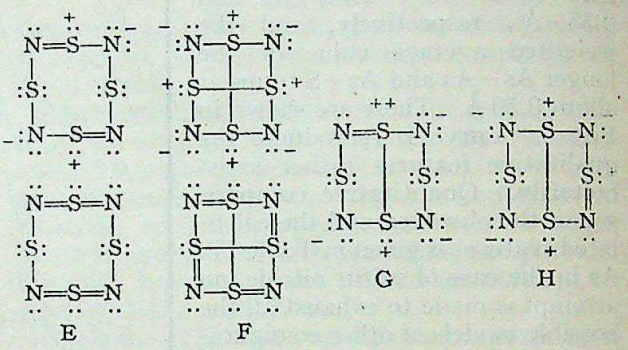
Our "cradle" structure for the realgar molecule is conventional as is indicated by the bond structure D and the observed bond lengths. Its



D.

simple relationship to the structure of the As_4S_6 molecule is borne out by the fact that orpiment and realgar can be easily converted into one another at high temperatures. The conversion of realgar to orpiment would involve simply inserting a sulfur atom between each As−As pair. Moreover, the chemical reactions of realgar are in general typical of sulfides and trivalent arsenic compounds.

If the arsenic atoms of this model for the realgar molecule were now replaced by nitrogen atoms and the N−N bonds across the "cradle" were made practically single bonds, then in order to make the side of the sulfur square *ca.* 2.7 Å. in length the non-bonded N−N distance and the sulfur bond angle would have to be too small to be reasonable; also, the stronger tendency of the sulfur atoms (compared with the nitrogen atoms) toward high coördination would never be realized. The "cradle" model for the sulfur nitride molecule, on the other hand, does not involve any such difficulty, although it should be noted that the S−S distances in this model are much shorter than the ordinary van der Waals separation (3.7 Å.[26]). Our structure probably involves resonance among the following bond structures, including some of those in which sulfur has a decet of electrons, and other less important ones.



Of these structures E is probably the most important. Hence each N−S bond is expected to have about 25% double bond character, which is borne out by the short bond length of 1.62 Å. The bond angles, *ca.* 112° for ∠ S−N−S and 106° for ∠ N−S−N, are also reasonable for this type of bond structure. However, it must be pointed out that the deviation of the S−N−S−N groupings from the "*cis*" configuration is great (*ca.* 58°). Since a similar situation is found in the similar compact structures of As_4O_6, P_4O_6 and P_4O_{10} molecules, where it has been argued[26] that the bonds have considerable amounts of double bond character, it may well be true that the coplanarity condition for the configuration of such groupings is not stringent when other than first first-row atoms are involved because of the available *d* orbitals for bond formation. It should also be noted that the short S−S distances across the "cradle" (*ca.* 2.69 Å.) give an indication of the importance of the bond structures F, G and H. We believe that the stability of such structures as these and the choice between the two "cradle" structures for the sulfur nitride and realgar molecules depends to a large extent upon a delicate balance between the difference in sizes, coördination tendencies, and multiple-bond-forming powers of the two kinds of atoms on one hand and the difference in their electronegativities and the distribution of formal charges on the other. This helps us to understand why such molecules as N_4O_4 and P_4S_4 are unstable and are not known to exist.

It may be mentioned that our "cradle" structure for the sulfur nitride molecule is rather closely related to Arnold, Hugill and Hutson's model,[8] and also to the formula IV proposed by Ruff and Geisel[3] and supported by Meuwsen.[4] It is accordingly not surprising that our structure accounts satisfactorily for the chemical considerations Ruff and Geisel,[3] Meuwsen,[4] and Arnold, Hugill and Hutson[8] brought forward to support

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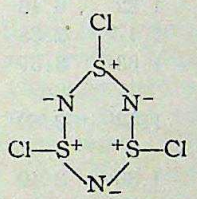
their respective formulas. Thus when sulfur nitride is hydrogenated the resulting substance $H_4N_4S_4$,[4] presumably has a ring structure with alternate sulfur and (imino) nitrogen atoms. (The structure of $H_4N_4S_4$ reported by Jaeger and Zanstra[5] cannot be correct for the same reasons which we have discussed in regard to their structure of sulfur nitride.) In the formation of the thiotrithiazyl ion[9] $(N_3S_4)^+$ on boiling sulfur nitride with acetyl chloride, the "cradle" structure with its eight-ring is apparently torn open, giving rise to an ion having possibly the following chain structure: $S{=}N-{}^+S{=}N-S-N{=}S$, which derives its stability from resonance between two identical bond structures. The molecule is also degraded on chlorination with the formation of $(SNCl)_3$,[4] which possibly has the structure



The existence of $(SNCl)_4$ is probable, although it has not been definitely established. Regarding the formation of coördination compounds of sulfur nitride with metallic chlorides such as $SnCl_4$ and $MoCl_4$,[32] Arnold, Hugill and Hutson's explanation[8] in terms of a "unique" sulfur atom in the sulfur nitride molecule is by no means necessary.

(32) O. C. M. Davis, *J. Chem. Soc.*, 1575 (1906); H. Wöbling, *Z. anorg. Chem.*, **57**, 280 (1908).

We wish to thank Dr. V. Schomaker for helpful suggestions and illuminating discussions.

Summary

Sulfur (S_8), orpiment (As_4S_6), sulfur nitride (S_4N_4), and realgar (As_4S_4) were studied by the method of electron diffraction. The S_8 molecule is a regular puckered-ring with S—S = 2.07 ± 0.02 Å. and ∠ S—S—S = 105 ± 2°, and it exhibits a rather large amplitude of thermal vibration. Orpiment sublimes at high temperatures, presumably to give As_4S_6 molecules which have the As_4O_6 structure and the following dimensions: As—S = 2.25 ± 0.02 Å., ∠ As—S—As = 100 ± 2° (∠ S—As—S = 114 ± 2°). The molecular structures of sulfur nitride S_4N_4 and realgar As_4S_4 cannot be established with certainty from the electron diffraction data alone, although several structures proposed by previous workers are definitely eliminated. We have shown that cradle-shaped configurations of an alternating eight-ring lead to satisfactory models. For sulfur nitride this "cradle" model consists of a bisphenoid of sulfur atoms and a square of nitrogen atoms, with N—S = 1.62 ± 0.02 Å., S—S = 2.69 Å., ∠ S—N—S = 112° and ∠ N—S—N = 106°. For realgar the model consists of a bisphenoid of arsenic atoms and a square of sulfur atoms with As—S = 2.23 ± 0.02 Å., As—As = 2.49 ± 0.04 Å., and ∠ As—S—As = 101 ± 4° (∠ S—As—S = 93°; ∠ S—As—As = 100°). These results are discussed, special attention being given to the unconventional sulfur nitride structure and its relation to the realgar structure.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Behavior of γ-Keto- and Aldehydo-Acid Derivatives at the Dropping Mercury Electrode. I. Esters and Anhydrides of 2-Benzoylbenzoic Acid

BY S. WAWZONEK,[1] H. A. LAITINEN AND S. J. KWIATKOWSKI

γ-Keto- and aldehydo-acids are of special interest since they and their derivatives can exist in two isomeric forms. Assignment of structure to these forms has been concerned mainly with the isomeric methyl and ethyl esters and has been accomplished both by chemical and physical means. Physical methods such as absorption spectra[2] and the use of refractive indices[3] have in general required both isomeric forms. Chemical methods used have been mainly generalizations. The most important of these is the rapid hydrolysis of the cyclic ester by means of concentrated sulfuric acid to give highly colored solutions in contrast to slow hydrolysis and a weaker color in the case of the normal esters.[4] Recent investigations have shown this test to be unsatisfactory in numerous cases.[5]

In this paper the use of the polarograph as a means of assigning structures to the esters of 2-benzoylbenzoic acid will be presented. The behavior of certain anhydrides at the dropping mercury electrode will likewise be mentioned. The study of certain amides of 2-benzoylbenzoic acid is described in the accompanying paper.[6] Work with other types of γ-keto- and aldehydo-acid derivatives is now in progress.

(1) Present address: Department of Chemistry, University of Tennessee, Knoxville, Tennessee.

(2) Hantzsch and Schwiete, *Ber.*, **49**, 215 (1916).

(3) (a) Egerer and Meyer, *Monatsh.*, **34**, 69 (1913); (b) von Auwer and Heinze, *Ber.*, **52**, 584 (1919).

(4) Meyer, *Monatsh.*, **25**, 477 (1904).

(5) (a) Blicke and Swisher, THIS JOURNAL, **56**, 904 (1934); (b) Newman and McCleary, *ibid.*, **63**, 1537 (1941).

(6) Wawzonek, Laitinen and Kwiatkowski, *ibid.*, **66**, 830 (1944).

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Results

The behavior of various esters and anhydrides of 2-benzoylbenzoic acid, their reduction products and related compounds was studied in both unbuffered and buffered media. A summary of the observed half-wave potentials and individual diffusion current constants in the various solutions is given in Tables I and II.

TABLE I

HALF-WAVE POTENTIALS AND INDIVIDUAL DIFFUSION CURRENT CONSTANTS OF 2-BENZOYLBENZOIC ACID DERIVATIVES AND RELATED COMPOUNDS IN VARIOUS SOLUTIONS

Compound	$\pi_{1/2}$ *vs.* S. C. E., volts	i_d, microamperes	C, millimoles/liter	i_d/C, microamperes/millimole/liter
0.1 *M* Tetrabutylammonium Iodide, 50% Dioxane				
Esters				
n-Methyl	1.51	3.51	0.87	4.03
	1.94	3.44		3.95
ψ-Methyl	1.85	5.33	0.83	6.53
n-Ethyl	1.49	4.95	1.34	3.86
	1.92	4.49		3.51
ψ-Ethyl	1.85	8.58	1.65	5.22
Phenyl (m. p. 83°)	1.30	3.69	1.07	3.45
	1.92	4.09		3.82
Phenyl (m. p. 162–163°)	1.53	2.85	0.77	3.70
	1.91	2.75		3.57
Thiophenyl (m. p. 112–113°)	1.17	3.75	1.15	3.36
	1.67	1.47		1.32
	1.92	2.92		2.62
Thiophenyl (m. p. 119–121°)	1.41	4.46	1.36	3.27
	1.91	4.16		3.05
β-Naphthyl (m. p. 103–105°)	1.25	3.02	1.00	3.02
	1.94	3.82		3.82
β-Naphthyl (m. p. 198–199°)	1.27	3.95	1.08	3.66
4-Bromophenyl (m. p. 92–94°)	1.22	4.15	1.05	3.95
	max.			
4-Bromophenyl (m. p. 170–172°)	1.47	4.29	1.05	4.09
	1.93	4.39		4.18
3-Phenylphthalide	1.89	3.90	1.00	3.90
Benzophenone	1.48	5.50	1.38	3.98
4′-Hydroxydiphenylphthalide	1.88	5.49	1.74	3.16
Ethyl benzoate	2.18	7.70	1.01	7.62
2-Benzoylbenzoic acid	1.11	1.87	1.00	1.87
	1.60	1.87		1.87
Benzoic acid	1.87	2.34	1.10	2.12
Acetic 2-benzoylbenzoic anhydride	1.48	3.90	1.00	3.90
	1.92	2.99		2.99
2-Benzoylbenzoic anhydride	1.28	2.73	1.00	2.73
	1.58	3.05		3.05
	1.90	2.60		2.60
3,3′-Diphenyldiphthalyl sulfide	1.35	2.92	0.82	3.56
	1.56	1.20		1.46
	1.91	1.90		2.32
0.1 *M* Hydrochloric Acid, 50% Dioxane				
2-Benzoylbenzoic acid	0.95	5.89	1.15	5.12

TABLE II

HALF-WAVE POTENTIALS AND INDIVIDUAL DIFFUSION CURRENT CONSTANTS OF 2-BENZOYLBENZOIC ACID DERIVATIVES IN BUFFERED MEDIA: BUFFER I

Compound	$\pi_{1/2}$ *vs.* S. C. E. volts	i_d, microamperes	C, millimoles/liter	i_d/C, microamperes/millimole/liter
Anthraquinone	0.63	2.61	1.06	2.50
Esters				
n-Methyl	1.33	4.71	1.19	3.96
ψ-Methyl	1.82	6.22	1.10	5.16
n-Ethyl	1.39	8.04	1.99	4.02
ψ-Ethyl	1.87	5.43	1.24	4.37
Phenyl (83°)	1.27	4.61	1.23	3.75
Phenyl (162–163°)	1.59	4.50	1.31	3.45
Thiophenyl	1.22	6.16	1.66	3.73
(112–113°)	1.47	2.38		1.43
	1.63	3.37		2.90
Thiophenyl (119–121°)	1.43	2.89	1.17	2.48
β-Naphthyl (103–105°)	1.30	3.49	1.07	3.26
β-Naphthyl (198–199°)	1.29	2.34	1.05	2.23
4-Bromophenyl (92–94°)	1.29	4.59	1.14	4.03
4-Bromophenyl (170–172°)	1.55	4.84	1.28	3.78
Benzophenone	1.33	6.28	1.38	4.55
Acetic 2-benzoylbenzoic anhydride	1.44	6.43	1.89	3.38
2-Benzoylbenzoic anhydride	1.20	5.57	0.82	6.75
3,3′-Diphenyldiphthalyl sulfide	1.15	3.71	0.82	4.53
2-Benzoylbenzoic acid	1.44	3.61	0.89	4.06
	BUFFER II			
Anthraquinone	0.76	2.65	1.06	2.50
Esters				
n-Methyl	1.51	4.19	1.13	3.75
ψ-Methyl	1.84	7.08	1.43	4.95
n-Ethyl	1.48	7.77	2.12	3.67
ψ-Ethyl	1.85	12.12	2.38	5.10
Phenyl (83°)	1.28	3.08	1.10	2.80
	1.53	0.79		0.72
	1.91	3.42		3.11
Phenyl (162–163°)	1.59	4.66	1.30	3.58
	1.93	1.28		0.99
Thiophenyl	1.15	4.12	1.29	3.20
(112–113°)	1.46	0.91		0.71
	1.69	1.32		1.02
Thiophenyl	1.42	4.02	1.36	2.96
(119–121°)	1.94	3.95		2.91
β-Naphthyl	1.29	4.99	1.65	3.03
(103–105°)	1.98	5.67		3.44
β-Naphthyl	1.30	4.19	1.18	3.55
(198–199°)	2.10	3.18		2.70
4-Bromophenyl (92–94°)	1.26	5.85	1.55	3.77

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TABLE II (*Concluded*)

Compound	$\pi_{1/2}$ *vs.* S. C. E. volts	*id*, micro amperes	*C*, millimoles/liter	*id*/*C*, micro amperes/millimole/liter
4-Bromophenyl (170–172°)	1.55	3.35	0.95	3.54
Benzophenone	1.45	9.91	2.40	4.13
Acetic 2-benzoylbenzoic anhydride	1.52	5.17	1.50	3.42
	1.91	1.72		1.14
2-Benzoylbenzoic anhydride	1.27	1.61	0.72	2.25
	1.55	3.06		4.28
	1.89	1.06		1.48
3,3′-Diphenyl diphthalyl sulfide	1.28	2.88	0.69	4.16
	1.48	1.03		1.48
	1.91	1.57		2.26
2-Benzoylbenzoic acid	1.53	5.23	1.31	4.00

In general all of the compounds gave well-defined reduction waves. Maxima could be suppressed in most cases by means of gelatin. Addition of gelatin was noticed to cause a catalytic hydrogen discharge wave which decreased the voltage range of the buffers and prevented evaluation of waves at more negative potentials.

Absolute *p*H values for the buffers are not given because erratic behavior of hydrogen electrodes made accurate measurements impossible. Comparative values however were determined from the half-wave potentials obtained for anthraquinone. Buffer II was found to be 2.2 *p*H units more alkaline than buffer I.

Discussion of Results

An examination of the half-wave potentials obtained in 0.1 *M* tetrabutylammonium iodide–50% dioxane solution, in which a wide range of potential is possible, indicates that in general all the esters of 2-benzoylbenzoic acid are reduced to the same product, 3-phenylphthalide. A final wave of approximately 1.9 volts, which is characteristic of 3-phenylphthalide, is obtained in practically every case. The cyclic methyl and ethyl esters, apparent exceptions, are reduced at such negative potentials that their wave is combined with that of the resulting 3-phenylphthalide and only one wave with a much higher diffusion current constant than that observed for the other esters is obtained. The formation of such a product from the cyclic derivatives indicates that these compounds are reduced directly to 3-phenylphthalide and ROH (RSH). The normal derivatives on the other hand, must be first reduced to the benzhydrol and then lose ROH (RSH) spontaneously to form 3-phenylphthalide. Further reduction of 3-phenylphthalide probably involves the CO grouping and not the lactone linkage since ethyl benzilate, a vinylog of 3-phenylphthalide, showed no reduction whereas ethyl benzoate can be reduced at the dropping mercury electrode.

Data obtained from the half-wave potentials in buffers I and II indicate that the esters can be divided into two classes. One group which includes the cyclic methyl and ethyl esters is characterized by a stability toward hydrolysis in the more alkaline buffer II, and by half-wave potentials which are independent of *p*H. The stability of this class toward alkali is not surprising since they are ketal-like in structure. A comparison of the half-wave potentials of this group indicates that the ease of reduction increases with increasing ionization constant of the alcohol or phenol concerned. Thus the thiophenyl ester is the easiest to reduce while the reduction of the methyl and ethyl esters becomes more difficult in that order. This behavior is in agreement with the mode of reduction of these compounds to 3-phenylphthalide. This class contains without doubt all the cyclic esters and by coincidence contains the higher melting isomers.

The second class of compounds which contains the normal ethyl and methyl esters is rather irregular in its behavior. The variation of half-wave potentials for the aliphatic esters, ethyl and methyl, with *p*H is similar to that for benzophenone. The shift in value in buffer II, however, may be due to hydrolysis to the acid. The aromatic esters on the other hand are reduced at approximately the same potential of 1.28 volts in both buffers. In the more alkaline buffer II the phenyl ester is slightly hydrolyzed since it gives in addition to the wave at 1.28 volts, a wave with a half-wave potential of 1.53 volts which is characteristic of the acid. The thiophenyl ester gives waves at 1.22, 1.47 and 1.63 volts. The wave at 1.47 volts indicates the probable presence of some of the cyclic derivative. No explanation can be offered for the wave at 1.63 volts. The behavior of this class, provided no interaction has taken place with the buffers, is surprising since due to their structural similarity to benzophenone their half-wave potentials would be expected to vary with *p*H. The similarity in behavior of the isomeric β-naphthol esters as far as the half-wave potentials are concerned is anomalous and is being investigated further. This second class contains all the lower melting esters and must without doubt consist of the normal esters.

The behavior of 2-benzoylbenzoic acid in unbuffered medium, 0.1 *M* tetrabutylammonium iodide–50% dioxane is rather difficult to explain. Neither of the two waves obtained at 1.11 and 1.60 volts, respectively, represents a hydrogen wave since benzoic acid which has approximately the same acidity gives a curve with a half-wave potential of 1.87 volts. The first wave at 1.11 volts no doubt represents a reduction by a mechanism possible only in acid media, the acid being provided by the compound itself. This interpretation is confirmed by results obtained for 2-benzoylbenzoic acid in 0.1 *N* hydrochloric acid, 50% dioxane solution in which a wave with a half-wave potential of 0.95 volt was obtained. After 50% of the acid is reduced in the 0.1 *M* tetra-

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butylammonium iodide, 50% dioxane solution, the solution around the drop is no longer acid and a second type of reduction occurs.

The nature of this reduction is not clear but it may possibly be a reduction of the pseudo acid. This same type of reduction appears with some of the anhydrides. In buffered media where the acid is present as an anion, the ion must exist in the open form since the half-wave potential changes with *p*H. Such a behavior is in agreement with absorption spectra data obtained in dilute alkali.[2]

No definite structures can be assigned to the anhydrides due to the fact that they are hydrolyzed or interact with the more alkaline buffer II. The mixed acetic anhydride is largely hydrolyzed in both buffers, and gives a reduction wave characteristic of the 2-benzoylbenzoate ion. The anhydride and 3,3′-diphenyldiphthalyl sulfide are apparently stable in buffer I. The approximately equal reduction potentials observed for these two compounds in buffer I would suggest similar structures provided no interaction has occurred with the buffer.

Experimental

The current–voltage curves were determined with a Model XI, Heyrovsky Polarograph having a current scale calibrated in microamperes. Curves for anthraquinone in buffer I and II were obtained with a Fisher Elecdropode. No changes in anode potential with increasing potential was observed with either of these buffers.

The electrolysis cell had a simple cylindrical shape with a mercury pool anode and was provided with side arms for anode connections and for admission of nitrogen for the removal of dissolved oxygen. Anode potentials were measured against a saturated calomel electrode (S. C. E.) by using a sintered glass salt bridge of the type described by Laitinen.[7]

(7) H. A. Laitinen, *Ind. Eng. Chem., Anal. Ed.*, **13**, 393 (1941).

The dropping mercury electrode had the following characteristics. At a pressure of 46.5 cm. of mercury, the drop time in the solvent used was 3.34 seconds (open circuit). The value of m was 2.05 mg. sec.$^{-1}$ with a calculated value of $m^{2/3}t^{1/6}$ of 1.973 mg. $^{2/3}$ sec.$^{-1/2}$.

Materials.—The solutions used had the following compositions and anode potentials: 0.1 *M* tetrabutylammonium iodide,[8] 50% dioxane, anode potential, −0.400 volt; 0.1 *M* hydrochloric acid, 50% dioxane, anode potential, −0.249 volt.

Buffer I.—A mixture which was 0.172 *M* in tetramethylammonium hydroxide, 0.1 *M* in tetramethylammonium iodide, 0.102 *M* in phosphoric acid and 50% dioxane by volume, anode potential, −0.390 volt.

Buffer II.—A mixture which was 0.196 *M* in tetramethylammonium hydroxide, 0.10 *M* in tetramethylammonium iodide, 0.092 *M* in phosphoric acid and 50% dioxane by volume, anode potential, −0.382 volt.

2-Benzoylbenzoic acid, benzophenone, benzoic acid, ethyl benzoate and anthraquinone were obtained from stock. The aromatic esters,[5a,9] 3-phenylphthalide,[10] 4′-hydroxydiphenylphthalide,[11] anhydrides,[12] 3,3′-diphenyldiphthalyl sulfide,[13] methyl,[4] and ethyl esters[3] were prepared by appropriate methods given in the literature.

Summary

The polarographic method is a suitable means of distinguishing between the cyclic and normal esters of 2-benzoylbenzoic acid.

The anhydrides of 2-benzoylbenzoic acid cannot be assigned structures with certainty since they hydrolyze in more alkaline solutions.

(8) Laitinen and Wawzonek, THIS JOURNAL, **64**, 1765 (1942).

(9) The authors wish to thank Dr. F. F. Blicke for small amounts of the isomeric thiophenyl and B-naphthyl esters which were used for mixed melting points with the compounds prepared for this study.

(10) Ullmann, *Ann.*, **291**, 23 (1896).

(11) Blicke and Swisher, THIS JOURNAL, **56**, 923 (1934).

(12) Freiherr and Von Pechmann, *Ber.*, **14**, 1865 (1881).

(13) O'Brochta and Lowy, THIS JOURNAL, **61**, 2766 (1939).

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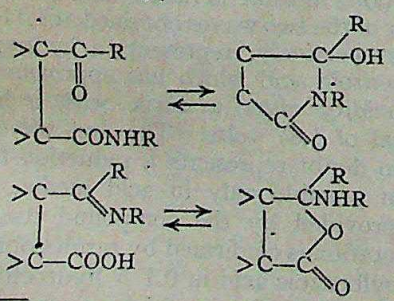
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Behavior of γ-Keto- and Aldehydo-Acid Derivatives at the Dropping Mercury Electrode. II. Amides of 2-Benzoylbenzoic Acid[1]

BY S. WAWZONEK,[2] H. A. LAITINEN AND S. J. KWIATKOWSKI

Amides of γ-keto- and aldehydo-acids can exist in two isomeric forms and can exhibit ring-chain tautomerism of the types



(1) Paper I, THIS JOURNAL, **66**, 827 (1944).

(2) Present address: Department of Chemistry, University of Tennessee, Knoxville, Tennessee.

Chemical evidence can indicate what type of ring-chain tautomerism exists or is possible but does not as a rule denote which form is the predominant one.

In this paper the use of the polarograph as a means of ascertaining the type and the approximate amount of ring-chain tautomerism present with amides of 2-benzoylbenzoic acid will be presented.

Results

The behavior of various amides of 2-benzoylbenzoic acid and their derivatives was studied in both unbuffered and buffered media. A summary of the observed half-wave potentials and individual diffusion current constants in the various solutions is given in Table I.

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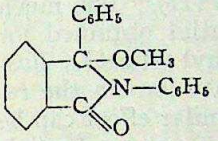
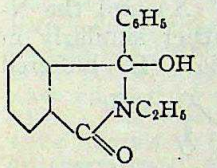
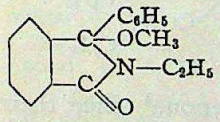
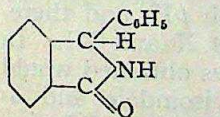
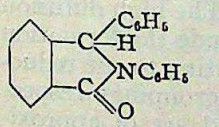
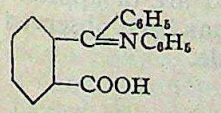
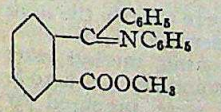
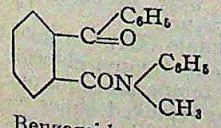
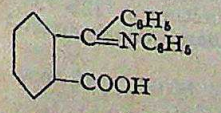
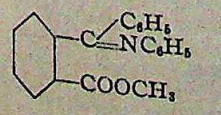
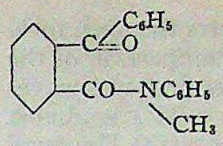
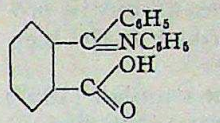
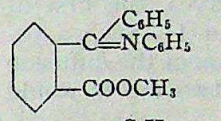
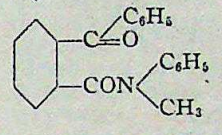
TABLE I

HALF-WAVE POTENTIALS AND DIFFUSION CURRENT CONSTANTS FOR THE AMIDES OF 2-BENZOYLBENZOIC ACID, THEIR DERIVATIVES AND RELATED COMPOUNDS IN VARIOUS SOLUTIONS

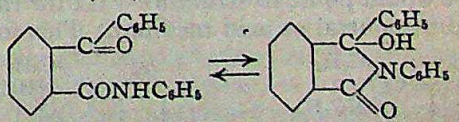
Compound	$E_{1/2}$ vs. S. C. E. volts	i_d, microamperes	c, millimoles/liter	i_d/c microamperes/millimole/liter
0.1 *M* Tetrabutylammonium Iodide, 50% Dioxane				
n-Anilide (m. p. 195°)	1.48	3.12	1.00	3.12
	max.	0.91		0.91
	2.20	3.59		3.59
	1.88	4.62	1.33	3.48
	2.20	5.56		4.19
Amide	1.52	1.36	1.00	1.36
	1.94	2.53		2.53
	2.26	4.42		4.42
	2.06	4.42	1.99	3.56
	2.22	5.74		4.54
	1.95	3.59	0.90	4.00
	2.38	5.19		5.76
	2.25	4.16	1.00	4.16
	2.16	4.42	1.00	4.42
	0.96	1.74	1.00	1.74
	1.70	2.21		2.21
	1.42	3.77	1.00	3.77
	2.11	5.85		5.85
	1.46	3.64	1.00	3.64
	1.97	6.37		6.37
Benzamide	1.82	10.14	1.10	9.21
Buffer I				
	1.15	2.24	0.82	2.72
	1.32	3.14	0.92	3.43
	1.30	4.92	1.16	4.24
Buffer II				
	1.61	4.36	1.01	4.33
	1.45	3.83	0.85	4.52
	2.15	5.02		5.94
	1.48	3.61	1.12	3.22
	2.05	4.38		3.91

In general all of the compounds gave well-defined reduction waves. Maxima could be suppressed in most cases by means of gelatin. The buffers used are the same as those reported in the first paper.[1] No curves were obtained for the amide or anilide (195°) in buffer I.

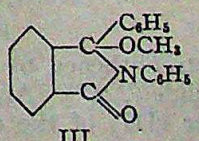
Discussion of Results

An examination of the half-wave potentials obtained in 0.1 *M* tetrabutylammonium iodide, 50% dioxane solution indicates that the amides and their derivatives are reduced in most cases to the corresponding 1-keto-3-phenylisoindole. In each case the final wave obtained corresponds to the values obtained for the related 1-keto-3-phenylisoindole. Both forms apparently yield the same reduction product through mechanisms similar in nature to those proposed for the production of 3-phenylphthalide from the normal and cyclic esters.[1] The normal N-methylanilide and anil-type compounds are reduced in a slightly different manner and will be discussed later.

The anilide (195°) assigned an open structure by Meyer[3] gave three waves. The first wave at 1.48 volts must be due to the reduction of the open form I since such a wave is not shown by the methyl ether (III). The second wave which could



I II



III

not be measured because of a maximum is due to the reduction of the cyclic form (II) and would without doubt be similar in value to the first wave obtained for the methyl ether (III). Disappearance of the wave at 1.48 volts in buffer I

(3) Meyer, *Monatsh.*, **28**, 1211 (1907).

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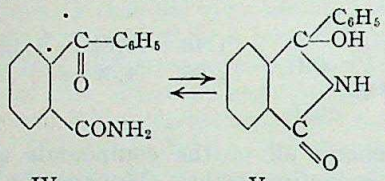
indicates that alkali easily converts the open form (I) into the cyclic form (II). Comparison of the diffusion current constants of the first two waves would indicate that the anilide (195°) is almost completely present as the open form (I). The small amount of the cyclic form (II) present may be produced by the hydroxide ions formed at the mercury drop during the reduction.[4]

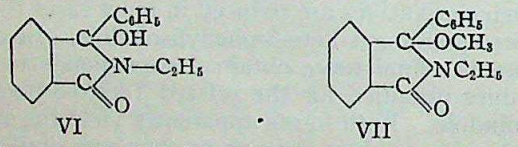
The amide is very similar to the *n*-anilide (195°) in its behavior giving three waves, the first at 1.52 volts disappearing in buffer I. Such a behavior together with a comparison of the diffusion current constants for the first two waves would



IV V

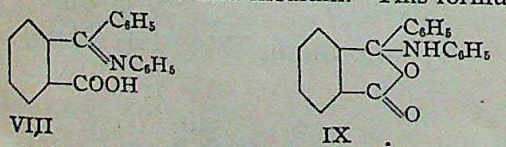
indicate an equilibrium structure for the amide in which approximately one-third is present as the open form (IV) and the remainder as the cyclic derivative (V).

The N-ethylamide (VI) gives only two waves which are very similar to those obtained for its methyl ether (VII). Such a behavior points to the existence of the N-ethylamide entirely in the cyclic form.



VI VII

The anilide (221°), which has been assigned the cyclic form (II) in neutral solution by Meyer,[3] exhibits a behavior at the dropping mercury electrode which is not in accordance with this structure. In unbuffered medium this compound's behavior resembles that of 2-benzoylbenzoic acid[1] in that an early reduction is obtained at 0.96 volt. This wave represents without doubt the reduction of the anil grouping in acid medium, the acid being provided by the compound itself. Such a behavior would point to structure VIII for the compound in neutral or acid medium. This formula-

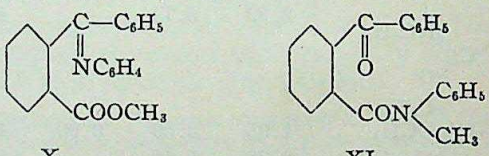


VIII IX

tion is further strengthened by the chemical behavior of the anilide (221°). Attempts to prepare the methyl ether (III) of the cyclic form using methanol and hydrochloric acid gave only the normal methyl ester of 2-benzoylbenzoic acid.

The behavior of the anilide (221°) in buffer I is somewhat irregular. The low diffusion current constant and positive half-wave potential (−1.15 volts) obtained are not in agreement with an anil structure for this compound in this buffer. The values would be expected to be similar to those obtained for the methyl ester (X). If the compound had a cyclic structure (IX), the value would likewise be expected to be more negative since cyclic forms are more difficult to reduce. In buffer II the value of −1.60 volts obtained is in agreement with the anil structure (VIII). The much more negative half-wave potential obtained for this compound than for the methyl ester (X) illustrates the effect of a carboxylate ion on the reduction of the anil group. A similar effect can be seen from a comparison of the half-wave potentials of 2-benzoylbenzoic acid and the normal methyl ester in buffer I.[1]

The methyl ester of the anil (X) and the N-methylanilide (XI) behaved rather similarly in buffered and unbuffered media. In buffered



X XI

media they resembled benzophenone[1] since their half-wave potentials varied with *p*H, and therefore they must have structures X and XI. In unbuffered media the final waves obtained would indicate the formation of an isoindole and 3-phenylphthalide, respectively. The high diffusion currents obtained however preclude the formation of such compounds, instead pointing to the reductions of the ester and anilide groupings respectively, since the values obtained are of approximately the same magnitude as has been observed for ethyl benzoate and benzamide.

Experimental[5]

The conditions and electrode used were exactly the same as described in the first paper of this series.[1]

Materials.—The amide,[6] anilides, anil, methyl ester of the anil, 1-keto-2,3-diphenylisoindole,[3] 1-keto-3-phenylisoindole[7] and N-ethylamide[8] were prepared by appropriate methods given in the literature.

1-Keto-2,3-diphenyl-3-methoxyisoindole (III).—A solution of the anilide (195°) (I) (1.0 g.) in thionyl chloride (10 ml.) was allowed to stand at room temperature for one hour. The excess thionyl chloride was removed under reduced pressure, the resulting solution treated with methanol (75 ml.) and allowed to stand for twelve hours. Addition of water followed by concentration in an air stream gave a white solid (1.0 g.) melting at 125–128°. After two recrystallizations from methanol the compound melted at 128–129°.

Anal. Calcd. for $C_{21}H_{17}O_2N$: C, 80.00; H, 5.40. Found: C, 79.97; H, 5.66.

(4) The estimation of the relative concentrations of the two tautomeric forms relative wave heights is based on the assumption that the rate of the tautomeric shift at the electrode surface is negligibly slow. Two opposing effects should be recognized. A shift to the more easily reduced open form because of its depletion would cause an abnormally high first wave to be obtained. However, the opposite shift is catalyzed by the hydroxyl ions produced at the electrode surface. The estimates of relative amounts of cyclic and open forms should be considered only semi-quantitative.

(5) Melting points are not corrected.

(6) Graebe and Ullmann, *Ann.*, **291**, 8 (1896).

(7) Rose, THIS JOURNAL, **33**, 388 (1911).

(8) Sachs and Ludwig, *Ber.*, **37**, 388 (1904).

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The compound could likewise be prepared in the following manner. A solution of the anilide (195°) (I) (1.0 g.) in methanol (100 ml.) treated with concentrated hydrochloric acid (2 ml.), was allowed to stand at room temperature for seven hours and then refluxed for eleven hours. The resulting solution was neutralized with a sodium carbonate solution, treated with water until precipitation occurred and then concentrated with an air stream. The white solid (1.0 g.) obtained melted at 128–129° and was identical with the compound from the thionyl chloride method.

The anil (221°) (VIII) when treated in a similar fashion to the above gave the normal methyl ester of 2-benzoylbenzoic acid.

Hydrolysis of 1-Keto-2,3-diphenyl-3-methoxyisoindole (III).—A solution of 1-keto-2,3-diphenyl-3-methoxyisoindole (III) (1.0 g.) in acetic acid (20 ml.) and concentrated hydrochloric acid (2 ml.) was allowed to stand for seventeen hours at room temperature. During this time white crystals (0.60 g.) melting at 195–197° separated. An additional amount (0.25 g.) was obtained by addition of water to the filtrate. A mixture with the anilide (195°) (I) gave no lowering when melted together.

1-Keto-2-ethyl-3-methoxy-3-phenylisoindole (VII).—A solution of the N-ethylamide (VI) (1.0 g.) in thionyl chloride (10 ml.) was allowed to stand at room temperature for twenty minutes. The excess thionyl chloride was removed under reduced pressure, methanol (50 ml.) added and the resulting solution allowed to stand at room temperature for eleven hours. Addition of water gave an oil which was taken up in ether and washed with a sodium carbonate solution. Removal of the ether gave an oil which gave white crystals (0.72 g.) upon the addition of 30–60° petroleum ether. After two crystallizations from the same solvent the compound melted at 73–75°.

Anal. Calcd. for $C_{17}H_{17}O_2N$: C, 76.40; H, 6.36. Found: C, 76.33; H, 6.68.

The compound (VII) could likewise be prepared in the following way. A solution of the N-ethylamide (VI) (1.0 g.) in methanol (40 ml.) and concentrated hydrochloric acid (1 ml.) was allowed to stand at room temperature for fourteen hours and then refluxed for ten hours. Neutralization with sodium carbonate followed by concentration in an air stream gave an oil which formed white crystals (0.45 g.) melting at 75–78° which were identical with the above (VII).

Hydrolysis of 1-Keto-2-ethyl-3-methoxy-3-phenylisoindole (VII).—A solution of 1-keto-2 ethyl-3-methoxy-3-phenylisoindole (VII) (0.5 g.) in a mixture of glacial acetic acid (10 ml.) and concentrated hydrochloric acid (1 ml.) was allowed to stand for twelve hours and poured into water. The N-ethyl amide (VI) (0.4 g.) thus obtained melted at 170–173° and gave no lowering when mixed with an authentic sample.

Normal N-Methyl Anilide (XI).—To a cold solution of the acid chloride of 2-benzoylbenzoic acid, prepared from the acid (7.5 g.) and thionyl chloride, in benzene (20 ml.), methylaniline (10 ml.) in dry benzene (10 ml.) was added and the resulting solution allowed to stand for twenty-four hours at room temperature and then poured into water. Extraction with ether followed by washing with dilute acid and sodium bicarbonate gave an oil upon removal of the solvent. The oil upon being taken up in a mixture of benzene and (80–90°) petroleum ether gave, after treatment with norite and aluminum oxide, upon cooling, white crystals (1.5 g.) (XI) which melted at 125–140°. Two crystallizations from the same mixture gave white crystals melting at 144–146°.

Anal. Calcd. for $C_{21}H_{17}O_2N$: C, 80.00; H, 5.39. Found: C, 80.23; H, 5.49.

Summary

The polarographic method offers a suitable means of ascertaining the type and the approximate amount of ring-chain tautomerism present with amides of 2-benzoylbenzoic acid.

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[CONTRIBUTION FROM THE RESEARCH DIVISION OF THE GENERAL PRINTING INK CORPORATION]

Orientation in the Biphenyl System.[1] Derivatives of 2-Aminobiphenyl[2]

BY A. H. POPKIN, G. M. PERRETTA AND R. SELIG

As a continuation of the studies of orientation in the biphenyl system, it was decided to prepare 2-dimethylaminobiphenyl and to observe its behavior in various reactions. This compound should prove more versatile than the 4-isomer[3] because of the possible existence of an activated hydrogen in the 5 position in competition with the known activity of the 4′ hydroxygen.[1,4]

Evans and Williams[5] reported the preparation of 2-dimethylaminobiphenyl in 94% yield from the reaction of dimethyl sulfate on 2-aminobiphenyl. In duplicating this reaction, a 92% yield of methylated product was obtained. On treatment with acetic anhydride followed by distillation, 2-dimethylaminobiphenyl and 2-(N-methyl)-acetamidobiphenyl were obtained in 66:34 ratio. This indicates that the yield previously reported is for a mixture of dimethyl and monomethyl compounds rather than pure dimethyl compound.

The action of methyl alcohol and sulfuric acid on 2-aminobiphenyl at elevated temperature and pressure gave 82–85% yields of a methylated mixture. This when acetylated was found to consist of 2-dimethylaminobiphenyl and 2-(N-methyl)-acetamidobiphenyl in the ratio of 87:13. The identity of the latter was established by analysis and synthesis in 84% yield by the reaction of sodium and methyl iodide on a solution of 2-acetamidobiphenyl in dry xylene.

2-(N-Methyl)-acetamidobiphenyl showed a greater stability toward hydrolysis than 2-acetamidobiphenyl and its derivatives[6] which is in agreement with the observation of Schoorl[7] on the stability of N-methylacetanilide.

(1) Previous paper, Popkin and McVea, THIS JOURNAL, **66**, 796 (1944).

(2) Presented before the Division of Organic Chemistry, Cleveland meeting of the American Chemical Society, April, 1944.

(3) Banus and Tomas, *Anal. Fis. Quim.*, **19**, 293 (1921); Vorländer, *Ber.*, **58**, 1913 (1925); Bell and Kenyon, *J. Chem. Soc.*, 2705 (1926); Kenyon and Robinson, *ibid.*, 3050 (1926).

(4) Popkin, THIS JOURNAL, **65**, 2043 (1943).

(5) Evans and Williams, *J. Chem. Soc.*, 1199 (1939).

(6) Popkin and Perretta, THIS JOURNAL, **65**, 2046 (1943).

(7) Schoorl, *Pharm. Weekblad*, **78**, 433 (1941).

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A preliminary study of the behavior of 2-dimethylaminobiphenyl indicated the existence of a para-bond activation similar to that in dimethylaniline. When dimethylaniline is oxidized with cupric chloride[8] Methyl Violet is formed. Oxidation of 2-dimethylaminobiphenyl under the same conditions resulted in a dyestuff having color and lake-forming properties characteristic of triphenylmethane dyes of the Methyl Violet type.

Experimental

Preparation of 2-Dimethylaminobiphenyl: Method 1.—Into a 2-liter beaker was placed 254 g. of 2-aminobiphenyl (Monsanto Chemical Company). To this was added slowly and with stirring 675 g. of dimethyl sulfate and 270 g. of 30% aqueous sodium hydroxide solution, the addition requiring four hours. The dimethyl sulfate was added in approximately 15-g. portions, each followed by a portion of sodium hydroxide solution until neutrality was obtained. The temperature was maintained below 30°. An additional 130 cc. of the sodium hydroxide solution then was required to bring about complete neutrality. The product was present as two layers. The upper layer, after separation and washing with two portions of 150 cc. of water, weighed 270 g., 92% yield. This was treated with 57 g. of acetic anhydride. A temperature rise of ten degrees was obtained indicating a substantial quantity of *n*-monomethylaminobiphenyl. The product was distilled at 30 mm. pressure through a Claisen flask to give: fractions 1 and 2, 26.5 g., 33–130°; 3–7, 161.8 g., 130–190°; 8 and 9, 84.0 g., 190–225°; 10, residue, 13.0 g.

Fractions 1 and 2 contained acetic acid and acetic anhydride. Fractions 3–7 are 2-dimethylaminobiphenyl, 0.82 mole, and 8–10 are 2-(N-methyl)-acetamidobiphenyl, m. p. 79–87°, 0.43 mole. This represents a ratio of 66% of dimethylaminobiphenyl to 34% of monomethyl compound.

Fractions 3–7 were redistilled through an efficient fractionating column of the total condensation, variable take-off type[9] having twelve theoretical plates. Acetic anhydride was not present in the first fractions and no appreciable residue was obtained. The purified 2-dimethylaminobiphenyl boiled at 115–116° (2–3 mm.); $n^{20}D$ 1.6052–1.6058.

Purification of a portion of fractions 8–10 by crystallization from a petroleum hydrocarbon (70–95°) gave 2-(N-methyl)-acetamidobiphenyl, m. p. 98–99°.

Anal. Calcd. for $C_{15}H_{15}NO$: C, 80.0; H, 6.71; N, 6.22. Found: C, 80.6; H, 6.77; N, 6.30.

Two similar reactions gave checking yields and comparable ratios of 2-dimethylaminobiphenyl and 2-(N-methyl)-acetamidobiphenyl.

Method 2.—A mixture was made of 67 g. of 2-aminobiphenyl, 74 g. of absolute methyl alcohol and 7 g. of concd. sulfuric acid. This was heated in an autoclave for five hours at 205–210° and 420–490 lb. pressure. The resulting mixture was brought to *p*H 11 with a 10% sodium hydroxide solution and the oil which formed was extracted with ether. The solvent was removed in a Claisen flask and the oil distilled at 143–147° (10 mm.); wt. 65.6 g., 85% yield. Several similar reactions gave 82–85% yield.

Treatment of this product with acetic anhydride and careful fractionation through an efficient column gave 2-dimethylaminobiphenyl, b. p. 118–120° (2.5 mm.), $n^{20}D$ 1.6046–1.6050, and a residue of 2-(N-methyl)-acetamidobiphenyl, m. p. 83–91°. Purification by crystallization from a low-boiling petroleum hydrocarbon resulted in crystals, m. p. 98–99°, which when mixed with the same material obtained above gave an identical melting point. The ratio of 2-dimethylaminobiphenyl to monomethyl compound was 87:13.

It was thought that the discrepancy in the boiling point and refractive index of 2-dimethylaminobiphenyl from the values obtained by Method 1 might be due to the presence of traces of 2-monomethylaminobiphenyl. A second treatment of the purified material with acetic anhydride followed by redistillation produced no change in the constants.

Preparation of 2-(N-Methyl)-acetamidobiphenyl.—A solution was made of 31.5 g. of 2-acetamidobiphenyl, m. p. 119–120°, in 200 cc. of dry xylene. To this was added 5 g. of metallic sodium and the mixture heated at 120–130° for three hours. A clear xylene solution was decanted from the excess of sodium and treated with 25 g. of methyl iodide. The mixture was refluxed and within fifteen minutes a white precipitate was formed. The xylene then was removed by heating and a thick white paste resulted. This was treated with 100 cc. of water and dilute acetic acid added to bring the *p*H to 6. The remaining xylene was removed by steam distillation until the density of the oil was greater than that of the water solution. The two phases were brought to room temperature, the upper aqueous portion decanted, and the oil washed with 300 cc. of water. This treatment converted the oil to a solid, m. p. 90–95°, wt. 28.2 g., 84% yield. One purification with Norite and two recrystallizations from a petroleum fraction (70–95°) gave crystals, m. p. 96–98°. A mixed m. p. with 2-(N-methyl)-acetamidobiphenyl (above) gave no depression in the melting point.

Stability of 2-(N-Methyl)-acetamidobiphenyl toward Hydrolysis.—Treatment of 2.5 g. of 2-(N-methyl)-acetamidobiphenyl in methyl alcohol solution with 5 cc. of concd. hydrochloric acid during fifteen minutes at reflux temperature[6] gave only unreacted 2-(N-methyl)-acetamidobiphenyl. Addition of 5 cc. of concd. hydrochloric acid to 1.5 g. of the same material resulted in a clear solution which when refluxed for fifteen minutes again gave the unhydrolyzed starting material. The reaction of 4 g. of the 2-(N-methyl)-acetamidobiphenyl, dissolved in 150 cc. of alcohol, with 3 cc. of a 30% sodium hydroxide solution at reflux temperature for ten hours,[7] produced only unreacted 2-(N-methyl)-acetamidobiphenyl.

Oxidation of 2-Dimethylaminobiphenyl.—A mixture of 2-dimethylaminobiphenyl, cupric sulfate, phenol, salt and water was treated in the usual manner.[8] A colored base thus was obtained corresponding to a Methyl Violet which has a phenyl group ortho to each of the three methylamino groups. It has the properties characteristic of Methyl Violet, resulting from oxidized dimethylaniline, *i. e.*, it forms a blue-violet solution with organic acids and alcohols, dissolves in concd. hydrochloric acid to give a reddish-brown solution which turns green and then blue on continued dilution with water, and forms insoluble tannic acid and phosphomolybdic acid salts.

Acknowledgment.—The authors are indebted to the General Printing Ink Corporation for permission to publish this work.

Summary

2-Dimethylaminobiphenyl was oxidized with cupric chloride to give a triphenylated Methyl Violet dyestuff indicating the existence of an active hydrogen in the 5 position.

The preparation of 2-dimethylaminobiphenyl by the reaction of 2-aminobiphenyl either with dimethyl sulfate or with methyl alcohol also gave the monomethyl compound, which was separated as 2-(N-methyl)-acetamidobiphenyl.

The stability of 2-(N-methyl)-acetamidobiphenyl toward hydrolysis is in agreement with the similar stability of N-methylacetanilide.

NEW YORK, N. Y. RECEIVED FEBRUARY 10, 1944

(8) Rowe, "Colour Index," Society of Dyers and Colorists, First Ed., 1924, p. 174.

(9) Whitmore and Lux, THIS JOURNAL, 54, 3448 (1932).

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[COMMUNICATION NO. 965 FROM THE KODAK RESEARCH LABORATORIES]

Sulfonamides in the Benzimidazole, Benzothiazole and Benzotriazole Series

BY C. F. H. ALLEN, ALAN BELL AND C. V. WILSON

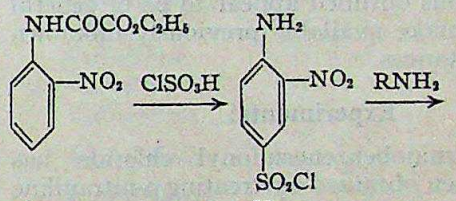
Conspicuously absent from the chemical literature are sulfonamides in the benzimidazole, benzothiazole and benzotriazole series. One reason for this may have been the lack of the corresponding sulfonic acids until the last decade.[1,2] Moreover, although the sulfonic acids are now available, they cannot be converted into the necessary sulfonyl chlorides by the usual methods, nor can the chlorides be prepared by the use of chlorosulfonic acid. A reaction appears to take place between this reagent and the heterocycle, but it is one of salt formation, for, on making the reaction product alkaline, the starting material is recovered unchanged. Benzimidazoles, however, after several hours of treatment with chlorosulfonic acid,[2] yield a sulfonic acid. Benzotriazole does not give a sulfonic acid under the same conditions; N-acetylbenzotriazole was unaffected by this reagent.

As a general reaction, the formation of sulfonic acids by ring closure of suitable *ortho* diamines is of doubtful utility, owing to the inaccessibility of the requisite starting materials, except 3,4-diaminobenzenesulfonic acid.[3,4,5,6] Even in this last instance we have failed to find references to the benzimidazole-5-sulfonic and benzotriazole-5-sulfonic acids, but we have found their preparations to be straightforward.

However, if there were other reactive groups in the molecule, the conversion of $-SO_3H$ to $-SO_2Cl$, without attacking the substituents, would be very difficult, even if it were possible. Since we had some interest in 2-mercapto derivatives, this method could not be used. A 2-mercaptobenzothiazole-5-sulfonic acid,[7] salts of 2-mercaptobenzimidazole-5-sulfonic acid,[8] and a benzotriazolesulfonic acid,[9] have been reported previously. 2-Aminobenzothiazole-6-sulfonamide appears in a table of compounds in a recent paper,[10] but its original source was not available nor was a method of preparation indicated.

Two procedures were therefore devised, whereby the sulfonamido group was introduced into the molecule prior to ring closure. The starting materials were relatively simple known substances.

In the first procedure, ethyl *o*-nitrophenyloxamate I,[11] was converted to 3-nitro-4-aminobenzenesulfonyl chloride in a single reaction by a treatment with chlorosulfonic acid—the protecting group was hydrolyzed off during the manipulation.



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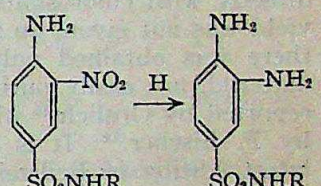
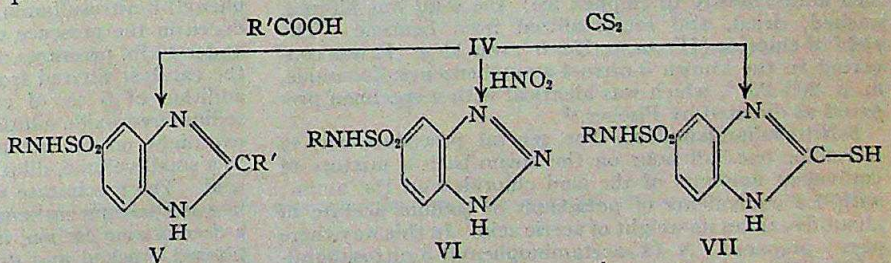


III IV

The sulfonyl chloride II was then treated with an amine to form a sulfonamide III. Finally, the nitro group was reduced and the resulting diamine IV closed to whatever heterocyclic ring system was desired. By this procedure there were prepared 5-sulfonamidobenzimidazoles V, 5-sulfonamidobenzotriazole VI, (R = H), and 2-mercapto-5-sulfonamidobenzimidazoles, VII.



V VI VII

The second procedure started with the known[12] 3-nitro-4-chlorobenzenesulfonyl chloride, which was converted into a sulfonamide VIII. Upon treatment with hydrazine, this afforded 6-sulfonamidobenzazimidoles IX, whereas with carbon disulfide and sodium polysulfide, 2-mercapto-5-sulfonamidobenzothiazoles X resulted.

Von Auwers[13] described an indazolesulfonyl-chloride, prepared from a sodium indazolesulfon-

(1) Sulfonation of benzimidazoles, (a) Swiss Patent 163,005; 164,730-6 [*C. A.*, **28**, 2918 (1934)]; (b) German Patent 578,488 [*Frdl.*, **20**, 843 (1935)]; (c) U. S. Patent 2,036,525 [*C. A.*, **30**, 3546 (1936)].

(2) Use of chlorosulfonic acid: (a) German Patent 605,687 [*Frdl.*, **21**, 1279 (1937)]; (b) French Patent 45,661 [*C. A.*, **30**, 3910 (1936)].

(3) Zincke and Kuchenbecker, *Ann.*, **330**, 23 (1904).

(4) Nietzki and Lerch, *Ber.*, **21**, 3221 (1888).

(5) Post and Hardtung, *Ann.*, **205**, 100 (1880).

(6) Ruggli and Hinovker, *Helv. Chim. Acta*, **17**, 973 (1934).

(7) Teppema and Sebrell, THIS JOURNAL, **49**, 1754 (1927).

(8) Swiss Patent 126,127 [*C. A.*, **23**, 849 (1929)].

(9) Fieser and Martin, THIS JOURNAL, **57**, 1838 (1935).

(10) Arnold, Helmert, Möbus, Prigge and Rauen, *Ber.*, **75**, 372 (1942).

(11) Pickard, Allen, Bowdler and Carter, *J. Chem. Soc.*, **81**, 1568 (1902).

(12) P. Fischer, *Ber.*, **24**, 3788 (1891).

(13) Von Auwers and Kleinel, *J. prakt. Chem.*, **118**, 75 (1928).

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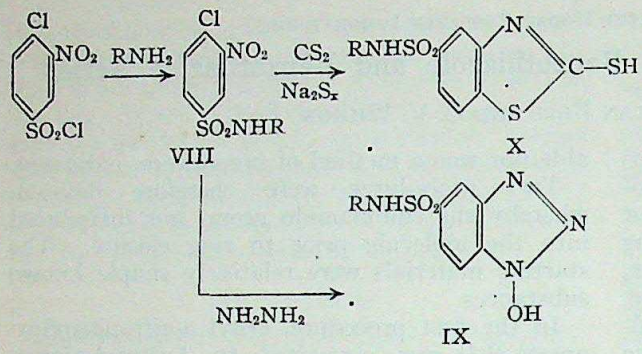

ate, but, when we employed sodium benzimidazolesulfonate under identical conditions, no sulfonyl chloride could be isolated.

The reactions outlined appear to be of general utility, and make available previously unknown types of substances.

Experimental

3-Nitro-4-aminobenzenesulfonyl chloride has previously been obtained by treating *o*-nitraniline directly with chlorosulfonic acid;[14] although the yield was not given, on repeating the procedure, there was obtained only 3–4% yield of crude material, not easily purified. It was incorrectly reported by Goslich,[15] whose error was corrected by P. Fischer.[12] It is still uncorrected in the latest edition of Beilstein's "Handbuch".[16] On treating the oxamic ethyl ester[11] with chlorosulfonic acid, an excellent yield of this chloride resulted; the oxalo group was hydrolyzed off during the manipulation.

To 187 g. of chlorosulfonic acid was added 45 g. of ethyl *o*-nitrophenyloxamate,[11] and the mixture was heated for three hours on the steam-bath. The cooled solution was then added slowly to chipped ice; the solid was filtered, washed, dried, and recrystallized from benzene. The yield of chloride (II), m. p. 152–3°, was 15 g. It was converted to the known 3-nitro-4-aminobenzenesulfonamide, m. p. 206–207°, which was identical with a specimen prepared as directed by Fischer.[12]

3-Nitrosulfanilamides.—The general procedure was to warm for one-half hour on the steam-bath a mixture of equivalent amounts of the acid chloride and the amine, with 1.5 equivalents of potassium or sodium acetate in about five times its weight of acetic acid. In this way there were prepared N′-(4′-acetaminophenyl)-3-nitrosulfanilamide (XI; III, R = 4-acetaminophenyl), and N′-(2′-hydroxyphenyl)-3-nitrosulfanilamide (XII; III, R = 2-hydroxyphenyl). Their properties are collected in Table I.

3-Nitro-4-chlorobenzenesulfonamides.—These were prepared by the same general procedure. In this way there were obtained N-(4′-chlorophenyl)-3-nitro-4-chlorobenzenesulfonamide (XIII; VIII, R = 4-chlorophenyl), N-(4′-acetaminophenyl)-3-nitro-4-chlorobenzenesulfonamide (XIV; VIII, R = 4-acetaminophenyl), N-(2′-hydroxyphenyl)-3-nitro-4-chlorobenzenesulfonamide (XV; VIII, R = 2-hydroxyphenyl), N-(2′-hydroxy-4′-methylphenyl)-3-nitro-4-chlorobenzenesulfonamide (XVI; VIII, R = 2-hydroxy-4-methylphenyl).

3,4-Diaminobenzenesulfonamide (XVII; IV, R = H) was secured by reducing the 3-nitro-4-aminobenzenesulfonamide preferably in the presence of a Raney nickel catalyst but also by the use of sodium hydrosulfite.

N-β-Hydroxyethyl Derivatives.—N-β-Hydroxyethyl-3-nitro-4-chlorobenzenesulfonamide, XVIII, was obtained as follows: to a boiling solution of 10 g. of 3-nitro-4-chlorobenzenesulfonyl chloride in 100 cc. of benzene was added 5 cc. of ethanolamine. The oil that separated was dissolved by the addition of a minimum of alcohol, the solution concentrated to a small volume, and diluted. After the last of the benzene had been removed, the solid that separated was crystallized from hot water.

N¹,N⁴-Di-β-hydroxyethyl-3-nitrosulfanilamide, XIX, was prepared in a similar manner, but using an excess of ethanolamine; the use of dioxane as a solvent was also satisfactory; there was no separation of an oil and the dioxane was evaporated on the steam-bath.

5-Sulfonamidobenzimidazole (XX; V; R,R′ = H), and 2-methyl-5-sulfonamidobenzimidazole (XXI; V, R = H, R′ = CH_3) were obtained by ring closure of 3,4-diaminobenzenesulfonamide, employing the desired acid and its sodium salt in the usual manner, and heating for at least three hours.

5-Sulfonamidobenzotriazole (XXII; VI, R = H) was prepared as follows: 2 g. of 3,4-diaminobenzenesulfonamide was dissolved in 20 cc. of water, 1.3 cc. of acetic acid, and 0.2 cc. of concentrated hydrochloric acid by warming. The solution was cooled to 10°, and 1 g. of sodium nitrite in 5 cc. of water was added all at once. After several color changes, the solid that separated was filtered, treated in hot aqueous solution with Norite, and allowed to crystallize.

Benzazimidoles were prepared by refluxing for two to three hours a mixture of the appropriate 3-nitro-4-chlorobenzenesulfonamide with twice its weight of 85% hydrazine hydrate in an equal volume of alcohol. They were not recrystallized; all melt with more or less violent decomposition. In this way there were secured 6-sulfonamidobenzazimidole (XXIII; IX, R = H), 6-sulfon-(2′-hydroxyanilido)-benzazimidole (XXIV; IX, R = 2-hydroxyphenyl), and 6-N-β-hydroxyethylsulfonamidobenzazimidole (XXV; IX, R = β-hydroxyethyl).

2-Mercaptobenzimidazoles; 2-mercapto-5-sulfon-(2′-hydroxyanilido)-benzimidazole (XXVI; VII, R = 2-hydroxyphenyl). A solution of 8.6 g. of N′-(2′-hydroxyphenyl)-3-nitrosulfanilamide in 25 cc. of alcohol was reduced in the presence of a Raney nickel catalyst at 90°, under 40 lb. pressure. The diamine was not isolated, but the catalyst filtered from the cooled solution. After the addition of 5 cc. of carbon disulfide and enough 40% sodium hydroxide solution to make it alkaline, it was heated overnight on the steam-bath, the solution concentrated to a small volume, diluted, and acidified with hydrochloric acid. The precipitate was filtered, washed, and dissolved in warm sodium carbonate solution. After treatment with a decolorizing carbon, it was acidified, and the precipitate filtered, washed and dried. The mercapto derivative so obtained melts, with decomposition, at 265°.

All these mercapto derivatives are slowly decomposed in solution, and are less pure after attempted recrystallizations. Sulfur analyses tend to give low results, but are useful in showing how many sulfur atoms have been introduced into the molecule.

Similarly, 2-mercapto-5-sulfon-(4′-acetaminoanilido)-benzimidazole (XXVII; VII, R = 4-acetaminophenyl) was obtained from the nitrosulfanilamide XI; upon hydrolysis for two hours on the steam-bath, using 12 g. of the acetyl derivative, 24 cc. of hydrochloric acid and 100 cc. of alcohol, the 2-mercapto-5-sulfon-(4′-anilidobenzimidazole) (XXVIII; VII, R = 4-aminophenyl) was formed.

2-Mercaptobenzothiazoles; 2-mercapto-5-sulfon-(4′-chloroanilido)-benzothiazole (XXIX; X, R = 4-chlorophenyl) was prepared by heating a mixture of 5.8 g. of sodium sulfide, 4.8 g. of sulfur, and 28 cc. of water until solution was complete, and then adding 8.5 parts of N-(4′-chlorophenyl)-3-nitro-4-chlorobenzenesulfonamide and 5 cc. of carbon disulfide, and warming on the steam-bath for

(14) German Patent 526,171 [*Frdl.*, **17**, 522 (1932)].

(15) Goslich, *Ann.*, **180**, 103 (1876).

(16) Beilstein–Prager–Jacobson, "Organische Chemie," Vol. 14, p. 709.

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TABLE I

PROPERTIES OF NEW SUBSTANCES

No.	Solvent	M. p., °C.	Yield, %	Empirical formula	Analyses, % Calcd.	Found
XI	Acetic acid	265–266	80	$C_{14}H_{14}N_4O_6S$		
XII	Alcohol	205–206	70	$C_{12}H_{11}N_3O_6S$	N, 13.6	N, 13.6
XIII	Benzene	120–121[a]	77	$C_{12}H_8Cl_2N_2O_4S$	Cl, 20.5	Cl, 20.4
XIV		188–190	79	$C_{14}H_{12}ClN_3O_5S$		
XV	Benzene	143–145	37	$C_{12}H_9ClN_2O_5S$	N, 8.5	N, 8.4
XVI	Benzene	155–156	47	$C_{13}H_{11}ClN_2O_5S$	N, 8.2	N, 8.0
XVII	Water	174–175	80	$C_6H_9N_3O_2S$	N, 22.5	N, 22.6
XVIII	Water	125	84	$C_8H_9ClN_2O_5S$	N, 10.0	N, 10.2
XIX	Water	158	85	$C_{10}H_{15}N_3O_6S$	N, 13.8	N, 13.6
XX	Alcohol	213–214	28	$C_7H_7N_3O_2S$	N, 21.3	N, 20.8
XXI	Alcohol	221	44	$C_8H_9N_3O_2S$	N, 19.9	N, 19.5
XXII	Water	236–237	71	$C_6H_6N_4O_2S$	N, 28.3	N, 28.3
XXIII		222[b]	50	$C_6H_6N_4O_3S$	N, 26.2	N, 26.2
XXIV		228[b]	70	$C_{12}H_{10}N_4O_4S$	N, 18.3	N, 18.1
XXV		168[b]	20	$C_8H_{10}N_4O_4S$	N, 21.7	N, 21.9
XXVI		265[b]	54	$C_{13}H_{11}N_3O_3S_2$	N, 13.1	N, 12.8
XXVII			68	$C_{15}H_{14}N_4O_3S_2$		
XXVIII		240–242[b]	95	$C_{13}H_{12}N_4O_2S_2$	C, 49.2 H, 3.5	C, 48.8 H, 3.6
XXIX		208–210[b]	55	$C_{13}H_9ClN_2O_2S_3$	S, 26.9	S, 25.1
XXX		284–285[b]	38	$C_{15}H_{13}N_3O_3S_3$[c]	S, 28.5	S, 27.8
XXXI	Alcohol	246–248[b]	53	$C_{13}H_{10}N_2O_3S_3$	N, 8.2	N, 8.3
XXXII		218–220[b]	65	$C_{14}H_{12}N_2O_3S_3$		

[a] Prepared in acetone, using two equivalents of the amine instead of acetic acid and sodium acetate. [b] With decomposition. [c] Upon hydrolysis the free amine, m. p. 230–232°,[b] was formed.

three hours. After filtering, the filtrate (at 20°) was acidified. The remainder of the treatment was similar to that in the previous example.

By a similar procedure there were prepared 2-mercapto-5-sulfon-(4′-acetaminoanilido)-benzothiazole (XXX; X, R = 4-acetaminophenyl), 2-mercapto-5-sulfon-(2′-hydroxyanilido)-benzothiazole (XXXI; X, R = 2-hydroxyphenyl), and 2-mercapto-5-sulfon-(2′-hydroxy-4′-methylanilido)-benzothiazole (XXXII; X, R = 2-hydroxy-4-methylphenyl).

Summary

A series of reactions is described, by which it is possible to obtain in considerable variety the hitherto unknown sulfonamides in the benzimidazole, benzotriazole, and benzothiazole series.

By these procedures there have been prepared 5-sulfonamidobenzimidazoles, 5-sulfonamidobenzotriazole, 6-sulfonamidobenzazimidoles, 2-mercapto-5-sulfonamidobenzimidazoles and 2-mercapto-5-sulfonamidobenzothiazoles.

ROCHESTER, N. Y. RECEIVED FEBRUARY 9, 1944

NOTES

1,3:2,4-Dibenzylidene-D-sorbitol

BY S. J. ANGYAL AND J. V. LAWLER

In their recent exhaustive paper, Wolfe, Hann and Hudson[1] proved that in dibenzylidine-D-sorbitol (m. p. 219–220°) the benzylidene groups are attached to carbon atoms 1,2,3,4 of D-sorbitol. They were unable, however, to assign a definite structure.

At the time their paper reached us, we were engaged in similar research. Our results agree with theirs, but in one respect we were able to go further. By careful hydrolysis of dibenzylidene-D-sorbitol with acetic acid in alcohol, we were able to isolate a monobenzylidene-D-sorbitol identical with Vargha's 2,4-monobenzylidene-D-sorbitol.[2] As under these mild conditions no migration is likely, we feel entitled to assign the 1,3:2,4 structure to dibenzylidene-D-sorbitol.

In a similar way we obtained 1,3:2,4-dibenzylidene-D-sorbitol from tribenzylidene-D-sorbitol,[3] which proves that the latter has the structure 1,3:2,4:5,6-tribenzylidene-D-sorbitol.

(1) Wolfe, Hann and Hudson, THIS JOURNAL, **64**, 1493 (1942).

(2) Vargha, *Ber.*, **68**, 23, 1337 (1935).

(3) Karrer and Büchi, *Helv. Chim. Acta*, **20**, 86 (1937).

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Neither during the synthesis from sorbitol and benzaldehyde, nor during hydrolysis experiments, did we encounter another isomer of dibenzylidene-D-sorbitol, such as the one described by Meunier,[4] m. p. 162°. This substance was probably a mixture of di- and tri-benzylidene-D-sorbitols.

In the experimental part we give improved physical constants of mono- and tri-benzylidene-D-sorbitol and of 5,6-diacetyl-1,3:2,4-dibenzylidene-D-sorbitol.

Experimental[5]

2,4-Monobenzylidene-D-sorbitol.—Vargha[2] gives m. p. 172–73°, $[\alpha]^{20}D$ 5.3°. His sample was obviously contaminated with dibenzylidene-D-sorbitol, because he recrystallized from alcohol, in which the latter substance is fairly soluble. We prepared the mono- compound according to his directions, but recrystallized it from 6 parts of water which left the diacetal undissolved. The substance so prepared had m. p. 176–77°, $[\alpha]^{17}D$ −1.1° (*c*, 1.0) in water.

Anal.[6] Calcd. for $C_{13}H_{18}O_6$: C_6H_5CH, 33.33. Found: C_6H_5CH, 33.1

2,4-Monobenzylidene-D-sorbitol from 1,3:2,4-dibenzylidene-D-sorbitol.—Three grams of the diacetal[1] was refluxed on the steam-bath with a mixture of 120 ml. 80% alcohol and 67 ml. glacial acetic acid for one hour. The solution was evaporated to dryness under reduced pressure. Thirteen ml. of water was added to the residue, the solution made carefully alkaline with sodium carbonate and boiled for a short time; 0.9 g. of unchanged dibenzylidene-D-sorbitol remained undissolved. The solution was filtered and on standing in the refrigerator deposited 0.27 g. of crystals (m. p. 173–74°, 17% yield on dibenzylidene-sorbitol not regained). After recrystallization from 1.5 ml. water the m. p. was 174–75°; mixed m. p. with the previous substance, 174–75°.

1,3:2,4:5,6-Tribenzylidene-D-sorbitol.—Prepared as directed by Karrer and Büchi.[3] Their method of purification is applicable to very small quantities only. We dissolved the crude triacetal (10 g.) in 100 ml. of chloroform, filtered from undissolved dibenzylidene-D-sorbitol and precipitated with 300 ml. alcohol (7–8 g.). The melting point of this substance shows a peculiar behavior. Pure samples recrystallized from chloroform–alcohol (1:3) or pyridine–water (3:1) have m. p.'s between 195 and 199°. Occasional pure samples had m. p.'s as low as 190°. When dissolved in pyridine and evaporated to dryness at 80° all these samples melted at 203°. Apparently the substance is dimorphous, one form melting at 203°, but we were unable to isolate the other in pure form. All pure samples have $[\alpha]^{16}D$ +26.9° (*c*, 2.0) in chloroform. Karrer and Büchi[3] give m. p. 191°, Simada and Matukawa[7] m. p. 201–204°, no rotation.

Anal. Calcd. for $C_{27}H_{26}O_6$: C_6H_5CH, 60.54. Found: C_6H_5CH, 60.4.

1,3:2,4-Dibenzylidene-D-sorbitol from Tribenzylidene-D-sorbitol.—Four grams of tribenzylidene-D-sorbitol (m. p. 203°) was dissolved in 40 ml. of hot chloroform, a mixture of 300 ml. 90% alcohol and 60 ml. of glacial acetic acid added, and refluxed on the steam-bath for two hours. The solution was evaporated to dryness under reduced pressure, the residue powdered and extracted, first with 50 ml. of chloroform, then with 30 ml. of boiling water. The residue weighs 2.1 g. (76% yield), and has m. p. 220–21°. On acetylation with pyridine (10 ml.) and acetic anhydride (6 ml.) it gives a substance similar in all properties to 5,6-diacetyl-1,3:2,4-dibenzylidene-D-sorbitol.

5,6-Diacetyl-1,3:2,4-dibenzylidene-D-sorbitol.—This substance shows the same peculiar behavior of its melting point as tribenzylidene-D-sorbitol. Samples from benzene or acetone have m. p.'s between 202 and 206°. On evaporation from pyridine at 80° it melts at 208–209°. Wolfe, Hann and Hudson[1] report 201–204°.

Anal. Calcd. for $C_{24}H_{26}O_8$: C_6H_5CH, 40.73. Found: C_6H_5CH, 40.8.

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MELBOURNE, AUSTRALIA RECEIVED NOVEMBER 26, 1943

(4) Meunier, *Ann. chim. phys.*, [6] **22**, 412 (1891).

(5) All melting points are corrected.

(6) For the benzylidene determination *ca.* 100 mg. of the substance was dissolved in 5 ml. of hot glacial acetic acid in an atmosphere of nitrogen. Forty ml. of a 0.5% solution of 2,4-dinitrophenylhydrazine in 2 N sulfuric acid was added, and the solution heated on a steam-bath under reflux for one hour. After cooling in ice the precipitate was collected in a Gooch crucible and dried *in vacuo* at 70°: wt. of precipitate × 0.3147 = benzylidene.

(7) Simada and Matukawa, *C. A.*, **33**, 5338 (1939).

An Orange-colored Pigment of Cottonseed

BY CHARLOTTE H. BOATNER, MAIZIE CARAVELLA AND CAROLYN S. SAMUELS

We have isolated an orange-colored pigment from cottonseed by the following procedure. An ethereal extract of cottonseed was re-extracted with a dilute aqueous solution of sodium hydroxide containing sodium dithionite ($Na_2S_2O_4$). The yellow-colored ethereal layer which separated from the aqueous extract when it was exactly neutralized with concentrated hydrochloric acid was withdrawn. Addition of an equal volume of glacial acetic acid to the ethereal solution caused the precipitation of gossypol "acetate" within a few minutes. When the filtrate was allowed to stand for about a week, an orange-colored solid slowly precipitated. This solid was extracted with hot acetone from which orange-colored crystals precipitated on cooling. The product was recrystallized first from hot acetone and finally from a mixture of hot chloroform and ether.

The orange-colored pigment differs markedly from gossypol. It is less soluble than gossypol in most organic solvents. It melts at 212° (cor.) to form a more deeply colored solid, which melts with decomposition at 238–239° (cor.). It is insoluble in alkali. It does not form a precipitate with aniline, reduce Fehling solution, or give a positive fuchsin-aldehyde test. The orange-colored pigment reacts with hydroxylamine and with dinitrophenylhydrazine, but the products differ in melting point from the corresponding products obtained with gossypol.

The orange-colored pigment forms a brilliant yellow solution in concentrated sulfuric acid which slowly changes to the scarlet color characteristic of gossypol in sulfuric acid.

The absorption spectrum of a chloroform solution of the orange-colored pigment exhibits a well defined maximum at 435 mμ, whereas that of gossypol occurs at 365 mμ.[1] The unstable reaction product of the orange-colored pigment with antimony trichloride has an absorption maximum at 450–460 mμ; whereas that of gossypol exhibits two maxima, one at 380 mμ and the other at 510–

(1) Boatner, *Oil & Soap*, 21, 10–15 (1944).

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520 mμ.[1] When a chloroform solution of the orange-colored pigment is treated with concentrated hydrochloric acid and then with antimony trichloride, the solution exhibits the absorption spectrum characteristic of the gossypol–antimony trichloride reaction product. This observation indicates that the final reaction products of both pigments are the same and that concentrated hydrochloric acid converts the orange-colored pigment into gossypol.

The absorption spectra curves of chloroform extracts of some raw cottonseeds and cottonseed meals, as well as those of their reaction products with antimony trichloride, have maxima which indicate the presence of the orange-colored pigment.[2] The production of a characteristic gossypol reaction when such extracts are treated with concentrated hydrochloric acid prior to their reaction with antimony trichloride[2] confirms the presence of the orange-colored pigment in the seeds and meals. The occurrence of this pigment in high concentration in certain cottonseed meals may account, at least in part, for the frequently observed lack of correlation[3] of gossypol content with toxicity of these meals when the gossypol is determined as the dianilino compound.

(2) Boatner, Caravella and Kyame, in press.
(3) Gallup, *Ind. Eng. Chem.*, **20**, 59–63 (1928).

BUREAU OF AGRICULTURAL AND INDUSTRIAL CHEMISTRY
AGRICULTURAL RESEARCH ADMINISTRATION
U. S. DEPARTMENT OF AGRICULTURE
SOUTHERN REGIONAL RESEARCH LABORATORY
2100 ROBERT E. LEE BOULEVARD
NEW ORLEANS, LOUISIANA RECEIVED FEBRUARY 16, 1944

The Preparation of Ethyl ϵ-Bromocaproate

BY GEORGE BOSWORTH BROWN AND C. W. H. PARTRIDGE

Ethyl ϵ-bromocaproate may be prepared conveniently and inexpensively from cyclohexanone. The crude mixed lactones of ϵ-hydroxycaproic acid, obtained by the procedure of Robinson and Smith,[1] may be treated directly with hydrobromic and sulfuric acids, thus obviating the losses involved in the use[2] of ethyl ϵ-hydroxycaproate as an intermediate.

The oxidation of 174 g. of cyclohexanone was carried out between 10 and 15° as described[1] in the preparation under the heading of ethyl 6-hydroxyhexoate using an oxidizing mixture prepared from 919 g. of potassium persulfate.

The 200 g. of crude lactones was then treated with a cooled mixture of 1 liter of 48% hydrobromic acid and 240 cc. of concentrated sulfuric acid. After standing for two hours at room temperature, this was heated for four hours on the steam cone, was cooled and poured into 2 liters of water. The organic layer was separated and the water solution was saturated with ammonium sulfate and was extracted four times with ether. The combined organic layer and extract were washed three times with saturated ammonium sulfate, and were dried and concentrated.

The 250 g. of crude bromo acid was esterified by refluxing for eight hours with 600 cc. of absolute alcohol and 15 cc. of sulfuric acid. After concentrating *in vacuo*, the residue was taken up in ether and was washed with water and with 5% sodium carbonate. The ether solution was dried over sodium sulfate and was distilled yielding 178 to 218 g. of the product distilling at 120–125° at 14 mm., $n^{21}D$ 1.4566, d^{23}_{23} 1.241, MR_D 48.92 (calcd. 48.57). This represents an over-all yield from cyclohexanone of 45–55%. No evidence of the inhomogeneity noted once by Barger, Robinson and Smith[2] has been observed. The product has been used satisfactorily in the preparation of η-ketopelargonic acid.[2]

(1) R. Robinson and L. H. Smith, *J. Chem. Soc.*, 371 (1937).
(2) G. Barger, R. Robinson and L. H. Smith, *ibid.*, 718 (1937).

DEPARTMENT OF BIOCHEMISTRY
CORNELL UNIVERSITY MEDICAL COLLEGE
NEW YORK, N. Y. RECEIVED FEBRUARY 19, 1944

Polymerization of Undecylenic Acid in the Presence of Boron Fluoride

BY JOHN R. CANN[1] AND E. D. AMSTUTZ

It has been found that when undecylenic acid is treated with gaseous boron fluoride at room temperature much heat is evolved and the acid polymerizes to a dark heavy oily material. This polymer, after having been freed of catalyst, exhibits the characteristic properties of an acid and also those of an ester. Thus it shows some tendency to dissolve in dilute aqueous caustic and regenerates carboxyl groups on refluxing in alkaline solutions.

The loss in carboxyl function has been found to be directly related to the fall in iodine value which indicates that one of the processes of polymerization is the esterification of the carboxyl group by means of the unsaturated linkage. (It had been previously demonstrated that the same treatment of stearic acid did not cause decarboxylation.) Since the fall in iodine value was stoichiometrically greater than the loss of carboxyl function it appeared that some double bond polymerization also took place. The analytical data show that this is a reaction of secondary importance with esterification assuming the major role.

The oil resulting from saponification of the polymer gave a positive iodoform test which indicates the hydroxy acid produced had the methylcarbinol structure. This proves the orientation of at least part of the polymerization process.

This type of polymerization[2] of undecylenic

(1) Raybestos-Manhattan Research Fellow in Chemistry 1942–1943. Present address, Frick Chemical Laboratory, Princeton, New Jersey.

(2) Unpublished results obtained in this Laboratory by Cann and by H. R. Nace indicate that this behavior is also shown by the fatty acids from drying oils and also by crotonic acid. The latter requires somewhat more strenuous conditions, however, due to its conjugated structure.

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acid in the presence of boron fluoride was to be expected from the work of Nieuwland and his collaborators[3] who found that simple olefins condensed with phenols and carboxylic acids to produce phenolic ethers and esters, respectively.

Experimental

The polymeric material was usually prepared by passage of gaseous boron fluoride[4] into the sample to the point of saturation. Heat was immediately evolved and the temperature was allowed to rise to 70–80°. The color darkened to a deep chocolate brown and the viscosity increased markedly. The material was then allowed to cool to room temperature overnight and was taken up in ether. The ethereal solution was washed exhaustively with water and dried over anhydrous magnesium sulfate. Removal of the ether was accomplished by heating on a hot-plate and finally in vacuum for several hours. The residual oil was clear brown in color, and possessed the odor of coconuts.

Saponification of the polymer was carried out in the usual manner with alcoholic potassium hydroxide. The alcohol was evaporated, the residue acidified and extracted with ether. The ether solution was then dried over magnesium sulfate, filtered and evaporated. The residual oil was finally warmed and placed in high vacuum.

The iodoform test on the saponified polymer was carried out in the usual manner using methanol (negative blank) as solvent. The unrecrystallized iodoform melted at 116–119.2°; authentic specimen, m. p. 116–118.5°; mixed m. p. 121°.

Anal. Calcd. for $C_{10}H_{19}CO_2H$: acid no., 184.2; I_2 no., 184.2. Found: acid no., 196.9; I_2 no., 173.4. Calcd. for polymer: I_2 no., 358; sap. eq., 196.9. Found: I_2 no., 429.7; sap. eq.,[5] 196.7; acid no., 467.8. Calcd. for saponified polymer: acid no., 207.3; I_2 no., 452.5; acetyl value (g./OH), 510. Found: acid no., 249[6]; I_2 no., 467.4; acetyl no., 505.

Acknowledgment.—The authors express their appreciation to the Raybestos Division for financial support. To C. W. Simmons the authors are grateful for his interest.

(3) Nieuwland, *et al.*, THIS JOURNAL, **54**, 3694 (1932); **56**, 2054, 2689 (1934).

(4) Samples of polymer prepared with boron fluoride etherate appeared to be identical with those upon which this report is based.

(5) Indicator used was Clearol Blue (see Fehnel and Amstutz, *Ind. Eng. Chem., Anal. Ed.*, **16**, 53 (1944).

(6) The acid number of the saponified polymer varied considerably and directly with the time and extent of heating during isolation. Reesterification occurred.

THE WM. H. CHANDLER LABORATORY OF CHEMISTRY
LEHIGH UNIVERSITY
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p-(2,5-Dimethylpyrryl-1)-phenyl-magnesium Bromide and -Lithium

BY HENRY GILMAN AND GORDON J. O'DONNELL

In connection with studies on nitrogen heterocycles, directions have been developed for the preparation of *p*-(2,5-dimethylpyrryl-1)-phenylmagnesium bromide and the corresponding organo-lithium compound. The yields of the RM compounds are quite satisfactory, and directions are also given for the preparation of the precursory *p*-(2,5-dimethylpyrryl-1)-phenyl bromide in 90% yield.

Experimental

***p*-(2,5-Dimethylpyrryl-1)-phenyl Bromide.**—This compound was prepared in accordance with the general procedure of Hazelwood, Hughes, and Lions.[1] To a warm solution of 172 g. (1 mole) of *p*-bromoaniline in 114 g. (1 mole) of acetonylacetone was added one or two drops of concd. hydrochloric acid. On the addition of the hydrochloric acid, the solution assumed a dark red color, and a vigorous reaction set in immediately with droplets of water forming on the surface of the solution. After the initial reaction subsided, the mixture was refluxed for three hours under an air condenser. The reaction mixture was poured upon crushed ice, and the precipitate was filtered. The yield of product melting at 72–74° was 240 g. (96%). Recrystallization from ethanol gave 225 g. (90%) of compound melting at 74°.

Reaction of *p*-(2,5-Dimethylpyrryl-1)-phenyl Bromide with Magnesium and with Lithium.—The Grignard reagent was prepared by conventional procedures, and the yield by acid titration[2] was 76%. From a second preparation, starting with 0.08 mole of the RBr compound, the yield of crude *p*-(2,5-dimethylpyrryl-1)-benzoic acid was 78%, and purification from ethanol gave a 72% yield of pure acid melting at 195–196°. The reaction with magnesium proceeds slowly, and ordinary catalysts like iodine or some activated magnesium, or some methylmagnesium iodide are helpful. There is no significant color change in the solution when reaction takes place, but color test I is of diagnostic value when methylmagnesium iodide is not used as a catalyst.

The organolithium compound was prepared by adding a solution of 12.5 g. (0.05 mole) of *p*-(2,5-dimethylpyrryl-1)-phenyl bromide in 60 cc. of ether to a stirred suspension of 1 g. (0.14 g. atom) of finely divided lithium in 30 cc. of ether. Twenty cc. of the solution was added at once, after which addition the mixture was warmed until the reaction started. The remaining solution was then added at a rate to maintain gentle refluxing. Carbonation by dry-ice gave 8.6 g. (80%) of *p*-(2,5-dimethylpyrryl-1)-benzoic acid which melted at 196–197° after crystallization from dilute ethanol. Identification was completed by a mixed m. p. determination with a sample prepared[1] by the condensation of *p*-aminobenzoic acid with acetonylacetone.

The observation that the bromide reacts more promptly with lithium than with magnesium finds a parallel in the preparation of RMgX and RLi compounds, in high yields, from *p*-dimethylarsinophenyl bromide and *p*-di-*n*-propylarsinophenyl bromide.[3]

Acknowledgments.—The authors are grateful to C. G. Stuckwisch and L. Fullhart, Jr., for assistance.

(1) Hazelwood, Hughes, and Lions, *J. Proc. Roy. Soc. N. S. Wales*, **71**, 92 (1937); [*C. A.*, **32**, 1695 (1938).]

(2) Gilman, Wilkinson, Fishel and Meyers, THIS JOURNAL, **45**, 150 (1923).

(3) Studies by L. Tolman and S. Avakian.

DEPARTMENT OF CHEMISTRY
IOWA STATE COLLEGE
AMES, IOWA RECEIVED FEBRUARY 15, 1944

Double Invert Soaps: Symmetrical Di-morpholinium Salts

BY JOSEPH B. NIEDERL AND EDWARD J. KENNEY[1]

Since it appears that up to the present few symmetrical double invert soaps have been described in the literature, report is herewith given of such types of compounds. Thus methylene- and ben-

(1) Abstracted from the thesis of Edward J. Kenney presented to the Graduate School of St. Peter's College, Jersey City, N. J., in partial fulfillment for the degree of Master of Science, May, 1944.

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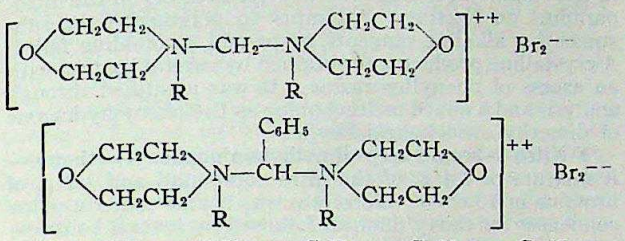
zal-di-morpholine, prepared according to M. Zief and J. P. Mason,[2] were condensed with a variety of alkyl bromides, such as *n*-butyl, *n*-heptyl, *n*-octyl, tetradecyl and hexadecyl bromides, to yield the corresponding symmetrical di-morpholinium di-bromides possessing the following structures



R: *n*-C_4H_9-, *n*-C_7H_{15}-, *n*-C_8H_{17}-, *n*-$C_{14}H_{29}$-, *n*-$C_{16}H_{33}$-

Procedure

To 0.01 mole of methylene- or benzal-di-morpholine was added 0.02 mole of the respective alkyl bromide and 11 ml. of 95% ethyl alcohol. The mixture was then gently refluxed for four hours. The reaction material when solid, or otherwise after removal of the alcohol by evaporation under reduced pressure, was crystallized from ethyl acetate; yields, 50–70%.

TABLE I

Compounds	Formulas	M. p., °C. (uncor.)	Analyses, % N Calcd.	Found
4,4′-Methylenedimorpholinium di-bromides				
4,4′-Di-*n*-butyl	$C_{17}H_{36}N_2O_2Br_2$	144 (dec.)	6.08	6.22
4,4′-Di-*n*-heptyl	$C_{23}H_{48}N_2O_2Br_2$	141 (dec.)	5.14	5.17
4,4′-Di-*n*-octyl	$C_{25}H_{52}N_2O_2Br_2$	143 (dec.)	4.89	4.95
4,4′-Di-tetradecyl	$C_{37}H_{76}N_2O_2Br_2$	165 (dec.)	3.78	3.90
4,4′-Di-hexadecyl	$C_{41}H_{84}N_2O_2Br_2$	180 (dec.)	3.52	3.31
4,4′-Benzaldimorpholinium di-bromides				
4,4′-Di-*n*-butyl	$C_{23}H_{40}N_2O_2Br_2$	174	5.22	5.34
4,4′-Di-*n*-heptyl	$C_{29}H_{52}N_2O_2Br_2$	153	4.51	4.63
4,4′-Di-*n*-octyl	$C_{31}H_{56}N_2O_2Br_2$	156	4.32	4.39
4,4′-Di-tetradecyl	$C_{43}H_{80}N_2O_2Br_2$	175	3.43	3.72
4,4′-Di-hexadecyl	$C_{47}H_{88}N_2O_2Br_2$	178	3.21	3.10

(2) M. Zief and J. P. Mason, *J. Org. Chem.*, 8, 1 (1943).

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NEW YORK UNIVERSITY, WASHINGTON SQUARE COLLEGE,
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The System Sulfur Dioxide–Acetic Acid

BY W. H. SCHEUB AND C. R. MCCROSKY

To find out whether a definite compound of sulfur dioxide and acetic acid exists, the melting points of a series of mixtures of these two substances have been measured.

The acetic acid was dehydrated by successive treatments of glacial acetic acid with triacetyl borate and 20% oleum. In each treatment the mixture was first refluxed and then fractionally distilled. The mixtures were prepared by dissolving previously dried sulfur dioxide in the anhydrous acetic acid and were then frozen in a bath of solid carbon dioxide and acetone, or of liquid air. The melting points were determined by means of a chromel–alumel thermocouple and were accurate to well within ±0.1°. Melting points rather than freezing points were measured since the mixtures were found to supercool to a marked degree.

TABLE I

MELTING POINT DATA OF THE SYSTEM SULFUR DIOXIDE–ACETIC ACID

Mole % SO_2	M. p., °C.	Mole % SO_2	M. p., °C.
0.0	16.6	33.5	−40.4
7.7	11.5	46.4	−38.0
9.6	8.3	59.6	−38.7
13.1	−44.1	63.3	−39.2
18.0	−44.2	78.3	−75.6
24.7	−41.9	100.0	−72.7

The observations are collected in Table I and are represented graphically in Fig. 1.

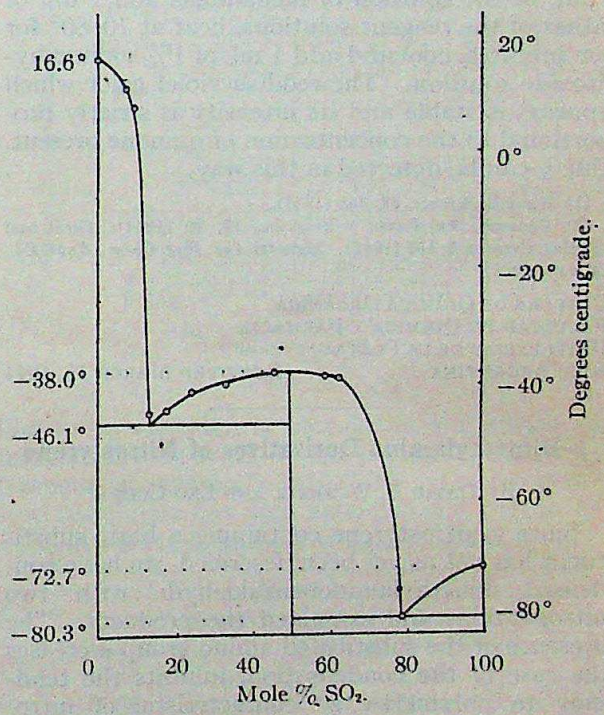

Fig. 1.

It can be seen that the melting point curve shows a maximum at 50 mole % sulfur dioxide and a temperature of −38°. The indicated compound, $HSO_2C_2H_3O_2$, solidifies in the form of thin, colorless flakes which show a tendency to sublime. The lower eutectic was established by a definite melting point at −80.3°; the upper eutectic at −46.1° was derived by extrapolation. These eutectic mixtures contained, respectively, 78.4 and 13.2 mole % of sulfur dioxide.

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SYRACUSE UNIVERSITY
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The Identification of 2-Methyl-1,4-naphthoquinone

BY ARMANDO NOVELLI AND JOSE S. CONTICELLO

2,4-Dinitrophenylhydrazine was proposed by Novelli[1] as a very sensitive reagent for 2-methyl-1,4-naphthoquinone (menadione), and it has been used for quantitative determinations.[2]

The reaction involves some inconvenience in that the colored substance formed is insoluble in water, and must be extracted with amyl alcohol; furthermore, when the amount of menadione is very small, the yellow color of 2,4-dinitrophenylhydrazine interferes with the green color of the reaction product. In order to avoid these disadvantages, we have tried other arylhydrazines of which the *p*-carboxy- and *p*-sulfonphenylhydrazine were the most convenient. The first is used in 1% alcoholic solution, and the latter in cold, saturated aqueous solution.

The reaction is carried out as follows: to 0.1–1 ml. of the solution of menadione, add 1 ml. of either of the reagent solutions, heat at 70–80° for ten minutes, cool and add 1 ml. of 1% sodium hydroxide solution. The reddish-violet color which appears is stable and its intensity is strictly proportional to the concentration of quinone present. One γ can be detected in this way.

(1) Novelli, *Science*, **93**, 358 (1941).

(2) Vonesch, *An. Farm. y Bioquim.*, **12**, 10 (1941); Giral and Iglesias, *Ciencia*, **3**, 157 (1942); Menotti, *Ind. Eng. Chem., Anal. Ed.*, **14**, 418 (1942).

CÁTEDRA DE QUÍMICA ORGÁNICA
FACULTAD DE QUÍMICA Y FARMACIA
UNIVERSIDAD DE LA PLATA
REP. ARGENTINA

RECEIVED MARCH 15, 1944

p-Dimethylamino Derivatives of Nitrostyrene

BY DAVID E. WORRALL AND LEO COHEN

Since a nitrostyrene containing a basic substituent has not as yet been described, we have condensed dimethylaminobenzaldehyde with two nitroparaffins and examined the products. The presence of the substituted amino group increases the ease of the condensation, inhibits the tendency to polymerize so characteristic of nitrostyrene itself and to a marked extent deepens the color of the resulting unsaturated nitro compound. It also destroys the weak additive capacity of the conjugated unsaturated system for organic bases.

Experimental

1-Nitro-2-(*p*-dimethylaminophenyl)-ethene.—A mixture of 14.9 g. (0.1 mole) *p*-dimethylaminobenzaldehyde and 18.3 g. (0.03 mole) nitromethane was placed in a flask which was then heated on a water-bath until a dark green solution resulted. Then 0.43 g. of amylamine was added. On heating the mixture for one minute, the solution turned dark brown, solidifying within twenty minutes to a red crystalline mass. The mixture was filtered after standing overnight. The residue recrystallized from 2-nitropropane yielded 16 g. of sparkling, ruby red plates, m. p. 179–180.5°.

Anal. Calcd. for $C_{10}H_{12}N_2O_2$: C, 62.5; H, 6.3. Found: C, 62.2; H, 6.4.

It dissolved readily in hydrochloric acid, presumably through salt formation. The colorless solution became red on further dilution with water. Concentrating the acid solution produced colorless crystals which rapidly became discolored when attempts were made to isolate them. The original substance was only sparingly soluble in the common solvents but dissolved readily in the nitroparaffins on heating. Attempts to polymerize the substance by alkaline reagents or to add *p*-toluidine failed. A crystalline product was obtained by careful heating with an excess of phenylhydrazine. It was identified through analysis and a mixed melting point as the phenylhydrazone of dimethylaminobenzaldehyde.

1-Nitro-2-bromo-2-(*p*-dimethylaminophenyl)-ethene.—A mixture of 1.4 g. of the nitro compound and 1.2 g. of bromine in 10 cc. of chloroform was heated under a reflux condenser for thirty minutes followed by several hours exposure to sunlight. After concentration to a small volume at room temperature, the resulting light yellow needles were separated, washed with ether and immediately warmed on a water-bath for half an hour with alcoholic potassium acetate. The mixture was poured into a large volume of ice water. The product separated from alcohol as dark red platelets, m. p. 121°.

Anal. Calcd. for $C_{10}H_{11}BrN_2O_2$: Br, 29.5. Found: Br, 29.1.

2-Nitro-1-(*p*-dimethylaminophenyl)-1-propene.—A similar condensation of the aldehyde and nitroethane after several days produced a fair yield of red plate-like crystals, m. p. 118–120°.

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.1; H, 6.8. Found: C, 64.1; H, 6.8.

Attempts to condense nitropropane failed.

PEARSON MEMORIAL LABORATORY
TUFTS COLLEGE
MEDFORD, MASS.

RECEIVED DECEMBER 4, 1943

Trimethyl Silane and Trimethyl Silicon Chloride

BY A. G. TAYLOR AND B. V. DE G. WALDEN

Mono- and dimethyl silicon chlorides have been described by Gilliam, Liebhafsky and Winslow[1] who drew attention to their b. p.'s in relation to tetramethyl silane and silicon tetrachloride. Referring to work in the same laboratory the b. p.'s are given by Rochow[2] as 66.0–67.0° at 766 mm. for the monomethyl and 69.0–70.2° at 744.5 mm. for the dimethyl derivative.

These authors used the reaction between silicon tetrachloride and magnesium methyl chloride to prepare mixtures of monomethyl silicon trichloride, dimethyl silicon dichloride and trimethyl silicon chloride, together with ether, from which by fractionation they isolated specimens corresponding in composition and vapor density fairly closely with monomethyl silicon trichloride and dimethyl silicon dichloride.

We have prepared trimethyl silicon chloride by direct chlorination of trimethyl silane which was made from silicochloroform. This method previously has been used by Kraus and Nelson[3] for the preparation of triethyl silane and triethyl silicon bromide.

(1) Gilliam, Liebhafsky and Winslow, THIS JOURNAL, **63**, 801 (1941).

(2) Rochow, U. S. Patent 2,286,763 (1942).

(3) Kraus and Nelson, THIS JOURNAL, **56**, 195 (1934).

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Experimental

Silicochloroform.—This was prepared by the action of hydrogen chloride gas on ferrosilicon containing 95–97% silicon.[4,5] The volatile products were condensed by alcohol and solid carbon dioxide and a fraction (75%) boiling between 28 and 36° was refractionated and a fraction boiling close to 31.8° collected (44.6% of original condensate).

Anal. Silicon and chlorine were determined after reaction with water as silica and hydrogen chloride. Calcd.: Si, 20.72; Cl, 78.53. Found: Si, 20.2, 20.6, 20.6; Cl, 79.6, 78.7, 78.7.

Trimethyl Silane.—To 500 cc. of an ether solution containing 175 g of methylmagnesium bromide was added slowly with strong cooling and stirring 60 g. of silicochloroform in 150 cc. of ether. The reflux condenser was cooled by circulating cold brine. After completion of the reaction, the reflux condenser was allowed to rise to room temperature and connection made to a cooled receiver through another condenser cooled by alcohol and solid carbon dioxide. Cooled dilute sulfuric acid was added slowly and trimethyl silane together with some ether distilled over. Concentrated sulfuric acid was added to the receiver and allowed to stand cold overnight. Trimethyl silane was then distilled off; b. p. uncor. 9 to 11°. A small amount of dissolved gas assumed to be methane was lost below 0°. The yield was poor. In each of several experiments 15 cc. of trimethyl silane was obtained from 40 cc. of silicochloroform.

Trimethyl Silicon Chloride.—Trimethyl silane was treated at −20° with chlorine and then allowed to stand at room temperature until most of the hydrogen chloride had escaped. A fraction boiling between 58 and 63° was collected and redistilled and collected between 57 and 59.4° at 747 mm. This represented 75% of the original total. There was a small residue, non-volatile at 100°, left from the first distillation.

Anal. Silicon content by adding concd. sulfuric acid, warming, then adding concd. nitric acid and finally weighing silica. Cl content by hydrolyzing and titration. Calcd.: Si, 25.85; Cl, 32.67. Found: Si, 25.4, 25.9, 25.8, 25.6; Cl, 32.1, 32.2, 33.0. Taking CH_3 by difference, the mean percentages correspond to $(CH_3)_{2.99}SiCl_{1.00}$.

Vapor Pressure of Trimethyl Silicon Chloride.—This was determined by the method of Smith and Menzies.[6] Temperatures were read on a thermometer corrected by reference to the b. p.'s of purified ether, carbon tetrachloride, and water. Interpolation by least squares gives

t, °C.	28.9	35.3	40.0	45.2	49.8	55.0	56.1
p, mm.	308	366	427	481	575	676	725

$\log_{10}p = 6.926 - 1344/T$. The b. p. at 760 mm. is calculated to be 59°; density, d^{25}_4, 0.846; freezing point, approx. −40°.

(4) Buff and Wöhler, *Ann.*, **104**, 94 (1857).

(5) Booth and Stillwell, THIS JOURNAL, **56**, 1529 (1934). Other references are given in this paper.

(6) Smith and Menzies, *ibid.*, **32**, 897 (1910).

RESEARCH LABORATORY
ALBRIGHT & WILSON, LTD.
OLDBURY, BIRMINGHAM
ENGLAND

RECEIVED SEPTEMBER 3, 1943

The Viscosity of the Methyl Ester of Dilinoleic Acid

BY DAVID W. YOUNG AND RUTH E. BIERTUEMPFEL

The purpose of this note is to present viscosity measurements on a pure sample of methyl dilinoleate over a range of temperature from −40 to 212°F. (−40–100°C.).

Experimental Procedure

The ester used for this work had been purified by double distillation in a molecular still by Dr. John C. Cowan in the Northern Regional Research Laboratory. The ester had an index of refraction of $n^{30}D$ 1.4766. Recently the method used to formulate and purify the methyl dilinoleate from soybean oil has been reported.[1]

The kinematic viscosity method used in the study is intended for determining the viscosity of any product which is a true viscous liquid at the temperature of the test. The viscometers available were the Ubbelohde type with one capillary tube. Care was taken to calibrate each viscometer against standard oils of known viscosity as determined in the National Bureau of Standards. The viscosity method is given under American Society for Testing Materials, Designation D 445-42 T.

For the viscosity determination at −40° the procedure given by Baldeschwieler and Wilcox[2] was used.

Results

Experimental results are listed in Table I and Fig. 1. A straight line relationship exists when

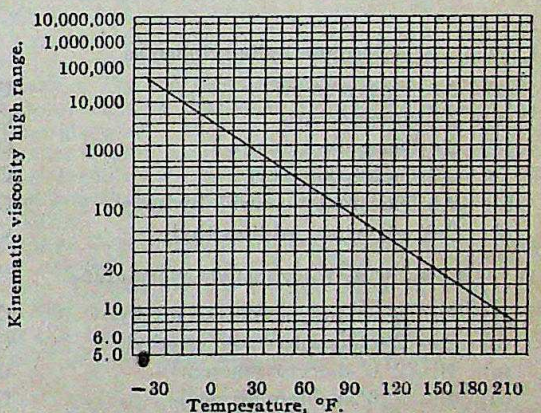

Fig. 1.

kinematic viscosity is plotted as a function of temperature on A. S. T. M. tentative viscosity–temperature chart (D 341–37 T). The temperature coördinate has been extended 10°, that is, to −40°, in order to present complete data.

TABLE I

KINEMATIC VISCOSITY OF METHYL DILINOLEATE

Temp., °F.	Viscosity in centistokes
−40	42,464
80	102.5
90	78.3
100	60.0
110	48.0
140	25.4
150	21.1
160	17.8
170	15.2
180	13.1
200	10.0
210	8.70

It was held that these results would be of interest as the pure material is rather difficult to

(1) Cowan and Wheeler, THIS JOURNAL, **66**, 84 (1944).

(2) Baldeschwieler and Wilcox, *Ind. Eng. Chem., Anal. Ed.*, **11**, 221 (1939).

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obtain and the dimer had a viscosity index (Dean and Davis system) of 123.0.

STANDARD OIL COMPANY OF NEW JERSEY
ELIZABETH, NEW JERSEY RECEIVED MARCH 3, 1944

NEW COMPOUNDS

New Phenolic Mercurials[1]

In a study of the preparation of new phenols of possible pharmaceutical interest the following new derivatives, which include mercurials of *p-t*-octylmono-,[2a] cyclohexylidenedi-,[2b] and hexyl-tetraphenols,[2c] have been prepared and characterized.

Polyacetoxymercurials.—A molar equivalent of mercuric acetate was allowed for each free position ortho-to-the-hydroxyl group per mole of phenol. Knowing the ratio of the reactants to be used, the quantities of phenol and mercuric acetate could be calculated for any size batch desired or found to be convenient. A 2–6% solution of the phenol with the calculated amount of mercuric acetate was refluxed in 95% ethyl alcohol containing 5% glacial acetic acid in an appropriate flask, fitted with a reflux condenser, for one to two hours. The flask was then chilled in the refrigerator overnight, the polymercurial filtered off and recrystallized from ethanol or glacial acetic acid. The yields were in the neighborhood of 70–90%.

Monoacetoxymercurials.—For these one mole of phenol was allowed to react with only one-half the quantity of mercuric acetate as calculated above, in a 50% aqueous ethyl alcohol solution containing 5% glacial acetic acid, at room temperature, over a period of one to two weeks. When the solution no longer contained free mercuric ions, as shown by the absence of a positive reaction when tested for such ions with potassium iodide solution (red precipitate of mercuric iodide soluble in excess of reagent), the solution was then chilled in the refrigerator and the crude mono-mercurial filtered off and dried. The monomercurial was recrystallized from 50% aqueous alcohol containing 5% glacial acetic acid. The yield was about 80–85%.

Chloromercurials.—These were obtained by pouring an alcoholic or a glacial acetic acid solution of the acetoxymercuri derivative into an equal volume of a 20% aqueous solution of reagent grade sodium chloride. The chloromercurial was filtered off and recrystallized from ethanol or glacial acetic acid. The yields varied from 70–90%.

THE CHEMICAL LABORATORIES OF
NEW YORK UNIVERSITY
WASHINGTON SQUARE COLLEGE JOSEPH B. NIEDERL
NEW YORK, N. Y. ANTHONY J. SHUKIS
RECEIVED FEBRUARY 8, 1944

TABLE I

NEW PHENOLIC MERCURIALS

Name	Formula	M. p., °C. (uncor.)	Yield, %	Percentage Hg[a] Calcd.	Found
I. 4-$\alpha,\alpha,\gamma,\gamma$-Tetramethylbutylphenols					
(a) 2-Acetoxymercuri-	$C_{16}H_{24}O_3Hg$	158	80	43.16	43.10
(b) 2-Chloromercuri-	$C_{14}H_{21}OHgCl$	161	90	45.46	45.30
(c) 2,6-Diacetoxymercuri-	$C_{18}H_{26}O_5Hg$	181	90	55.46	54.60
(d) 2,6-Dichloromercuri-	$C_{14}H_{20}OHg_2Cl_2$	238D[a]	80	59.18	58.60
(e) 2,6-Diacetoxymercuri-3-hydroxy-	$C_{18}H_{26}O_6Hg_2$[b]	183D[a]	75	54.26	54.68
(f) 2-Acetoxymercuri-6-methyl-	$C_{17}H_{26}O_3Hg$	149	80	41.87	42.05
II. 1,1-Bis-(4′-hydroxyphenyl)-cyclohexane					
(a) Bis-(2′-acetoxymercuri-6′-methyl)-	$C_{24}H_{28}O_6Hg_2$	200D	90	49.33	49.60
(b) Bis-(2′-chloromercuri-6′-methyl)-	$C_{20}H_{22}O_2Hg_2Cl_2$	225D	80	53.05	52.10
(c) Bis-(2′,6′-diacetoxymercuri)-	$C_{26}H_{28}O_{10}Hg_4$	210D	82	61.60	61.50
(d) Bis-(2′,6′-dichloromercuri)-	$C_{18}H_{16}O_2Hg_4Cl_4$	222D	75	66.45	66.10
III. 2,2,5,5-Tetrakis-(4′-hydroxyphenyl)-hexanes					
(a) Tetrakis-(2′,6′-diacetoxymercuri)-	$C_{46}H_{46}O_{20}Hg_8$	308D	91	63.60	63.00
(b) Tetrakis-(2′,6′-dichloromercuri)-	$C_{30}H_{22}O_4Hg_8Cl_8$	247D	80	68.74	67.70

[a] Decomposes. [b] The chloromercurial is an oil.

(1) Abstracted from the thesis of Anthony J. Shukis presented to the Graduate School of New York University, New York, N. Y., in partial fulfillment for the degree of Master of Science, June, 1940.

(2) J. B. Niederl and co-workers, (a) THIS JOURNAL, **55**, 2571 (1933); (b) *ibid.*, **61**, 345 (1939); (c) *ibid.*, **63**, 1235 (1941).

(3) A. J. Shukis and R. C. Tallman, *Ind. Eng. Chem., Anal. Ed.*, **12**, 123 (1940).

Double Invert Soaps: Symmetrical Di-piperidinium Salts[1]

Several long chain substituted dipiperidinium salts have been prepared in the course of investigation of various types of symmetrical double invert soaps. Methylene- and benzal-di-piperidine, prepared by condensing formaldehyde or benzaldehyde respectively with two moles of piperidine, were treated with double molar quantities of various *n*-alkyl bromides, such as *n*-heptyl, *n*-octyl, *n*-tetradecyl and *n*-hexadecyl bromides. Reaction took place rather readily in all cases and evidently proceeded as follows

$$(C_5H_{10}N)_2CH_2 + 2RBr \longrightarrow [(C_5H_{10}NR)_2CH_2]^{++}\ 2Br^{--}$$

$$(C_5H_{10}N)_2CHC_6H_5 + 2RBr \longrightarrow [(C_5H_{10}NR)_2CHC_6H_5]^{++}\ 2Br^{--}$$

$$R = -C_7H_{15-n},\ -C_8H_{17-n},\ -C_{14}H_{29-n},\ -C_{16}H_{33-n}$$

Procedure.—To 0.02 mole of methylene- or benzal-dipiperidine was added 0.04 mole of the respective alkyl bromide and 20 ml. of 95% ethyl alcohol. The mixture was then refluxed gently for four hours. The alcohol was then removed by evaporation under reduced pressure. The remaining residue was repeatedly crystallized from ethyl acetate; yields, 50–70%.

(1) Abstracted from the thesis of Anthony E. Lanzilotti presented to the Graduate School of St. Peter's College, Jersey City, N. J., in partial fulfillment for the degree of Master of Science, May, 1944.

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Compounds	Formulas	M. p., °C. (uncor.)	Analyses, % N Calcd.	Found
N,N′-Methylene-di-piperidinium di-bromides				
N,N′-Di-*n*-heptyl	$C_{25}H_{52}N_2Br_2$	178	5.19	5.38
N,N′-Di-*n*-octyl	$C_{27}H_{56}N_2Br_2$	162	4.92	5.07
N,N′-Di-*n*-tetradecyl	$C_{39}H_{80}N_2Br_2$	183	3.80	3.87
N,N′-Di-*n*-hexadecyl	$C_{43}H_{88}N_2Br_2$	176	3.53	3.70
N,N′-Benzal-di-piperidinium di-bromides				
N,N′-Di-*n*-heptyl	$C_{31}H_{56}N_2Br_2$	177	4.54	4.91
N,N′-Di-*n*-octyl	$C_{33}H_{60}N_2Br_2$	165	4.34	4.45
N,N′-Di-*n*-tetradecyl	$C_{45}H_{84}N_2Br_2$	181	3.45	3.82
N,N′-Di-*n*-hexadecyl	$C_{49}H_{92}N_2Br_2$	179	3.22	3.42

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NEW YORK UNIVERSITY
WASHINGTON SQUARE COLLEGE
NEW YORK, N. Y., AND OF
ST. PETER'S COLLEGE JOSEPH B. NIEDERL
JERSEY CITY, N. J. ANTHONY E. LANZILOTTI

RECEIVED FEBRUARY 10, 1944

o-Biphenyl Isocyanate, *o*-Bicyclohexyl Isocyanate, N,N′-Di-*o*-biphenyl Urea, N,N′-Di-*o*-bicyclohexyl Urea

The isocyanates were prepared by the reaction of *o*-biphenylamine and *o*-bicyclohexylamine[1] with phosgene. Solutions of the amines in dry toluene were added gradually to a sixfold excess of phosgene, dissolved to 20 to 30% solution in toluene. The solutions were warmed during and after the addition of the base and finally refluxed for several hours. Most of the white crystals (hydrochloride) which formed with *o*-biphenylamine dissolved during heating. No precipitate appeared with *o*-bicyclohexylamine. Subsequently, the toluene and phosgene were distilled off; the residue was heated with carbon tetrachloride,[2] the solution was filtered if necessary, and the solvent was removed by distillation. From the residue the isocyanates were distilled as colorless oils, in yields of 60 to 70%. *o*-Biphenyl isocyanate distilled at 100° (0.5–1 mm.); *o*-bicyclohexyl isocyanate, at 89–90° (0.5–1 mm.).

o-Biphenyl isocyanate—calcd. for $C_{13}H_9NO$: N, 7.18. Found: N, 7.10.

o-Bicyclohexyl isocyanate—calcd. for $C_{13}H_{21}NO$: N, 6.75. Found: N, 6.63.

The corresponding symmetrical disubstituted ureas were prepared by treating the isocyanates with water containing 10% of pyridine as a catalyst. The biphenyl compound reacted in the cold but the bicyclohexyl isocyanate had to be heated on a steam-bath. The product obtained from the former showed a sharp and constant melting point of 182° (uncor.) after two recrystallizations from absolute alcohol. The crystals obtained from bicyclohexyl isocyanate showed a protracted melting point (218–228°) which did not become sharp after repeated recrystallizations (from methanol-water or, preferably, from dioxane). The final melting point was 225–228° (uncor.). Since several of the stereoisomeric ureas may be present, the lack of a sharp melting point is not surprising.

N,N′-Di-*o*-biphenyl urea—calcd. for $C_{25}H_{20}N_2O$: C, 82.5; H, 5.5; N, 7.7. Found: C, 82.2; H, 5.6; N, 7.2.

N,N′-Di-*o*-bicyclohexyl urea—calcd. for $C_{25}H_{44}N_2O$: C, 77.4; H, 11.4. Found: C, 77.2; H, 11.4.

We thank L. M. White for the analytical data.

(1) The amines were kindly furnished by the Monsanto Chemical Co.

(2) Shriner, Horne and Cox, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Coll. Vol. II, 1943, p. 453.

WESTERN REGIONAL RESEARCH LABORATORY
BUREAU OF AGRIC. AND IND. CHEM.
AGRICULTURAL RESEARCH ADMINISTRATION
U. S. DEPARTMENT OF AGRICULTURE
ALBANY, CALIF. HEINZ FRAENKEL-CONRAT
HAROLD S. OLCOTT

RECEIVED FEBRUARY 14, 1944

Methyl 3-Methyl-4,6-ethylidene-α- and β-Glucosides

During the course of some work on the optical rotations of substituted glucose derivatives, preparations of the α- and β-methylglucosides of 3-methyl-4,6-ethylideneglucose were required. Catalytic deacetylation with sodium methylate of 16.5 g. of the non-crystalline triacetate, sp. rot. (D line, 25°) + 84° ($CHCl_3$, *C*, 7.8) gave 10.8 g. of a sirupy mixture of methyl 3-methyl-α- and β-glucosides. This was shaken with 45 ml. of freshly distilled paraldehyde and 0.2 ml. of concentrated sulfuric acid until solution was complete. The solution was allowed to stand at room temperature for fifteen minutes after which water and petroleum ether were added. The aqueous layer was separated, washed twice with petroleum ether, and extracted four times with chloroform. Evaporation of the chloroform solution left a crystalline mixture from which 0.6 g. of a substance of m. p. 106–107° and 0.022 g. of another of m. p. 133–134° were separated by fractional crystallization from ether–petroleum ether mixtures. An additional 0.215 g. of the high-melting substance (methyl 3-methyl-4,6-ethylidene-β-glucoside) was obtained in better yield from methyl 3-methyl-β-glucoside. Methylation of the high-melting compound with methyl iodide and silver oxide gave the known methyl 2,3-dimethyl-4,6-ethylidene-β-glucoside[1] melting at 103–105° alone or mixed with an authentic specimen, hence the high-melting compound is regarded as methyl 3-methyl-4,6-ethylidene-β-glucoside. The analyses and properties of the low-melting substance indicate that it is methyl 3-methyl-4,6-ethylidene-α-glucoside. It is noted that the difference in molecular rotation for the high and low-melting compounds is 42,120, while the corresponding value calculated for the α- and β-methylglucosides of 4,6-ethylidene glucose would be 40,920.[2]

Methyl 3-methyl-4,6-ethylidene-α-glucoside: melting point 106–107° (cor.); sp. rot. (D line, 25°) + 114° (H_2O, *C*, 0.6); (Hg blue line, 25°) + 246° (H_2O, *C*, 0.6).

Methyl 3-methyl-4,6-ethylidene-β-glucoside: melting point 133–134° (cor.); sp. rot. (D line, 25°) − 66° (H_2O, *C*, 0.7); (Hg blue line, 25°) − 126° (H_2O, *C*, 0.7).

			C	H	OCH_3
Anal.	Calcd. for $C_{10}H_{18}O_6$ (234):		51.28	7.69	26.50
	Found:	α-compound	51.5	7.79	26.3
			51.3	7.67	26.5
		β-compound	51.2	7.82	26.4
			51.1	8.07	26.5

(1) B. Helferich and H. Appel, *Ber.*, **64**, 1841 (1931).

(2) H. Appel and W. N. Haworth, *J. Chem. Soc.*, 793 (1938).

SOUTHERN REGIONAL RESEARCH LABORATORY
U. S. DEPARTMENT OF AGRICULTURE
NEW ORLEANS, LA. RICHARD E. REEVES

RECEIVED JANUARY 24, 1944

n-Nonatriacontane

During some attempts to mono-alkylate acetone dicarboxylic ester (diethyl β-ketoglutarate) with octadecyl iodide, the dialkylated ester was also formed as a by-product, which after hydrolysis and decarboxylation yielded nonatriacontanone-20. Reduction of the latter by Clemmensen's method gave *n*-nonatriacontane. An alkyl halide having *n* carbon atoms thus yields a hydrocarbon with $2n + 3$ carbon atoms.

Nonatriacontanone-20.—To a solution of 1.15 g. of sodium in 30 cc. of dry *n*-butanol were added 10 g. of acetone-dicarboxylic ester and 19 g. of *n*-octadecyl iodide prepared from *n*-octadecanol-1 of f. p. 57.8° (thermometer in the liquid); the iodide was distilled *in vacuo* (b. p. 221–224°, 9 mm.) and crystallized twice from acetone and once from methanol–ether (2:1)) and the mixture refluxed until the reaction was neutral (ten hours). The solid which separated on cooling was collected and refluxed with 60 cc. of concentrated hydrochloric acid for 9.5 hours. The neutral material resulting from this treatment was separated and crystallized from hot ethanol; 4.5 g. of nonatria-

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contanone-20 melting at 90–92.5° resulted. After treatment with charcoal to remove a yellow discoloration and two recrystallizations from light petroleum (b. p. 70–80°) the ketone melted at 91.2–91.4°.[1]

The long X-ray spacing (melted specimen) was 51.5 Å., indicating that this ketone, like the lower homologs, crystallizes with vertical molecules.

Anal.[2] Calcd. for $C_{39}H_{78}O$: C, 83.1; H, 13.9. Found: C, 83.1; H, 13.9.

n-Nonatriacontane.—1.9 grams of the ketone, 48 g. of amalgamated zinc, 48 cc. of concentrated hydrochloric acid and 10 cc. of glacial acetic acid were boiled under reflux. Every sixth hour the mixture was cooled, the liquid decanted and fresh hydrochloric acid, glacial acetic acid and zinc (10 g.) added. The reduction was followed by determination of the m. p. of the product. After eighty hours the m. p. became constant at 79.0–79.4°. The hydrocarbon was collected and purified by treatment with concentrated sulfuric acid at 130° for two hours.[3] Considerable darkening occurred and the process was repeated until on the fourth treatment darkening no longer took place. The hydrocarbon was carefully washed with hot water and treated with charcoal in benzene. It crystallized from benzene in small white lustrous plates and after three crystallizations from this solvent the m. p. was 80.0–80.2°. The phenomena observed on heating and cooling the hydrocarbon through the m. p. are similar to those observed for the lower homologs.[3] On heating the opaque crystalline material a transition is observed at approximately 75° (change into a transparent form with vertical rotating chains). The s. p. on cooling the melt lies at 79.8°. At this point transparent needles are formed in the melt. On further cooling to 75°, the transparent solid is changed to an opaque form stable at lower temperatures.

The X-ray investigation of the hydrocarbon, crystallized from benzene and pressed on to glass, gave a long spacing of 51.3 Å., corresponding to the normal (A) form with vertical molecules. A specimen melted on to glass by means of the hot-wire technique gave, however, a different diffraction pattern with a long spacing of 47.1 Å., indicating tilted molecules. Odd number hydrocarbons containing more than eleven carbon atoms have previously been found to crystallize only in the A form with vertical molecules.[3] The dimorphism of *n*-nonatriacontane was therefore unexpected, and the compound provides an exception to the rule[4] that a longer chain and an odd number of carbon atoms (and also a higher temperature and the presence of impurity) favors crystallization in vertical forms.

Anal.[2] Calcd. for $C_{39}H_{80}$: C, 85.4; H, 14.6. Found: C, 85.1; H, 14.6.

(1) The m. p.'s and s. p.'s were determined in capillary tubes using a glycerol bath and totally immersed calibrated Anschütz type thermometers. Heating and cooling were carried out very slowly.

(2) Microanalysis by Dr. Max Möller, Copenhagen.

(3) S. A. Piper, A. C. Chibnall, S. J. Hopkins, A. Pollard, J. A. B. Smith and E. F. Williams, *Biochem. J.*, **25**, 2072 (1931).

(4) *Cf.* J. C. Smith, *Ann. Reports*, **35**, 259 (1938).

DEPARTMENT OF MEDICAL CHEMISTRY
UNIVERSITY OF UPPSALA — EINAR STENHAGEN
UPPSALA, SWEDEN — BIRGITTA TÄGTSTRÖM

RECEIVED MARCH 3, 1944

COMMUNICATIONS TO THE EDITOR

STERIC STRAIN AND THE ANOMALOUS BASE STRENGTH OF THE NORMAL ALIPHATIC AMINES

Sir:

The strength of the normal aliphatic acids and amines changes with chain length in a peculiar manner. Thus K_a decreases for the first three members, but increases for the fourth (Table I). This curious behavior has been ascribed in the case of the carboxylic acids to hydrogen bond formation between the end methyl group of butyric acid (or of the γ-methylene group of the higher acids) with the carbonyl oxygen of the carboxyl group.[1] A similar explanation could be used for the amines.

As part of a study of generalized acids and bases in gaseous systems,[2] the measurement of the base strength of the normal aliphatic amines with trimethylboron as the reference acid was undertaken. The base strength thus measured (Table I) first increases markedly from ammonia to methylamine, then decreases with ethylamine, rises again with propylamine and then increases regularly. This behavior is so similar to that of the normal aliphatic acids and of the corresponding amides that it is not unreasonable to seek one fundamental explanation for the phenomena.

TABLE I

ACIDITY CONSTANTS FOR THE NORMAL ALIPHATIC ACIDS AND AMINES

R	RCOOH at 25°[a]	RNH_3^+ at 25°[b]	RNH_2:BMe_3 at 100°
H	17.12×10^{-5}	5.38×10^{-10}	4.62
CH_3	1.75	0.229	0.036
C_2H_5	1.33	.214	.071
n-C_3H_7	1.38	.263	.060
n-C_4H_9	1.32	.229	.047
n-C_5H_{11}	1.28	.228	.042

[a] From Dippy, ref. 1. [b] From Hall and Sprinkle, THIS JOURNAL, **54**, 3469 (1932), and from Hoerr, McCorkle and Ralston, *ibid.*, **65**, 328 (1943).

One important difference will be noted between the order obtained with trimethylboron and the orders obtained by classical methods. With trimethylboron the irregularity appears with the third member of the series, $C_2H_5NH_2$:BMe_3, rather than with the fourth. Since ethylamine cannot form a hydrogen bridge of the type postulated to account for the behavior of butyric acid and propylamine in aqueous solution, it is reasonable to seek some other explanation. (It might also be pointed out that according to the hydrogen bridge hypothesis the order should be independent

(1) Dippy, *Chem. Rev.*, **25**, 151 (1939).

(2) THIS JOURNAL, **66**, 431, 435 (1944).

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of the reference acid, a conclusion which is contrary to the observed facts.)

We suggest that the origin of this behavior is steric in nature—the observed weakening of the base occurring with the first member of the series in which the alkyl group of the base can interfere with the acid (H^+ or BMe_3). It is obvious that the point in the series at which the weakening is observed will depend upon the size of the reference acid. In the case of a large acid, such as trimethylboron, such interference occurs in a base having a shorter chain than in the case where the acid is the small proton. It would be expected that an even larger acid, *e. g.*, triethylboron or tri-*n*-propylboron, would lead to a shift of the irregularity to methylamine, or even to ammonia. This prediction is now being tested.

The assistance afforded by a grant from the Penrose Fund of the American Philosophical Society is gratefully acknowledged.

DEPARTMENT OF CHEMISTRY
WAYNE UNIVERSITY
DETROIT 1, MICHIGAN
HERBERT C. BROWN

METALLURGICAL LABORATORIES
UNIVERSITY OF CHICAGO
CHICAGO 37, ILLINOIS
MODDIE D. TAYLOR

RECEIVED APRIL 19, 1944

THE RELATIONSHIP OF STRUCTURE TO ACTIVITY OF SULFANILAMIDE TYPE COMPOUNDS

Sir:

Kumler and Daniels[1] have suggested that the resonating form of the *p*-amino group with a separation of charge is a fundamental factor for the bacteriostatic activity of sulfanilamide type compounds. The experimental evidence for this suggestion is "that sulfanilamide has a higher (ultraviolet) extinction coefficient in base than in water."[2]

Because of the theoretical importance placed on this single observation, and since previous studies in this Laboratory[3] were not in agreement with it, we have repeated the work using a more suitable instrument (Beckman Spectrophotometer Model DU).[4] The data obtained for sulfanilamide are recorded in Fig. 1 and Table I. The additive function $-\log_{10}T$ was used in Fig. 1 to demonstrate the reliability of the method of correcting for solvent absorption.

TABLE I

ULTRAVIOLET SPECTRAL DATA ON SULFANILAMIDE

Form	Wave length of peak absorption, Å.	Extinction coefficient
Molecular (1 *N* NaCl)	2585	16,380 ± 49[a]
Ionic (1 *N* NaOH)	2505	16,150 ± 48
Difference	80	230 ± 97
Per cent. difference		1.42 ± 0.6

[a] The limits of error are those encountered in quadruplicate determinations.

(1) Kumler and Daniels, THIS JOURNAL, 65, 2190 (1943).
(2) Kumler and Strait, *ibid.*, 66, 2349 (1943).
(3) E. J. Robinson and D. Richardson, personal communication.
(4) This instrument was made available to us through the courtesy of Dr. V. du Vigneaud and Dr. W. Summerson, Department of Biochemistry, Cornell University Medical School, New York, N. Y.

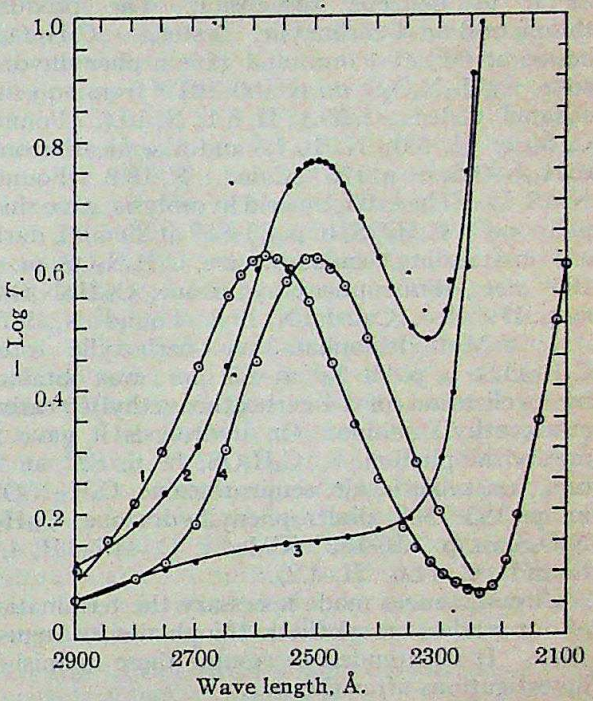

Fig. 1.—Log_{10} of per cent. light transmitted by a 1-cm. sample of: 1, 3.78×10^{-5} *M* sulfanilamide in 1 *N* NaCl, 1 *N* NaCl blank; 2, 3.78×10^{-5} *M* sulfanilamide in 1 *N* NaOH, water blank; 3, 1 *N* NaOH, water blank; 4, 3.78×10^{-5} *M* sulfanilamide in 1 *N* NaOH, solid line obtained by subtracting curve 3 from 2, and points -⊙- from measurements with 1 *N* NaOH blank.

These results do not confirm those of Kumler and Strait, and there appears to be no adequate experimental basis for the assumption that the resonating form with a separation of charge contributes more in a sulfonamide ion. Moreover, the lack of correlation between the base constants and bacteriostatic activity of sulfanilamide type compounds in general[5] does not support the hypothesis that the base weakening resonance form is a fundamental factor for activity.

(5) Bell and Roblin, THIS JOURNAL, 64, 2905 (1942).

STAMFORD RESEARCH LABORATORIES
AMERICAN CYANAMID COMPANY
STAMFORD, CONN.
PAUL H. BELL
J. FOSTER BONE
RICHARD O. ROBLIN, JR.

RECEIVED MARCH 15, 1944

SYNTHETIC THIOPHANE DERIVATIVES

Sir:

Karrer and Schmid[1] have recently described the synthesis of thiophanone-3 and of 2-methylthiophanone-3. Results essentially in agreement with those of the Swiss investigators have been obtained in this Laboratory.

(1) Karrer and Schmid, *Helv. Chim. Acta*, 27, 116, 124 (1944).

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(Carboethoxymethyl)-(β-carboethoxyethyl) sulfide, obtained by the reaction of thioglycolic ester with acrylic ester in the presence of a small amount of piperidine, was cyclized by means of sodium metal in benzene suspension. The product, thiophan-3-on-4-carboxylic ester,[2] $C_7H_{10}O_3S$, boiled at 96° at 4 mm. and gave a phenylhydrazone, $C_{13}H_{16}N_2O_2S$, m. p. 100–101°[3] from aqueous ethanol (Calcd.: C, 59.1; H, 6.1; N, 10.6. Found: C, 59.1; H, 6.0; N, 10.7), and a semicarbazone, $C_8H_{13}N_3O_3S$, m. p. 176° (Calcd.: N, 18.2. Found: N, 18.1). The ester, on acid hydrolysis, gave thiophanone-3, C_4H_6OS, b. p. 83–85° at 29 mm., darkens on standing, semicarbazone, $C_5H_9N_3OS$, m. p. 196° dec., dinitrophenylhydrazone, $C_{10}H_{10}N_4O_4S$, m. p. 179° dec. (Calcd.: N, 19.8. Found: N, 19.7).

2-Methylthiophan-3-on-4-carboxylic ester, $C_8H_{12}O_3S$, b. p. 93–95° at 4.5 mm., was obtained by cyclization of (α-carboethoxyethyl)(β-carboethoxyethyl) sulfide. On hydrolysis it gave 2-methylthiophanone-3, C_5H_8OS, b. p. 82° at 28 mm., unstable in air, semicarbazone, $C_6H_{11}N_3OS$, m. p. 185–186°, dinitrophenylhydrazone, $C_{11}H_{12}N_4O_4S$, m. p. 161–162° (Calcd.: C, 44.7; H, 4.1. Found: C, 44.6; H, 4.2).

Circumstances made necessary the termination of our studies on synthetic thiophanes in August, 1942. It is intended to resume these unfinished investigations after the war.

(2) The assigned formula is based on analogy; see Prill and McElvain, THIS JOURNAL, **55**, 1235 (1933).

(3) Karrer and Schmid (ref. 1, p. 127) obtained two phenylhydrazones, m. p. 141.5–142.5° and m. p. 167°; possible explanations to account for this discrepancy cannot be investigated at this time.

GATES AND CRELLIN LABORATORIES OF CHEMISTRY
CALIFORNIA INSTITUTE OF TECHNOLOGY
PASADENA 4, CALIFORNIA EDWIN R. BUCHMAN
HARRY COHEN

RECEIVED APRIL 21, 1944

THE NATURE OF THE LUCIFERIN–LUCIFERASE SYSTEM

Sir:

In the luminescent system extracted from *Cypridina*, the substrate, luciferin, is dialyzable, while the enzyme, luciferase, is not.[1] Reduced luciferin undergoes reversible dark oxidation by oxygen or ferricyanide, and apparently irreversible luminescent oxidation by luciferase plus oxygen. Like dihydrocoenzyme, with an absorption maximum at 3400 Å., considerably purified, reduced luciferin solutions have an absorption peak near 3200 Å. On adding oxygen this absorption diminishes, while a new peak at 4300 Å. appears, shifting quickly to 4700 Å., then disappearing.[2] In presence of oxygen, aqueous luciferin is unstable. The absorption at 4700 Å. resembles that of certain flavoproteins, and practically coincides with the luminescence maximum at 4750 Å. The energy of this luminescent transition corresponds to 59,430 calories as compared to 57,340 calories available by direct oxidation of two hydrogen atoms on glucose, the substrate known to increase tremendously the luminescence of washed luminous bacteria.

We have now observed that a concentrated solution of luciferase, after prolonged dialysis with several hundred volumes of distilled water, and storage for some eighteen months in a refrigerator, will luminesce with oxygen, following reduction by (1) $Na_2S_2O_4$, (2) reduced Coenzyme I solution (partially reduced by pure hydrogen and platinized platinum, then added anaerobically to luciferase), (3) reduced riboflavin (similarly treated), (4) washed cells of *E. coli* plus glucose, and (5) growing culture of *E. coli*.[3] A portion of the luciferase solution gave luminescence repeatedly on successive additions of an excess of hydrosulfite then oxygen, but finally ceased. Luminescence continuous for some hours resulted when hydrogen, plus slight oxygen impurity, was passed through some luciferase solution containing platinized asbestos. Oxidized coenzyme, oxidized riboflavin, ferrocyanide, or glucose without bacteria, as expected, did not reduce the luciferase.

A consideration of the above facts indicates that the luminescent system consists of a pyridine nucleotide plus flavoprotein. According to the absorption spectrum, "luciferin" apparently contains both Coenzyme (I or II) and a flavine prosthetic group, the former component providing a reductant, and the latter, after loose combination with its specific protein, comprising molecules excitable by oxidation. Some of the excited molecules radiate and are not destroyed, but others, failing to radiate are destroyed by their absorbed energy. This phenomenon causes the "irreversible reaction" of luminescence. Such destruction of non-radiating excited molecules is responsible for the familiar degradation of riboflavin in solution in the light, and also phthalhydrazides during luminescent oxidation.

Thus, in luminous bacteria, light emission presumably occurs when flavoprotein, reduced by hydrogen from suitable substrates (*e. g.*, glucose) via the dehydrogenase–coenzyme system, is oxidized directly by oxygen. The effects of cyanide on oxygen consumption and luminescence, respectively, indicate that most of the hydrogen proceeds step-wise, by electron transfer, through the cytochrome–heme system to oxygen. With chlorophyll substituted for the related heme molecule, the same system of catalysts operating in the reverse direction would lead to photosynthesis. In luminescence two hydrogens are oxidized for the quantum emitted, while in photosynthesis single hydrogens are made available.

PRINCETON UNIVERSITY
PRINCETON, N. J. FRANK H. JOHNSON
HENRY EYRING

RECEIVED APRIL 17, 1944

(1) Harvey, "Living Light," Princeton University Press, Princeton, N. J., 1941.

(2) Chase, *J. Biol. Chem.*, **150**, 435 (1943).

(3) Doctors Chase, Schlenk and Kunitz kindly supplied experimental materials.

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THE TOTAL SYNTHESIS OF QUININE[1]

Sir:

Quinine preparations have been known and used for centuries in the treatment of malaria. The pure crystalline alkaloid was isolated in 1820, and the extensive degradative researches of the last century culminated in the proposal of the correct structure in 1908, but the complexity of the molecule has placed hitherto insurmountable difficulties in the way of the total synthesis of the drug. We wish to record the first total synthesis of quinine.

7-Hydroxyisoquinoline was converted through its 8-piperidinomethyl derivative (m. p. 81.5–82.5°; *Anal.* Calcd. for $C_{15}H_{18}ON_2$: C, 74.36; H, 7.49; N, 11.57. Found: C, 73.79; H, 7.65; N, 11.86) into 7-hydroxy-8-methylisoquinoline (m. p. 232.0–233.5°; *Anal.* Calcd. for $C_{10}H_9ON$: C, 75.44; H, 5.70; N, 8.80. Found: C, 74.96; H, 5.51; N, 8.94). Hydrogenation over platinum oxide to 7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline (m. p. 246–250°; *Anal.* Calcd. for $C_{10}H_{13}ON$: C, 73.59; H, 8.03; N, 8.58. Found: C, 73.41; H, 8.26; N, 8.63), and acetylation gave N-acetyl-2,7-hydroxy-8-methyl-1,2,3,4-tetrahydroisoquinoline (m. p. 191–198°; *Anal.* Calcd. for $C_{12}H_{15}O_2N$: C, 70.22; H, 7.35. Found: C, 70.54; H, 7.20). Further hydrogenation over Raney nickel led to a mixture of stereoisomeric N-acetyl-7-hydroxy-8-methyldecahydroisoquinolines (*Anal.* Calcd. for $C_{12}H_{21}O_2N$: C, 68.20; H, 10.02; N, 6.63. Found: C, 68.06; H, 9.75. Pure *cis*-isomer, m. p. 126.0–128.0°. *Anal.* Found: C, 68.34; H, 9.58; N, 6.59) which was oxidized directly to the corresponding N-acetyl-7-keto-8-methyldecahydroisoquinolines. From the latter, the pure *cis*-N-acetyl-7-keto-8-methyldecahydroisoquinoline (*cis* refers to the mode of locking of the rings) was isolated as the crystalline monohydrate (m. p. 80.5–82.5°; *Anal.* Calcd. for $C_{12}H_{19}O_2N \cdot H_2O$: C, 63.40; H, 9.32; N, 6.16. Found: C, 63.34; H, 8.85; N, 6.40) and converted by ethyl nitrite and sodium ethoxide to N-acetyl-10-oximinodihydrohomomeroquinene ethyl ester (two polymorphic forms—*labile*, m. p. 96–98°; *stable*, m. p. 108.5–109.0°; *Anal.* Calcd. for $C_{14}H_{24}O_4N_2$: C, 59.14; H, 8.51; N, 9.85. Found: C, 59.39; H, 8.24; N, 10.02). Reduction of the oximino-ester to the corresponding amine (characterized as the free 10-aminodihydrohomomeroquinene dihydrate, m. p. 186.5–188°; *Anal.* Calcd. for $C_{10}H_{20}O_2N_2 \cdot 2H_2O$: C, 51.20; H, 10.24; N, 11.86. Found: C, 50.83; H, 9.90; N, 12.04), complete methylation by methyl iodide and potassium carbonate, followed by alkali treatment of the resulting quaternary salt (*Anal.* Calcd. for $C_{17}H_{33}O_3N_2I$: C, 46.45; H, 7.55; N, 6.35. Found: C, 46.67; H, 7.14; N, 6.18) gave *dl*-homomeroquinene, isolated as the N-uramido derivative (m. p. 165.2–165.8° [dec.]; *Anal.* Calcd. for $C_{11}H_{18}O_3N_2$: C, 58.40; H, 8.02; N, 12.39; CH_3-C, nil. Found: C, 58.13; H, 7.45; N, 12.39; CH_3-C, nil). The free *dl*-homomeroquinene (m. p. 219–220° [dec.]) obtained on cleavage of the uramido group was converted by esterification and benzoylation to N-benzoylhomomeroquinene ethyl ester. Condensation of the latter with ethyl quininate, following the general methods elaborated by Rabe [*Ber.*, **51**, 1360 (1918); *ibid.*, **52**, 1842 (1919)], working with related natural materials [*cf.* Prožtenik and Prelog, *Helv. Chim. Acta*, **26**, 1965 (1943)], gave *dl*-quinotoxine. The racemic alkaloid was resolved through its salts with dibenzoyl-*d*-tartaric acid. The pure synthetic *d*-quinotoxine dibenzoyl-*d*-tartrate had m. p. 185.5–186°, and showed no depression in melting point on admixture with a sample of authentic material prepared from natural quinotoxine. The synthetic *d*-quinotoxine regenerated from the salt was a very pale yellow viscous oil, $[\alpha]_D$ +43°. Conversion of *d*-quinotoxine to quinine was first effected over twenty-five years ago by Rabe [*Ber.*, **51**, 466 (1918)], working with natural materials, during the course of his elegant work which resulted in the determination of the correct structures of the cinchona alkaloids.

RESEARCH LABORATORY, POLAROID CORPORATION
CONVERSE MEMORIAL LABORATORY
HARVARD UNIVERSITY R. B. WOODWARD
CAMBRIDGE 38, MASS. W. E. DOERING

RECEIVED APRIL 11, 1944

(1) This work was undertaken as a research project of Polaroid Corporation by the senior author, instructor in chemistry at Harvard University and chemical consultant to Polaroid Corporation.

THIOPHANE DERIVATIVES

Sir:

The appearance of reports by Karrer, Schmid and Kehrer [*Helv. Chim. Acta*, **27**, 116, 124, 127, 142 (1944), Received April 3, 1944] on thiophane derivatives prompts us to record our experiments in that field.

The dimethyl ester of β-mercaptopropionic acid S-acetic acid, obtained by addition of methyl thioglycolate to methyl acrylate in the presence of piperidine, was cyclized in two ways. With sodium methoxide in toluene at 110°, the main product was 4-carbomethoxy-3-ketothiophane (m. p. 37–38°, b. p. 128.5–129.5° [20 mm.]. *Anal.* Calcd. for $C_6H_8O_3S$: C, 45.1; H, 5.0; S, 20.0. Found: C, 44.3; H, 5.2; S, 19.8). This substance gave a permanent red-violet coloration with ferric chloride, and from it a *semicarbazone* (m. p. 189.5–190.0°. *Anal.* Calcd. for $C_7H_{11}O_3N_3S$: C, 38.7; H, 5.1; N, 19.3. Found: C, 39.2; H, 4.7; N, 19.1), a *monobenzylidene derivative* (m. p. 158–159°. *Anal.* Calcd. for $C_{13}H_{12}O_3S$: C, 62.9; H, 4.8. Found: C, 62.7; H, 5.2) and a *monofurfurylidene derivative* (m. p. 157–158°. *Anal.* Calcd. for $C_{11}H_{10}O_4S$: C, 55.5; H, 4.2. Found: C, 55.6; H, 4.6) were obtained. When the initial condensation was carried out at room temperature in ether with sodium

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methoxide, the major product was 2-carbomethoxy-3-ketothiophane (oil, b. p. 116–116.5° [9 mm.]). From this keto-ester, a *semicarbazone* (m. p. 187–187.5° [mixed with the semicarbazone of the other isomer, m. p. 170–176°]. *Anal.* Calcd. for $C_7H_{11}O_3N_3S$: C, 38.7; H, 5.1. Found: C, 38.8; H, 4.7), a *monobenzylidene derivative* (m. p. 129–130°. *Anal.* Calcd. for $C_{13}H_{12}O_3S$: C, 62.9; H, 4.8. Found: C, 62.7; H, 4.9) and a *monofurfurylidene derivative* (m. p. 139.5–140.0°. *Anal.* Calcd. for $C_{11}H_{10}O_4S$: C, 55.5; H, 4.2. Found: C, 55.7; H, 4.3) were prepared.

Either of the isomeric β-keto-esters gave on hydrolysis 3-ketothiophane (oil, b. p. 58.2–58.4° [7 mm.]. *Anal.* Calcd. for C_4H_6OS: S, 31.4. Found: S, 30.3). A *dibenzylidene derivative* (m. p. 187.5°. *Anal.* Calcd. for $C_{18}H_{14}OS$: C, 77.8; H, 5.1; S, 11.5. Found: C, 77.9; H, 5.3; S, 11.7) and a *difurfurylidene derivative* (m. p. 191–192°. *Anal.* Calcd. for $C_{14}H_{10}O_3S$: C, 65.1; H, 4.2. Found: C, 65.1; H, 3.9) were prepared.

The 2-carbomethoxy-3-ketothiophane is remarkable in that on treatment with weak oxidizing agents (iodine, ferric chloride) it is rapidly and quantitatively converted to a double compound, $C_{12}H_{14}O_6S_2$ (m. p. 188.5–189.5°. *Anal.* Calcd. for C, 45.3; H, 4.4; S, 20.1. Found: C, 45.3; H, 4.6; S, 20.3), *dibenzylidene derivative* (m. p. 236°. *Anal.* Calcd. for $C_{26}H_{22}O_6S_2$: C, 63.0; H, 4.5. Found: C, 63.0; H, 4.6). From the double compound, by desulfurization, a *substance*, $C_{12}H_{18}O_6$ (m. p. 125–126°. *Anal.* Calcd. for C, 55.8; H, 7.0. Found: C, 56.7; H, 7.3), and from the latter by treatment with dilute mineral acids, an *acid*, $C_{10}H_{12}O_5$ (m. p. 152–153°. *Anal.* Calcd. for C, 56.7; H, 5.7. Found: C, 56.8; H, 6.0) were obtained, which we believe to be, respectively, dimethyl α,α'-dipropionyl succinate, and 2,5-diethylfuran-3,4-dicarboxylic acid.

We should like to take this opportunity to point out that the 2-furfurylidene-3-ketothiophane-4-carboxylic acid methyl ester described above possesses the complete continuous carbon–sulfur skeleton of biotin.

CONVERSE MEMORIAL LABORATORY
HARVARD UNIVERSITY R. B. WOODWARD
CAMBRIDGE 38, MASS. R. H. EASTMAN

RECEIVED APRIL 20, 1944

NEW BOOKS

The Chemistry of Organic Medicinal Products. By GLEN L. JENKINS, Dean and Professor of Pharmaceutical Chemistry, School of Pharmacy, Purdue University, and WALTER G. HARTUNG, Professor of Pharmaceutical Chemistry, School of Pharmacy, The University of Maryland. Second Edition. John Wiley & Sons, Inc., New York, N. Y.; Chapman and Hall, Ltd., London. iv + 675 pp. 14.5 × 12 cm. $6.50.

The second edition of this excellent compilation of organic medicinal compounds according to the accepted scheme of chemical classification is, in many respects, a much improved revision of the first planographed edition of 1941. Care has been taken to eliminate the trivial typographical errors, misspellings, misuse of words and phrases, and careless punctuation which marred the initial text. Rearrangement of the material into more compact paragraphs and better classified sections, and the gathering of the literature references into terminal chapter bibliographies have made the matter more easily and pleasantly readable. New material has been introduced and in many sections the explanatory text has been expanded, particularly in the chapter on Stereoisomerism where an excellent discussion of *cis–trans* isomerism about the ethylene bond is presented; a matter of some present importance in view of the recent revival of interest in the vitamin properties of the unsaturated fatty acids. A novel and interesting chapter entitled "Some Physical Chemical Properties of Medicinal Products" has been added. It is realized that a critical review and discussion of all theories and hypotheses is beyond the scope of this book but one would have liked to have seen some mention of the importance of physical chemical factors in the evaluation of the sulfonamides. This present text is intended for students in the more advanced courses in pharmaceutical, chemical, biological and medical science but will undoubtedly prove of great value and interest, not only to practitioners in these fields, but to the growing army of workers in the medicinal chemical industry.

C. R. ADDINALL

The Extra Pharmacopoeia. By MARTINDALE. 22nd Edition in Two Volumes. Published by Direction of the Council of the Pharmaceutical Society of Great Britain. The Pharmaceutical Press, 17 Bloomsbury Square, W.C. 1, London, England, 1943. xxxiii + 1217 pp. 11.5 × 18 cm. Price, 27/6; postage 6d. extra.

The first edition of "The Extra Pharmacopoeia" appeared in 1883 as a manual of 313 pages. The latest edition, the 22nd, published by direction of the Council of the Pharmaceutical Society of Great Britain, consists of two volumes: volume I, published in 1941, contains 1289 pages; volume II, the subject of this review, is a book of 1217 pages. It hardly seems possible to account for the 60-year existence and the continual growth in size of this particular "pharmacopoeia" except by the explanation that there has been a steady demand for a work of this nature, and that these volumes have satisfied the demand.

"The Extra Pharmacopoeia" is a repository of a vast amount of important, interesting and up-to-date information, and has been written particularly for the pharmacist, the physician, and the chemist who deals with foods and medicinal products. A rough estimate of the number of very diverse subjects, listed in the common index for the two volumes, is 13,000. Although too much space would be required to mention all of the chapter headings for volume II, 42 in number, the following examples will convey some idea of the nature of the topics which are discussed: Proprietary Medicines, Nomenclature of Organic Compounds, Chemotherapy, Polarographic Analysis, Nutrition and Food Values, Notes on Water Analysis, X-Ray Diagnosis and Actinotherapy.

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Naturally, due to its brevity, the chapter which deals with some particular subject is hardly apt to contain information which will be new to the specialist in that field. However, this very brevity will be appreciated by the specialist who may wish to review very rapidly the developments and most outstanding facts in some cognate field with which he is only partially acquainted.

It is to be regretted that so much of the text appears in very fine print; probably any improvement in this respect is not feasible because of economic factors.

F. F. BLICKE

Supplement to The Extra Pharmacopoeia, Vol. I, 22nd Edition, 1941. By MARTINDALE. The Pharmaceutical Press, 17 Bloomsbury Square, London, W.C. 1, England, 1943. 48 pp. 11 × 17.5 cm. Price 2s., postage 2d.

The best manner in which to describe this Supplement is to mention a few of the fifteen subject headings listed in the table of contents: Summary of the Principal Changes made by the 4th, 5th and 6th Addenda to the British Pharmacopoeia, 1932, Additions in the 2nd, 3rd, 4th and 5th Supplements to the British Pharmaceutical Codex, 1934, Deletions from the British Pharmaceutical Codex, 1934, Amendments in the 2nd, 3rd, 4th and 5th Supplements to monographs of the British Pharmaceutical Codex, 1934, Preparations of the National War Formulary, 1943, Articles added to the United States Pharmacopoeia (U. S. P. XII) and Volume I Corrigenda.

It seems evident that the information in this booklet will be of especial importance to those who manufacture and dispense pharmaceutical products.

F. F. BLICKE

Semimicro Qualitative Analysis. A Course in Applied Chemical Equilibrium. By JOHN F. FLAGG, Ph.D., Assistant Professor of Chemistry, and WILLARD R. LINE, Ph.D., Professor of Chemistry, The University of Rochester. D. Van Nostrand Company, Inc., 250 Fourth Avenue, New York, N. Y., 1943. viii + 140 pp. 2 figs. 14.5 × 22.5 cm. Price, $1.50.

This book is another addition to the already large list of semi-micro texts with chapters on related theoretical and factual matter. Its six preliminary chapters deal with the definition and field of qualitative analysis, chemical equilibrium, homogeneous equilibria, heterogeneous equilibria, oxidation–reduction reactions and technique of semimicro qualitative analysis, all in 56 pages. The treatment of the topics is clear and readable, but necessarily brief.

The analytical part takes up cation, anion and alloy analysis. The cations are separated and identified in much the usual way, some interesting points being: separation of the acid sulfide group with sodium sulfide reagent; separation of lead and bismuth with ammonia from copper and cadmium; use of salicylaldoxime to divide copper and cadmium; the precipitation of zinc as sulfide in a formate buffer prior to the rest of the alkaline sulfide family; and the separation of calcium and magnesium nitrates with methyl alcohol from barium and strontium. The anion analysis is not treated very systematically. The alloy section deals very briefly with certain alloys, giving the appropriate methods, including additional ones needed for silicon, tungsten, molybdenum, vanadium and titanium.

Although it should prove to be a good average text for the student, the book suffers from bad planning and poor style editing. The trimmed head margin is $^3/_8$", the side margin $^7/_8$", while the bottom is $1^3/_8$", giving a distinctly "short-skirted" appearance which belies the prominent statement that production was carried out in line with war economy. There are several places where additional section heads might well have been used, especially on pp. 95 and 99. A good and consistent editorial style seems almost absent, resulting in numerous irregular and unsightly details, such as: bold, roman and italics for mathematical symbols, formulas instead of names, the use of P for procedure, and the space-wasting use of bulky text type for illustrative chemical and mathematical formulas.

ALLEN D. BLISS

Pyrotechnics, Civil and Military. By G. W. WEINGART. Chemical Publishing Co., Inc., Brooklyn, New York, 1943. xii + 220 pp. 96 figs. 14.5 × 22 cm. Price, $5.00.

Books on fireworks are rare. Weingart's book, so far as the reviewer knows, is the only book devoted entirely to this subject which has been published in the United States since the three volumes of Faber's "Military Pyrotechnics" were issued by the Government Printing Office in 1919. The present revision is really a third edition, or, more exactly, a fourth if the early mimeographed edition is counted. It contains more and better pictures than its predecessors, and new formulas which the author has tried for himself. Its price seems rather high. It lacks a much needed index. The glossary is important and useful. The List of Pyrotechnical Books which terminates the volume gives titles which are too much abbreviated, does not indicate which books are translations, and fails to show the places of publication. It does not by any means furnish "a complete record of the development of the art of pyrotechny up to the present time." Except for a few passing references to military uses, the book deals entirely with recreational fireworks and contains nothing which justifies the assertion on the title-page that it deals with military pyrotechnics as well.

Weingart's book is a practical book by a practical man. Recognized as such, it is extremely valuable. It summarizes an experience of about fifty years. Its principal parts deal, respectively, with I. Ingredients, with II. Manipulation, Tools and Appliances Used, with III. Articles of Manufacture and Formulas, and with IV. Exhibition Fireworks. It contains many observations, sometimes homely but always useful, on safety, on procedure, on the properties of substances. It tells the amateur how to construct fireworks pieces, and it shows the chemist what the tricks and contrivances are by which a few rather ordinary chemical substances are made to produce some extraordinary audible and visible effects. The same devices are applied in military as in civil pyrotechnics—and Weingart's book will supply a needed acquaintance with them to anyone who may have to work with explosive and pyrotechnic instruments of war.

TENNEY L. DAVIS

The Optical Properties of Organic Compounds. By ALEXANDER WINCHELL, University of Wisconsin. University of Wisconsin Press, Madison, Wisconsin. 1943. xiii + 342 pp. 157 figs., 1 chart. 17.8 × 26.2 cm. (Photo offset.) Price, $5.00.

While optical methods have been widely used in identifications of natural and synthetic inorganic compounds they have seldom been applied to organic compounds. This limitation has several causes, among which are: faults of an educational scheme, some difficulties in application, and absence of a summary of previous observations. Professor Winchell has successfully answered the last need.

Optical data for about 1700 compounds are tabulated, in a determinative scheme, according to their mean refractive indices and 910 are plotted on a chart, according to their birefringences and mean refractive indices. The limited numbers and types of compounds are disappointing from the point of view of usefulness in determinative organic chemistry, but the lists are quite complete as far as published data are concerned and previously unpublished values are included. Alkaloids are the most numerous class treated, being represented by 280 compounds. Optical properties are listed for approximately 250 salts.

The designation of refractive indices is confusing and does not follow the widely accepted usage of α, β and γ.

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Since the book is strictly a tabulation of constants the untrained worker must look elsewhere for methods of measurement.

S. B. HENDRICKS

Synthetic Resins and Rubbers. By PAUL O. POWERS, Chief, Organic Research, Armstrong Cork Company. John Wiley & Sons, Inc., 440 Fourth Avenue, New York, N. Y., 1943. v + 296 pp. 49 figs. 13.5 × 21.5 cm. Price, $3.00.

This little book gives a clear and interesting account of the chemistry of more important synthetic resins and rubbers. It opens with a general historical and statistical introduction, including a table listing the name, structural formula, physical properties and source of the raw materials from which the industrially important resins are derived. The next chapter discusses the mechanism and kinetics of polymerization and the distinction between linear and cross linked polymers and the behavior of catalysts and inhibitors of polymerization. This is followed by separate chapters describing the more important classes of resins now in use industrially. Trade names are avoided throughout. Finally there is a very brief summary of solvents and plasticizers and of the technique of molding and the use of resins in formulating protective coatings. Each chapter is followed by review questions and a few additional references, but there is no attempt to cite a literature reference in support of every statement in the text.

This book does not compete with the larger books available in completeness, in detail and in giving numerous references. It does not give enough numerical data as to properties of the commercially available resins to be of much help to anyone trying to choose the best resin for a particular application. However, this book can be recommended to a chemist who has not specialized in the field but wishes a readable and reliable general introduction to synthetic resins and synthetic rubbers.

GRINNELL JONES

Principles and Applications of Electrochemistry. Volume II. Applications. By W. A. KOEHLER, Professor of Chemical and Ceramic Engineering, West Virginia University. Second Edition. John Wiley and Sons, Inc., New York, N. Y., 1944. v + 573 pp. 260 figs. 14.5 × 21.5 cm. Price, $5.00.

This volume on applications of electrochemistry is intended for use in conjunction with Prof. H. J. Creighton's volume dealing with the principles of electrochemistry. The author has included the following new topics in the second edition: continuous tin strip plating, magnesium from sea water, hydrogen peroxide manufacture, fluorescent lamps, induction heating of non-conducting materials, new carbon bisulfide furnace, new phosphorus furnace, and nickel–cadmium alkaline storage battery.

The second chapter, "Review of Theoretical Electrochemistry," leaves some confusion in the reader's mind regarding the relative merits of the Arrhenius theory and the complete dissociation theory. The author presents both theories and then arbitrarily chooses the Arrhenius theory for the balance of his discussion.

The descriptions of the various applications are as complete as is practical in one volume. The descriptions are, for the most part, accurate; there are numerous errors that will no doubt be corrected in the subsequent printings. One of the more notable errors is the statement on page 175: "the platinum metals go into solution in the electrolytic parting." They remain in the slimes along with gold, but go into solution in the gold refining cell.

The book is well illustrated with photographs and line drawings of the various types of equipment used and operating data given for all of the important applications. This is supplemented with numerous references to the literature for the use of the reader interested in any one particular application.

The following classes of applications are discussed: primary and secondary cells, electroplating, refining and electrometallurgy of metals, electrolysis of halides, electrolytic oxidation and reduction, hydrogen and oxygen, corrosion, electroanalysis, electric furnaces, electronics, ozone, nitrogen fixation, separation by electrical means, and miscellaneous electrochemical processes (such as anodizing, electrolytic polishing, etc.).

The revised edition is now up to date and will no doubt continue to serve the same purposes as the first edition, that is, as a text for college students and a reference for those in the industry.

HENRY B. LINFORD

A Short Course in Quantitative Analysis. By HOBART H. WILLARD, Ph.D., Professor of Analytical Chemistry, University of Michigan, N. HOWELL FURMAN, Ph.D., Professor of Chemistry in Princeton University, and JOHN F. FLAGG, Ph.D., Assistant Professor of Chemistry, University of Rochester. D. Van Nostrand Company, Inc., 250 Fourth Ave., New York, N. Y., 1943. ix + 253 pp. 15 × 22 cm. Price, $2.50.

This book is intended as a text for brief, one-semester courses in elementary quantitative analysis for premedical, agricultural, and certain classes of engineering students, and not for students concentrating in chemistry. As the authors state in the Preface the book is more or less an abbreviated version of the two senior authors' well-known "Elementary Quantitative Analysis," and a number of the good features of the latter text have been retained.

The first three chapters, I, Introduction; Fundamental Theory, II, Introduction to Laboratory Work, and III, The Measurements of Quantitative Analysis, furnish a concise introduction to techniques that are common to both gravimetric and volumetric analysis. As an example of one way in which brevity has been attained it may be noted that in Chapter III in connection with the discussion of the analytical balance and weighing no mention is made of the use of calibrated weights, nor of correction for air buoyancy. Such omissions are probably necessary in short courses for which the book is intended.

The following eight chapters are devoted to the theory and practice of volumetric analysis. Procedures are given for the following volumetric determinations: Sodium Oxide in Soda Ash; Replaceable Hydrogen in an Acid; Nitrogen in Organic Compounds by the Kjeldahl method; Chloride by the Mohr, Fajans (adsorption indicator), and Volhard methods; Iron in ores by the permanganate, dichromate, and ceric sulfate methods; Calcium Oxide in "calcium carbonate"; Available Oxygen in Pyrolusite (oxalic acid–permanganate method); Available Chlorine in Bleaching Powder (iodometrically); Copper in ores; and Arsenic in "arsenious oxide" (iodometrically). These determinations illustrate most of the important types of volumetric methods. Considerable emphasis has been placed on the theory of protolytic titrations (the illustrative titration curves on pages 58 and 59 are excellent), on the interpretation of oxidation–reduction titrations in terms of the oxidation potential, and on the use of modern oxidation–reduction indicators.

Most of the procedural details appear to be quite satisfactory. As one of the few exceptions may be noted the recommendation on p. 155 that *ammonium* thiocyanate be used to metathesize cuprous iodide in the iodometric copper determination; ammonium thiocyanate may not be used because it usually contains impurities which consume iodine, and the potassium salt should be employed.

Gravimetric analysis is discussed in the last three chapters, and procedures are provided for the following determinations: Chloride; Sulfate in a soluble sulfate; Magnesium Oxide; Phosphoric Anhydride in a soluble phosphate; and an abbreviated analysis of limestone for loss on ignition, siliceous matter, "R_2O_3," calcium oxide, and magnesium oxide. Among the few novelties noted in the gravimetric procedures is the employment of calcium carbonate as the final weighing form for calcium, which avoids

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the difficulty of weighing ignited calcium oxide, but which usually is not attempted in elementary courses because it requires rather careful control of temperature (electric furnace) during the ignition of the calcium oxalate.

In keeping with its intended use in abbreviated courses the text contains no mention of electrolytic, colorimetric, or other special analytical methods.

Most of the chapters conclude with sets of problems which, in the words of the authors, "have been roughly arranged in order of increasing difficulty, with answers to about one-third included."

In the reviewer's opinion one undesirable feature of the text is the consistent disregard of the actual molecular and ionic states of the substances involved in the reaction equations which are given. For example the equation "$Fe^{+++} + 6KCNS = Fe(CNS)_6^{=} + 6K^{+}$" given on p. 96 leads to some rather weird conclusions when interpreted literally. The same is true of numerous other equations throughout the text, of which the following on p. 115 is typical: "$5Na_2C_2O_4 + 2KMnO_4 + 8H_2SO_4 = 10CO_2 + 5Na_2SO_4 + K_2SO_4 + 2MnSO_4 + 8H_2O$." Since equations of this sort are misleading, and serve only to obscure the real reactions that take place as well as the essential equilibria involved, the reviewer cannot agree with the statement on p. 104 that they "are very useful in understanding the fundamental stoichiometry of a process."

The Appendix contains an outline of the general literature of analytical chemistry, a section on Mathematical Operations, a list of stock solutions of protolytic indicators, a table of dissociation constants of the commoner acids and bases, a table of solubility products, and a five-place logarithm table.

Since the reviewer has the highest regard for Willard and Furman's "Elementary Quantitative Analysis," which has contributed so much to the maintenance of high standards in the teaching of quantitative analysis, he cannot become very enthusiastic over this emasculated version.

JAMES J. LINGANE

Industrial Chemistry of Colloidal and Amorphous Materials. By WARREN K. LEWIS, Ph.D., Professor in the Department of Chemical Engineering, Massachusetts Institute of Technology, LOMBARD SQUIRES, S.M., Chemical Engineer with E. I. du Pont de Nemours Company, Wilmington, Delaware, and GEOFFREY BROUGHTON, Sc.D., A.I.C., Chemical Engineer with the Eastman Kodak Company, Rochester, N. Y. The Macmillan Company, 60 Fifth Avenue, New York, N. Y., 1942. xi + 540 pp. Illustrated. 16 × 24 cm. Price, $5.50.

The authors of this very interesting and well-written manual set out to write a text on the industrial chemistry of colloidal and amorphous materials. These they list as emulsions and foams, thermoplastics, glass, paper, plastic fibers, leather, rubber, clays, synthetic resins and plastics, and textile fibers.

The technology of each of these materials is clearly and briefly discussed, together with the scientific interpretation of each process and product. For example, the X-ray diagrams and other physical chemical data are correlated with the industrial procedures. This provides a very interesting and clarified conspectus such as is hardly to be found elsewhere.

In order to lay a foundation for this treatment, the authors devote the first half of the book to a review of physics and of colloid science, beginning with structure of liquids and proceeding through viscosity, surface tension, orientation, adsorption, suspensoids, amorphous solids, emulsoids, electrochemical behavior of colloids, gelation, to plastic distortion and flow.

The treatment as well as the choice of the data is orthodox, and in accordance with the earlier development of the subject. For example, there is no mention of the essential stabilizing agent in the whole chapter on suspensoids, whereas a stabilizing agent is as necessary here as it is in the formation of emulsions or foams. On the other hand, the authors have rationalized for themselves the subject matter that they discuss, and this is done so clearly that the reader is shown the facts as well as the way in which the authors interpret them. The explanations are reasonable and appeal to the engineering mind. The reader is invited by the authors to formulate his own opinions.

The authors state—"In a specific problem knowledge of the facts is often inadequate and occasionally in dispute, while understanding of underlying causes is limited and uncertain. Experts disagree on the explanations of phenomena of fundamental importance. In such a situation the scientist tends to withhold judgment but the technologist is faced with the necessity of making decisions and taking action. Many individuals prefer a purely empirical approach, but it is the conviction of the writers that it is best to submit each problem to a careful, theoretical analysis, even though in the nature of the specific case this may be known to be inadequate. A major purpose, therefore, is the introduction of the student to such a method of attack." To assist in this purpose they supply numerous cross references and append a bibliography to each chapter.

The book has stood the test of time, embodying the results of twenty-five years teaching of the subject at the Massachusetts Institute of Technology. The preparation of the manuscript was begun over a dozen years ago by Dr. P. K. Frolich and it has been constantly revised because of the very rapid developments in most of the fields discussed.

This admirable book is not only an excellent text but is a unique contribution to the advancement of science and industry.

JAMES W. MCBAIN

Laboratory Manual of Spot Tests. By Dr. FRITZ FEIGL. Translated from the German manuscript by Ralph E. Oesper, Ph.D., Professor of Chemistry, University of Cincinnati. Academic Press, Inc., 125 E. 23d Street, New York, N. Y., 1943. xii + 276 pp. 46 figs. 15.5 × 23.5 cm. Price, $3.90.

To one familiar with Dr. Feigl's previous books on spot reactions the first question prompted by this book is its relation to the earlier works. The other two translations—that by Matthews in 1937 and that by Oesper in 1940—covered, respectively, the practical and the theoretical parts of the German edition, "Qualitative Analyse mit Hilfe von Tüpfelreaktionen." Whereas they are primarily reference monographs, this book, containing both old and new material, is a laboratory manual based upon them, designed for teaching the analytical applications of the principle of accomplishing a chemical reaction within the volume of one drop of solution.

To achieve best pedagogic results with it, Dr. Feigl recommends a special course following elementary training in inorganic, organic, and physical chemistry. The possibility of adding much of this undoubtedly meritorious technic to our present curricula seems to the reviewer unpromising. Educational institutions in the United States are moving in the opposite direction. In the course of buying, making, using, and selling commodities and products, chemical industry and research are applying more and more analytical methods and apparatus, of greater and greater complexity. But perhaps even more rapidly analytical chemistry is being accorded less and less academic importance. If we are to reverse the process and incorporate new technics into our courses, analytical teachers having breadth of training and interest in the subject must be selected, and they must have better support of administrators.

The opening summary of the theoretical foundations of spot test analysis (22 p.) is followed by an adequately illustrated section on technic (40 p.). The appendix lists the reagents and includes a floor plan of a spot test laboratory.

There follows a section on surface and capillary effects (38 p.), especially interesting in connection with the use of filter paper as a medium for observing the reactions. Some

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thirty experiments are described which, quite apart from spot tests, should prove suggestive to demonstratively inclined instructors.

The portion devoted to actual analytical applications covers the following divisions: (a) inorganic analysis (69 p.), including inorganic and organic reagents, masking and catalytic reactions, and induced precipitations; (b) organic analysis (29 p.), including selected elements, groups and compounds; (c) rocks and minerals (16 p.); (d) technical products (17 p.); (e) biological material (12 p.); and (f) spot colorimetry by means of a standard series technic (16 p.). In the first two of these divisions the material is arranged systematically under the headings chemical basis, procedure, identification and concentration limits, and application in the presence of other materials.

Although mistakes noted are rare, a few items of usage seem to the reviewer to be questionable. Illustrative of his preference to that of the author are the following examples: (a) the spellings buret, pipet, and dichromate; (b) the I. U. C. names biacetyl, 2,2′-bipyridyl, and 1,10-phenanthroline; (c) the names recently recommended by an international committee for various inorganic complex ions; and (d) consistency in the formulation of heteropoly compounds, preferably in accordance with Keggin's work (including naming in terms of the central atom).

As a whole, the selection, arrangement, and treatment of material seems well done for teaching purposes. The smoothly reading translation renders American chemists indebted to Professor Oesper for making the information readily available. The book should prove valuable, not only for teaching but also as a source of ideas for practical analysts and research workers.

M. G. MELLON

The Organic Chemistry of Sulfur. Tetracovalent Sulfur Compounds. By CHESTER MERLE SUTER, Director of Chemical Research, Winthrop Chemical Company, Formerly Professor of Chemistry, Northwestern University. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y., 1944. v + 858 pp. 14.5 × 21.5 cm. Price, $10.00.

Chemists, academic as well as industrial, are indebted to Dr. Suter, who has been prominent as a university professor and as a director of industrial research, for a comprehensive review of this important field.

This book covers organic compounds of the types: $RO{\cdot}SO_2{\cdot}OR$, $R{\cdot}SO_2{\cdot}OR$, $R{\cdot}SO_2{\cdot}R$ and $R{\cdot}SO_2{\cdot}X$ in which R is either aliphatic or aromatic and X is —OH, —Cl, $—NH_2$, —NHR, etc. Sixty per cent. of the space is devoted to aromatic sulfonic acids and their derivatives, 93 pages to esters of sulfuric acid, 101 pages to aliphatic sulfonic acids and 117 pages to sulfones which include aliphatic, aromatic and mixed. There are about 4700 numbered references, but as there are frequently five, ten or twenty references under one number the total may pass ten thousand. *Chemical Abstracts* references are given for patents. This vast amount of material is arranged in an orderly way and presented clearly.

Aromatic sulfonic acids and their derivatives have been an important part of the old organic chemistry and aliphatic sulfates and sulfonates are of intense present interest as wetting agents and detergents; the old and the new are here brought together. This book is an important addition to chemical literature; no chemical library can be complete without it.

E. EMMET REID

BOOKS RECEIVED

March 10, 1944–April 10, 1944

HARRY BARRON. "Modern Synthetic Rubbers." Second Edition, Revised and Enlarged. D. Van Nostrand Company, Inc., 250 Fourth Avenue, New York, N. Y. 355 pp. $6.50.

G. GAMOW. "Mr. Tompkins Explores the Atom." The Macmillan Company, 60 Fifth Avenue, New York, N. Y. 97 pp. $2.00.

EMIL HEUSER. "The Chemistry of Cellulose." John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y. 660 pp. $7.50.

MARTINDALE. "Supplement to The Extra Pharmacopoeia, Vol. I, 22nd Edition, 1941." The Pharmaceutical Press, 17 Bloomsbury Square, London, W. C. 1, England. 48 pp. Price 2s., postage 2d.

FOREST RAY MOULTON, Editor. "Surface Chemistry." Publication of the American Association for the Advancement of Science, No. 21. American Association for the Advancement of Science, Smithsonian Institution Bldg., Washington, D. C. 160 pp. Price to members, $2.75; to others, $3.25.

CHARLES ELI REED. "Chemical Engineering." Bellman Publishing Company, Inc., 6 Park Street, Boston, Mass. 20 pp. $0.75.

JOSEPH REILLY AND WILLIAM NORMAN RAE. "Physico-Chemical Methods." Volumes I and II. D. Van Nostrand Company, Inc., 250 Fourth Avenue, New York, N. Y. 610 + 585 pp. $17.50.

"Synthetic Menthol. A Collection of the Literature Concerning its Pharmaceutical Properties and its Uses." Givaudan-Delawanna, Inc., 330 West 42nd Street, New York 18, N. Y. 238 pp.

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Claims for missing numbers will not be allowed (1) if received more than sixty days from date of issue (owing to the hazards of war-time delivery, no claims can be honored from subscribers outside of North America), (2) if loss was due to failure of notice of change of address to be received before the date specified in the preceding paragraph, or (3) if the reason for the claim is "missing from files."

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The American Chemical Society also publishes *Chemical Abstracts*, *Industrial and Engineering Chemistry* (Industrial and Analytical Editions), and *Chemical and Engineering News*. Rates on request.

NOTICE TO AUTHORS OF PAPERS

Manuscripts for THIS JOURNAL should be submitted to the Editor ready for publication, typewritten (double space), with 2–3 cm. margins, on a good quality, durable paper, preferably of 8.5″ × 11″ size. In addition to the original typewritten copy, one or more carbon copies should be submitted so that the time required for examination by the Editorial Board may thus be considerably shortened. Care should be taken that all pages in a manuscript, including tables (but not the diagrams) be numbered consecutively. In preparing manuscripts authors are requested to observe, for reasons of economy, the utmost conciseness consistent with clarity of presentation. The manuscripts should be addressed to specialists in their particular field rather than to the general reader. Extensive reviews of the literature cannot be accepted. When well-known or previously published procedures have been followed in the experimental work they should only be designated or referred to.

Form of Presentation.—There should be one or more introductory paragraphs setting forth the occasion, significance and main objectives of the investigation and the method of attack. This should be followed by the experimental results and a discussion of them, either *seriatim* or at their conclusion. Finally, there should be a brief summary of the main achievements of the investigation. Sometimes, particularly when the subject matter is involved and there are many details which, though essential for a successful repetition of the experiments, are unnecessary for the main account of the investigation, these details can with advantage be relegated to an appendix or supplement, just preceding the Summary. In intermediate cases it is often advisable to retain a single, straightforward presentation but to intercalate sections in fine print giving the experimental details of procedure. This has the great advantage of keeping the experimental details close to the more general statements based upon them and yet at the same time permitting the reader if he wishes to pass over this section without inconvenience.

It will be of great assistance to the Editor's Office if the style, arrangement and orthography of the manuscripts are made to conform to the usages of the JOURNAL as exemplified in its recent issues and as set forth in the following paragraphs.

Center headings should be employed sparingly; side headings should be indented and run into the text to which they apply, using period and dash. References to the literature and all footnotes regardless of their nature (except those in tables) should be numbered in one consecutive series, repetition of notes being avoided by using simply the superscript number corresponding to the original reference. They should follow immediately in separate lines the line of text containing the text words to which they refer, and may be set off by short rules above and below. The items in the references to the literature should conform to the uniform usages of the Journal as regards order and punctuation, and to the abbreviations as given by *Chemical Abstracts* in its "List of Periodicals Abstracted." The names of all simple compounds rather than their formulas should be used whenever they occur in the text. Periods of time (unless fractional) should be written in words and quantities of material in Arabic numerals, unless occurring at the beginning of a sentence. Letters used to represent quantities in mathematical expressions should be underscored to indicate that they are to be printed in italics, and Greek or other unusual characters should be written plainly or should be explained by annotations. Simple fractional expressions should be written with a slant line rather than in the conventional manner, so that only a single line of type is required. All subscripts and superscripts should be carefully made and placed (the degree sign ° or a small o should not be used to represent zero). For economy, except in unusual circumstances the abbreviations %, °A., cm., cc., ml., g., Å., m. p., f. p., b. p., cal., kcal., expt. and Fig., should be used rather than the words.

Figures and graphs should be carefully prepared line drawings on plain white drawing paper, blue drawing cloth or coördinate paper printed in blue only. The

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originals are preferable, but clear, well-prepared photographic prints or photostats are acceptable. Illustrations are most conveniently handled when made in the conventional 8.5″ × 11″ manuscript size; if they are of necessity larger, and therefore liable to damage in mailing, duplicate rough sketches or photographic prints of smaller size should be furnished for dispatch to the Referees. Diagrams should be designed to occupy a single column width and should therefore be tall rather than wide. Particular attention should be given to the correct proportions of the various parts of the figure, especially the experimental points, and if any letters, numbers, or legends must be placed on the diagram to their proportions also. In graphs the frame and actual curves should be ruled and inked more heavily than the coördinate lines, and these latter should not be too close together. Experimental points should always be given and should be indicated not by crosses but by circles or other symbols carefully drawn with drafting instruments. Where feasible it is often helpful to have the diameter of the circles indicate the precision of the measurements. The numbers and legends on coördinate axes are set up in type by the printer; the author, therefore, should place them in pencil outside the axes. The numbers and titles of figures should be placed below the diagrams, or on the back, or collected on a separate sheet. Small photographic prints should be mounted on cardboard and any composite series of photographic prints should be mounted in the order and arrangement desired. Each piece of illustration copy should be marked on the margin or back with the name of the author and brief title of the article (for identification purposes).

Tables.—Tables should not be used indiscriminately as they are much more expensive, line for line, than running text. If reasonably possible, they should be designed to occupy fully a single column (3 inches), which will take 50–75 characters and spaces. Tables occupying the full width can be used, but they are undesirable for the same reasons advanced with regard to page wide figures; their preparation should follow the same principles as for those of single width. Care should be taken to avoid any arrangement which unduly increases the depth of a table, and column heads should be made as small as possible, using abbreviations liberally. Lines of data should not be numbered nor run numbers given unless these numbers are needed for reference in the text. Columns should not be used to contain only one or two entries, nor should the same entry be repeated numerous times consecutively, since these cases may be taken care of more economically in footnotes, or by entries following the title of the table. Data should not be included in one column which are deducible easily by simple arithmetic from data in another column. Tables should be interspersed in the manuscript as near as possible to the places where they are referred to in the text, and need not be placed alone on separate sheets.

Formulas and Equations.—Empirical and structural formulas and mathematical and chemical equations should be arranged to fill adequately the width of a single column. This will often require a continuation of the equation in additional lines, and although this is a disadvantage it is in general preferable to intrusion into the adjoining column. Subscripts and superscripts, especially the latter, should be written with care and the conventional fractional arrangements should not be used in exponents. Organic structural formulas should be arranged to fill the space economically, and arrows should be used horizontally or vertically, not diagonally, wherever possible.

Notes do not differ fundamentally from Articles. They describe fragmentary or less complete studies and hence particular attention must be given to brevity and conciseness of presentation. Summaries are not included. They are collected in a special section near the end of each number of the Journal.

New Compounds.—This department is for brief accounts of new substances which do not appear of sufficient importance to justify separate publication and cannot be described appropriately as part of any other Article or Note. These accounts should report the preparation of the new compound succinctly, yet fully enough so that the operations can be duplicated. Significant properties, formulas and analytical data to establish the identity and purity of the substance should be given. Material appearing in this classification will not be accepted for subsequent publication.

Communications to the Editor are designed to afford prompt, brief, preliminary publication in our Journal of new and significant observations or discoveries. Their total length may in no case exceed 500 words or the equivalent. They will be given as rapid editorial consideration as possible, but at best it will usually be out of the question to include them in a given issue of the Journal if they arrive at the Editor's office later than the 20th of the preceding month. Communications like other contributions should be self-sustaining; that is, they should present experimental or other evidence adequate to establish the *prima facie* credibility of the results or conclusions stated or to permit their appraisal by an expert in the field although because of the 500-word limit a complete presentation cannot usually be expected. These requirements make Communications on many subjects impracticable, particularly those of an involved or theoretical nature.

Communications differ from ordinary Articles or Notes in that their publication does not prevent the re-publication of their subject matter in a later, more complete article in the Journal. In view of this special provision and their expedited publication, it is clear that the contribution made by the Communication should be of special interest or timeliness; mere abstracts of forthcoming articles cannot be accepted. Proof and reprint order will be sent to authors whenever possible, but as this cannot always be done, a memorandum as to the reprints desired should accompany the manuscript.

Microfilm Supplements.—By arrangement with Science Service material supplementary to articles in THIS JOURNAL, such for instance as extensive tables, graphs or calculations, can be distributed at small cost as American Documentation Institute Documents in the form of microfilms with images 25 mm. high on standard 35-mm. film or photoprints 6 × 8 inches legible to the unaided eye. Such material must, however, have been submitted to the Editor of the Journal and must have been approved by him for publication. Attention will then be called to these documents by means of footnotes at appropriate points in the text of the article concerned.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA AT LOS ANGLES]

Polyenes. II. The Purification of β-Ionone[1,2]

BY WILLIAM G. YOUNG, STANLEY J. CRISTOL, LAWRENCE J. ANDREWS AND SEYMOUR L. LINDENBAUM

The purification of commercial β-ionone by decomposition of its highly purified semicarbazone[3] according to the frequently reported method of steam distilling the semicarbazone in the presence of phthalic anhydride was carried out in the usual manner.[4] A spectrophotometric comparison of the β-ionone prepared by this procedure with the original starting material indicated that both products had identical maximum extinction coefficients. The failure of this well-known method of purification led to an investigation of the effects of various acidic media on the decomposition of β-ionone semicarbazone. The results of this study are presented in this paper along with a brief report of an attempted purification of β-ionone based on an expected difference in reaction rates of α- and β-ionone with perbenzoic acid.

The Purity of β-Ionone Prepared from its Semicarbazone.—Commercial β-ionone having absorption maxima at 296 mμ (ε 8600) and 222 mμ (ε 7350) was converted to the semicarbazone. This derivative was recrystallized repeatedly to constant melting point (148–149°) and extinction coefficient.[5] The purified semicarbazone was decomposed in various acidic media, and the extinction coefficients (296 mμ) of the product were measured in 95% ethanol to determine the degree to which isomerization into α-ionone occurred (see Table I).

TABLE I

THE PURITY OF β-IONONE

Method of semicarbazone decomposition	Semicarbazone, g.	Amount of acid	$n^{20}D$	ϵ_{max} (296 mμ)[a]	% Purity
Phthalic anhydride[b]	72	72 g.	1.5175	8600[c]	80
Phthalic anhydride[b]	5	5 g.	1.5157	9600	90
Succinic acid[b]	5	0.17 eq.	1.5198	10100	95
Phosphoric acid[b]	5	0.12 eq.	1.5200	10100	95
Sulfuric acid[c]	68	1.0 eq.	1.5205	10100	95
Sulfuric acid[b]	5	0.12 eq.	1.5211	10500	98
Cold sulfuric acid[d]	5	0.10 eq.	1.5211	10700	100

[a] The solvent was 95% ethanol. [b] The liberated β-ionone was steam distilled from the acid mixture. [c] Refluxed three hours with 300 ml. of 3 *N* sulfuric acid. [d] Method of Heilbron and co-workers[6]; it should be noted that the properties of purified β-ionone obtained by Heilbron (ε 12900, $n^{19}D$ 1.5178) are considerably different from those reported here. [e] Burawoy[4b] reports ε max 8700 (abs. ethanol) and Ruzicka[4c] reports ε max 8900 in absolute ethanol using the phthalic anhydride method.

Of the several methods tried for decomposing the semicarbazone, the one using sulfuric acid was the most reliable. In fact the modification of this procedure reported by Heilbron and co-workers[6] while these studies were in progress has been tried and found to give β-ionone of the highest maximum extinction coefficient (λ_{max} 296 mμ, ϵ_{max} 10700). This is considerably higher than that of the product obtained by the usual method with phthalic anhydride. In view of the fact that neither β-ionone nor its semicarbazone are isomerized by the conditions used in the hydrolysis it is likely that this method of Heilbron gives pure β-ionone. The extinction coefficients of β-ionone samples were not altered by exposing the samples to cold or hot dilute sulfuric acid.

(1) This paper was presented before the Organic Division of the American Chemical Society, Pittsburgh, Pa., September, 1943.

(2) This work was made possible by a research grant from Sharp and Dohme, Inc. Original manuscript received September 7, 1943.

(3) Tiemann, *Ber.*, **31**, 867 (1898).

(4) (a) Kuhn and Morris, *ibid.*, **70B**, 853 (1937); (b) Burawoy, *J. Chem. Soc.*, 20 (1941); (c) Ruzicka, Seidel and Firmenich, *Helv. Chim. Acta*, **24**, 1434 (1941).

(5) The commercial ionones (Ionone Beta Extra and Ionone Alpha Extra White) were obtained from Maywood Chemical Works, Maywood, N. J. Purified β-ionone semicarbazone had λ_{max} 282 mμ, ε 22300 in 95% ethanol.

(6) Heilbron, Johnson, Jones and Spinks, *J. Chem. Soc.*, 727 (1942).

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Neither did exposing a sample of β-ionone semicarbazone to cold dilute sulfuric acid until about one-third of it had been hydrolyzed change the spectrum of the unhydrolyzed semicarbazone.

It does not seem likely that the presence of α-ionone in the product from the hydrolysis of β-ionone semicarbazone with phthalic anhydride should be attributed to the effect of the acidic medium on the liberated β-ionone since the ionone was steam distilled from the mixture as soon as it was formed. Attempts to study the effects of the phthalic anhydride medium on the semicarbazone itself have so far failed owing to difficulties involved in purifying the partially decomposed semicarbazone recovered from the medium.

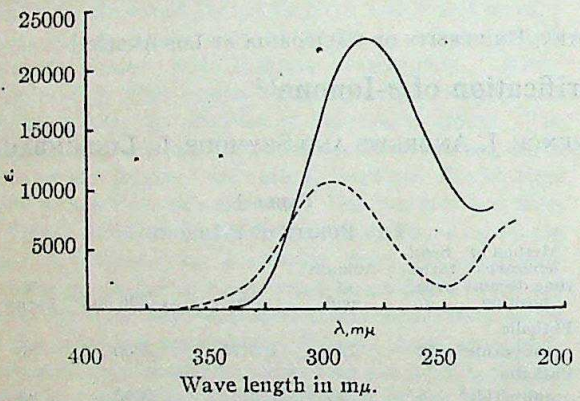

Fig. 1.—Spectra of pure β-ionone and β-ionone semicarbazone: β-ionone, – – –; β-ionone, —— semicarbazone.

In Fig. 1 are presented the absorption spectra of pure β-ionone semicarbazone and of β-ionone liberated from the semicarbazone by the use of sulfuric acid at room temperature measured in a solution of 95% ethanol. In Fig. 2 are given the spectra of commercial α- and β-ionone. The commercial α-ionone has absorption maxima at 227 mμ, ε 12850 and 296 mμ, ε 1950. Assuming that β-ionone obtained from its semicarbazone by decomposition with sulfuric acid at room temperature is 100% pure and that pure α-ionone

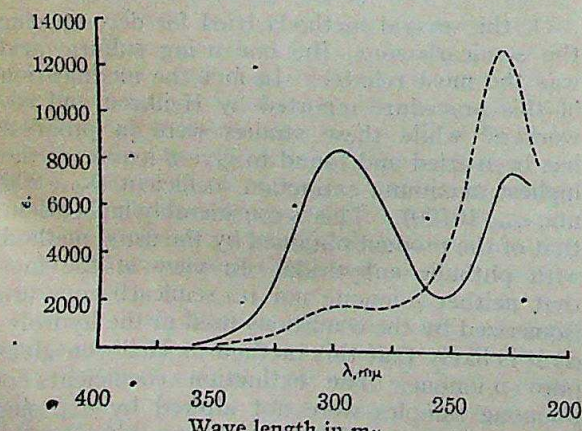

Fig. 2.—Spectra of commercial α- and β-ionone: α, – – –; β, —·—.

displays no light absorption at 296 mμ it was calculated by use of the extinction coefficients at 296 mμ that the commercial α-ionone sample was 82% pure and that the commercial β-ionone (λ_{max} 296 mμ, ε 8600) was 80% pure.[7]

The Rates of Reaction of Some Unsaturated Carbonyl Compounds with Perbenzoic Acid.—It has been reported that α,β-unsaturated carbonyl compounds react only very slowly with perbenzoic acid.[8] It was hoped that this hindered reactivity toward perbenzoic acid would be transmitted through two double bonds conjugated with a carbonyl group and that the isolated double bond in the α-ionone ring would react with perbenzoic acid much faster than would the double bond in the β-ionone ring, affording a means of purifying β-ionone. A comparative study of the rates of reaction of perbenzoic acid with commerical β-ionone (ϵ_{max} 8600) and with relatively pure β-ionone (ϵ_{max} 10100) showed that the samples consumed perbenzoic acid at an equal rate which was much faster than the rate for ordinary α,β-unsaturated carbonyl compounds (ethylideneacetone, crotonaldehyde, and benzalacetone).

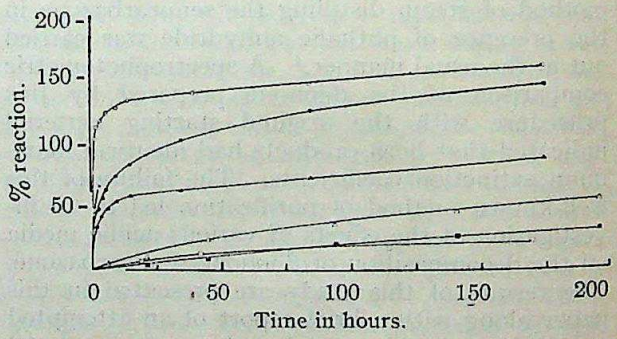

Fig. 3.—Reaction rates of unsaturated carbonyl compounds with perbenzoic acid at 8°.

Compound	Init. concn.	Init. concn. $C_6H_5CO_3H$
○, β-ionone (ϵ_{max} 10100)	0.0297*M*	0.0605*M*
×, β-ionone (ϵ_{max} 8600)	.0309	.0313
×, β-ionone (ϵ_{max} 10100)	.0332	.0313
●, cinnamalacetone	.0275	.0605
▲, dibenzalacetone	.0309	.0605
△, ethylideneacetone	.0288	.0299
■, crotonaldehyde	.0333	.0299
□, benzalacetophenone	.0394	.0312

In Fig. 3 are plotted the rates of reaction of several unsaturated carbonyl compounds with perbenzoic acid at 8° in toluene or benzene solution. Values of the per cent. reaction vary from 0 to 200, since in some of the rate studies on dienes sufficient perbenzoic acid was used to react with two moles of carbon–carbon double bond.

In order to determine whether or not the rapid reaction of β-ionone with perbenzoic acid was

(7) These are the commercial ionones used in synthetic work reported by Young, Andrews and Cristol, THIS JOURNAL, 66, 520 (1944).

(8) Böeseken, *Rec. trav. chim.*, 45, 838 (1926).

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characteristic of α,β-, γ,δ-unsaturated carbonyl compounds the rates of reaction of β-ionone and cinnamalacetone with two moles of perbenzoic acid were measured and compared. In both cases when one mole of perbenzoic acid was consumed, the reaction rate dropped off rapidly and became comparable to that of an α,β-unsaturated carbonyl compound. Presumably, then, the double bond in the β-ionone ring is the one which consumes the first mole of perbenzoic acid. Dibenzalacetone in the presence of two moles of perbenzoic acid reacted very rapidly until about half a mole of perbenzoic acid had been consumed. Then the rate of reaction decreased to that of a compound having one ethylenic linkage to a carbonyl group.

Experimental Part

β-Ionone Semicarbazone.—To a solution of 50 g. of semicarbazide hydrochloride and 44 g. of potassium acetate in 150 ml. of water was added a solution of 85 g. of commercial β-ionone in 150 ml. of ethanol. Sufficient ethanol to dissolve the β-ionone was added. The solution was cooled in an ice-bath to induce crystal formation. The crude product was purified by four to six recrystallizations from absolute ethanol or 75% methanol to constant melting point (148–149°) and extinction coefficient in 95% ethanol (λ_{max} 282 mμ, ϵ_{max} 22300). Fifty grams of purified product was obtained (45%).

Acid Decomposition of β-Ionone Semicarbazone.—β-Ionone semicarbazone (68 g.) was refluxed with 300 ml. of 3 *N* sulfuric acid for three hours. The liberated oil was extracted with 100 ml. of ether, and the ether solution was dried over sodium sulfate. After removal of the ether, the β-ionone was distilled, b. p. 142–144° (18 mm.) (wt. 35 g., 76%).

In one experiment carried out according to the directions of Kuhn and Morris[4a] a mixture of 58.6 g. of β-ionone semicarbazone and an equal weight of phthalic anhydride was steam distilled and the β-ionone in the distillate extracted with ether. The distilled product, b. p. 143–146° (18–20 mm.), weighed 35.7 g. (75%).

In separate experiments 5.0 g. of β-ionone semicarbazone was steam distilled from a constant volume of 40 ml. of water containing 5 g. of phthalic anhydride, 0.17 equiv. of succinic acid, 0.12 equiv. of phosphoric acid, or 0.12 equiv. of sulfuric acid. The recovered β-ionone weighed 3.0 g. (78%) in each case (properties in Table I).

Five grams of the semicarbazone was shaken at room temperature for three and one-half days with a mixture of 20 ml. of petroleum ether and 48 ml. of 2 *N* sulfuric acid.[6] The organic layer was washed with water and dilute sodium bicarbonate solution and dried. The distilled β-ionone weighed 2.7 g. (70%).

The Stability of β-Ionone and its Semicarbazone toward Dilute Sulfuric Acid.—Five grams of β-ionone semicarbazone (m. p. 148–9°, ϵ_{max} 21400), 20 ml. of petroleum ether, and 48 ml. of 2 *N* sulfuric acid were shaken at room temperature for twenty-four hours. The remaining white solid was filtered, washed with petroleum ether and water and dried. The 3.1 g. of recovered semicarbazone melted 148–149.5° and had ϵ_{max} 21300 in 95% ethanol.

Five grams of β-ionone (ϵ_{max} 8600) was shaken for two days with petroleum ether and 2 *N* sulfuric acid as described for the decomposition of β-ionone semicarbazone. The β-ionone recovered (3.3 g.) as previously described had ϵ_{max} 8900 in 95% ethanol.

Ten-gram samples of β-ionone were refluxed for four hours with 100 ml. of 3 *N* sulfuric acid. The ionone was extracted with ether and the solution washed with water and dilute sodium bicarbonate solution and dried. The distilled product weighed 8 g. A sample of β-ionone, ϵ_{max} 8600, gave a product, ϵ_{max} 8400, and a sample having ϵ_{max} 5560 gave a product of ϵ_{max} 5200 in 95% ethanol.

Absorption Spectrum Measurements.—The ultraviolet absorption spectra in 95% ethanol solution of the several ionone samples were measured on a Beckman spectrophotometer.

Reaction Rates of Unsaturated Carbonyl Compounds with Perbenzoic Acid.—A chloroform solution of 0.343 *M* perbenzoic acid was prepared according to the method of Braun.[9] A sample (about 0.003 mole) of the unsaturated compound was weighed into a 100-ml. volumetric flask which was then partially filled with solvent (dry benzene or toluene), and a 10 or 20 ml. pipet sample of the perbenzoic acid solution was added. The flask was filled to the mark with solvent and placed in the refrigerator (8°). Ten-ml. pipet samples were removed from time to time and analyzed according to the method of Braun.[9] A blank run was made to follow the rate of perbenzoic acid decomposition. These determinations were not strictly quantitative owing to the somewhat inaccurate temperature control and timing used. The percentage of the unsaturated compound which had reacted over any given length of time *t* was calculated from the amount of perbenzoic acid consumed in this length of time by the use of the equation

$$\%\ \text{unsaturated compound reacted at time } t = \frac{\text{moles of perbenzoic acid consumed at time } t}{\text{moles of unsaturated compound at } t = 0} \times 100$$

Summary

The method of purification of β-ionone by decomposition of its semicarbazone in acid media has been studied. Decomposition with sulfuric acid gives β-ionone of greater purity than decomposition with weaker acids.

A study of the reaction rates of perbenzoic acid with α,β-, γ,δ-unsaturated carbonyl compounds including β-ionone, indicates that the hindrance to reactivity furnished to one double bond by a carbonyl group is not transmitted through two conjugated double bonds.

LOS ANGELES, CALIFORNIA RECEIVED FEBRUARY 8, 1944

(9) Braun, "Organic Syntheses," **13**, 86 (1933).

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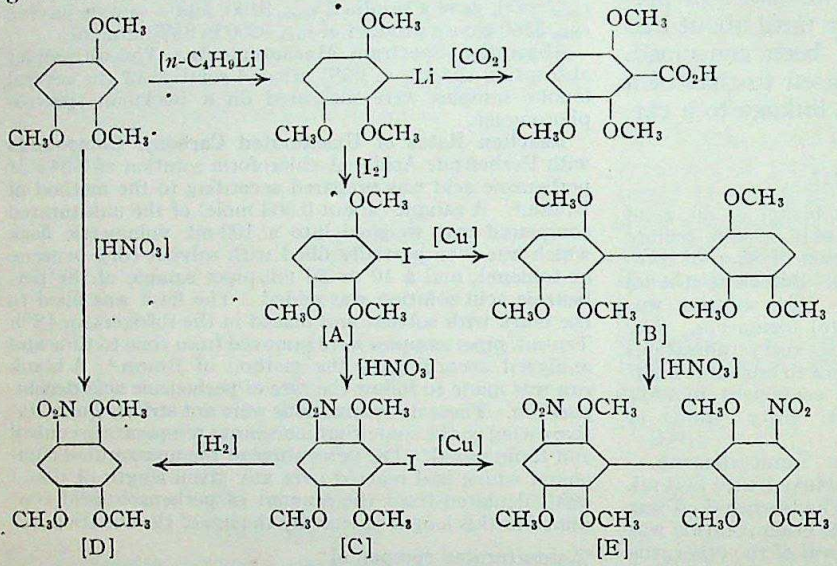
Dibenzofuran. XXI. Benzene and Biphenyl Intermediates for 1,9-Derivatives[1]

BY HENRY GILMAN AND JOHN R. THIRTLE

In the preparation of intermediates which, by ring-closure reactions, might give some reference 1,9-dibenzofuran derivatives, several benzene and biphenyl derivatives have been prepared. The general transformations are as follows:



Metalation of 1,2,4-trimethoxybenzene by *n*-butyllithium was shown to take place almost entirely in the 3-position. This was particularly interesting because of the possibilities of three isomeric monolithium derivatives due to the ortho-directing effect of methoxy groups in metalation. A parallel illustration is the metalation of resorcinol dimethyl ether to give, subsequent to carbonation and hydrolysis, practically exclusively 2,6-dimethoxybenzoic acid.[2]

The structure of the metalation product was established by carbonation to 2,3,6-trimethoxybenzoic acid and comparison with a sample prepared earlier by Smith and LaForge[3] by another procedure. Treatment of the lithium compound with iodine gave 2,3,6-trimethoxyiodobenzene [A] from which was obtained, by an Ullmann coupling, the 2,2′,3,3′,6,6′-hexamethoxybiphenyl [B]. Attempted ring closure of [B], by heating with an acetic acid solution of hydrobromic acid, gave a colored unstable polyphenolic type. Under corresponding conditions using hydrochloric acid there was recovered 85% of [B]; and with constant boiling hydriodic acid much as yet unresolved tarry material resulted.

Nitration of [A] gave 2,3,6-trimethoxy-5-nitroiodobenzene [C] the structure of which was established by hydrogenolysis to 1,2,4-trimethoxy-5-nitrobenzene [D]. The authentic specimen used to identify [D] was prepared, in accordance with the directions of Schüler,[4] by the nitration of 1,2,4-trimethoxybenzene. 2,2′,3,3′,6,6′-Hexamethoxy-5,5′-dinitrobiphenyl [E] was prepared by the coupling of [C] and also, in excellent yield, by the direct nitration of [B]. Inasmuch as [B] was essentially unaffected by hydrochloric acid, it was hoped that the nitro groups in [E] might preferentially labilize the ortho-methoxy groups in a cleavage reaction. However, no dibenzofuran derivative has been isolated.

Experimental

Quinone was converted to 1,2,4-triacetoxybenzene in 80% yield by the method of Thiele.[5] 1,2,4-Trimethoxybenzene was prepared in one step in 90% yield from 1,2,4-triacetoxybenzene by the procedure of Bargellini and Martegiani.[6]

2,3,6-Trimethoxyiodobenzene.—To a stirring and refluxing solution of 9.8 g. (0.0583 mole) of 1,2,4-trimethoxybenzene in 100 cc. of dry ether was added 0.0655 mole of *n*-butyllithium dissolved in 100 cc. of ether. The reaction mixture was refluxed with stirring for two hours. The system was allowed to cool under nitrogen, and a Gooch adapter was placed between the reaction flask and the reflux condenser. A Soxhlet thimble was charged with 17.8 g. (0.14 g. atom) of iodine and was supported in the adapter by means of a piece of clay plate. Stirring was continued and heating was regulated in such a manner that the iodine was dissolved slowly. The reaction of the iodine with the organolithium compound was very vigorous at the start. As the reaction heat diminished, heating was regulated to extract the iodine more rapidly. The entire extraction required forty-five minutes. Toward the end a distinct yellow to orange color due to excess iodine was noted and the white, insoluble, organolithium compound had disappeared, a clear solution resulting.

The ether solution was extracted with dil. sodium bisulfite to remove iodine and lithium iodide. After drying over calcium chloride, the ether was evaporated, leaving 10.6 g. (61.5% crude yield) of somewhat oily crystals. Recrystallization from 40 cc. of ethanol gave 8.7 g. (51%) melting at 107–108°. A second recrystallization raised the melting point to 108–108.5°.

Anal. Calcd. for $C_9H_{11}O_3I$: OCH_3, 31.63. Found: OCH_3, 31.61, 31.61.

2,3,6-Trimethoxybenzoic Acid.—Carbonation of the *n*-butyl-lithium-metalation product of 6.72 g. (0.04 mole) of 1,2,4-trimethoxybenzene by dry-ice gave, subsequent to hydrolysis, 4 g. (47%) of crystals melting at 148–149°.

(1) Paper XX; Gilman, Swiss, Willis, and Yeoman, THIS JOURNAL, **66**, 798 (1944).

(2) Gilman, Willis, Cook, Webb and Meals, *ibid.*, **62**, 667 (1940).

(3) Smith and LaForge, *ibid.*, **53**, 3072 (1931).

(4) Schüler, *Arch. Pharm.*, **245**, 267, 276 (1907) [*Chem. Zentr.*, **78**, II, 806 (1907); see, also, *C. A.*, **2**, 1965 (1908)].

(5) Thiele, *Ber.*, **31**, 1247 (1898).

(6) Bargellini and Martegiani, *Gazz. chim. ital.*, **41**, II, 445 (1911) [*C. A.*, **6**, 625 (1912)]; *Atti. accad. Lincei*, **20**, II, 18 (1911) [*C. A.*, **5**, 3405 (1911), and *Chem. Zentr.*, **82**, II, 1026 (1911)].

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Recrystallization from water raised the melting point to 149–150°. Smith and LaForge[3] reported a melting point of 145–146°, and a mixed m. p. with the sample kindly provided by them and our acid was 146–149°.

Anal. Calcd. for $C_{10}H_{12}O_5$: neut. equiv., 212. Found: neut. equiv., 219.

Methyl 2,3,6-Trimethoxybenzoate.—2,3,6-Trimethoxybenzoic acid was esterified with great difficulty. One gram was dissolved in 10 cc. of methanol and saturated with dry hydrogen chloride. After refluxing for one hour and cooling no crystals formed, but evaporation left an oil. The oil was dissolved in ether and washed twice with 10% sodium carbonate solution. From the dried ethereal solution there was obtained 0.3 g. (28%) of white crystals melting at 54–56°. Recrystallization from petroleum ether (b. p. 60–68°) raised the melting point to 57–57.5°.

Anal. Calcd. for $C_{11}H_{14}O_5$: OCH_3, 54.87. Found: OCH_3, 54.88.

Ethyl 2,3,6-Trimethoxybenzoate.—One gram of 2,3,6-trimethoxybenzoic acid was dissolved in 6 cc. of ethanol and 1 cc. of concd. sulfuric acid. After refluxing for one-half hour the reaction mixture was poured into 20 cc. of water. The solid was dissolved in ether and shaken with dilute sodium carbonate solution. After drying the ether layer over anhydrous potassium carbonate, the ether was evaporated, leaving an oil which crystallized on agitation. The crude product melted at 38–41°. Recrystallization from petroleum ether (b. p. 60–68°) raised the melting point to 42.5–43°.

Anal. Calcd. for $C_{12}H_{16}O_5$: alkoxyl, 57.50. Found: alkoxyl, 57.41.

2,2′,3,3′,6,6′-Hexamethoxybiphenyl.—Copper powder (50 g.) was purified by the method of Kleiderer and Adams.[7] After drying, an intimate mixture was made with 17.3 g. (0.0588 mole) of 2,3,6-trimethoxyiodobenzene. The mixture was heated by an oil-bath at 185–190° for three hours, in a nitrogen atmosphere. The temperature was finally raised to 210–215° for fifteen minutes.

Extraction in a Soxhlet apparatus was effected by 250 cc. of acetone. Concentration of the extract to a small volume and dilution with water gave 9.5 g. (97%) of crystals melting at 122–124°. Recrystallization from 30 cc. of hot acetone, diluted with water until crystals began to form, gave 7.5 g. (76.4%) of product melting at 125.0–125.5°.

Anal. Calcd. for $C_{18}H_{22}O_6$: OCH_3, 55.69. Found: OCH_3, 55.50, 55.68.

2,2′,3,3′,6,6′-Hexamethoxy-5,5′-dinitrobiphenyl.—This preparation is similar to the procedure used for 2,2′,6,6′-tetramethoxy-3,3′-dinitrobiphenyl.[8]

One gram (0.003 mole) of 2,2′,3,3′,6,6′-hexamethoxybiphenyl in a shell vial was dissolved in 10 cc. of acetic anhydride and 0.5 cc. of concd. nitric acid, which was prepared by warming fuming nitric acid until colorless. The mixture was heated gently on a hot-plate to start the reaction and then removed from the heat. After boiling had ceased, heating was continued at incipient boiling for five minutes. When cool, the product was isolated as follows. Six reaction mixtures were combined in an Erlenmeyer flask. Ten cubic centimeters of boiling acetic acid was used to rinse all of the shell vials. The crystals which formed were redissolved by slight warming, and 10 cc. of water was added dropwise to hydrolyze the excess acetic anhydride. The solution was kept at 0° overnight giving 6.9 g. (90.5%) of yellow crystals melting at 149–150°. Recrystallization from ethanol raised the melting point to 151–151.5°.

Anal. Calcd. for $C_{18}H_{20}O_{10}N_2$: OCH_3, 43.87. Found: OCH_3, 43.91, 43.77.

2,3,6-Trimethoxy-5-nitroiodobenzene.—A solution of 3.34 g. (0.0114 mole) of 2,3,6-trimethoxyiodobenzene in 12 cc. of glacial acetic acid at 60° was stirred while 6 cc. of concd. nitric acid in 20 cc. of acetic acid was added over a period of five minutes. Stirring was continued at 60° for fifteen minutes longer. After cooling, the crystals were filtered and washed with acetic acid and with water. Two and nine-tenths grams (75.3%) of pale yellow needles melting at 119.5–120° was obtained. Dilution of the filtrate gave 0.8 g. melting at 115–118°. Crystallization of the latter from acetic acid gave 0.45 g. more pure product. Dilution of the filtrate again and crystallization from dilute acetic acid gave an additional 0.27 g. The total yield of pure product was 3.62 g. (94.1%).

Anal. Calcd. for $C_9H_{10}O_5NI$: OCH_3, 27.43. Found: OCH_3, 27.25.

The position of the nitro group was proved by removal of the iodine atom by hydrogen and palladium–calcium carbonate catalyst. Two-tenths g. of the compound was shaken with 1 g. of the catalyst in 20 cc. of absolute ethanol at 30 pounds pressure of hydrogen for two hours. After filtering, concentrating to small volume, and cooling, crystals formed which melted at 125–127°. Recrystallization from ethanol raised the melting point to 128–129° and a mixed melting point with an authentic sample of 2,4,5-trimethoxynitrobenzene[4] was not depressed.

Coupling of 2,3,6-Trimethoxy-5-nitroiodobenzene.—An intimate mixture of 2.0 g. (0.0059 mole) of 2,3,6-trimethoxy-5-nitroiodobenzene and 6.0 g. of the specially prepared copper powder[7] was placed in a Pyrex test-tube, covered with a thin layer of copper powder, and protected from air by a closely-fitting cork stopper placed just above the reaction mixture. The tube was placed in a heating bath at 210°. Heating was continued at 210° for one hour and ten minutes. The temperature was raised to 230° and held there for thirty minutes.

The reaction mixture was extracted in a Soxhlet apparatus with acetone. Evaporation of the acetone gave 0.9 g. of a tarry material. Extraction of this product with boiling petroleum ether (b. p. 60–68°) gave 0.2 g. of yellow crystals melting at 142–149°. Recrystallization from dilute acetic acid raised the melting point to 147–149°. A recrystallization from ethanol gave pale yellow crystals melting at 149.5–151°, and a mixed melting point with the 2,2′,3,3′,6,6′-hexamethoxydinitrobiphenyl prepared by direct nitration, was not depressed. This establishes the nitro groups in the 5,5′-positions.

Summary

It has been shown that the metalation of 1,2,4-trimethoxybenzene by *n*-butyllithium gives almost exclusively 2,3,6-trimethoxyphenyllithium. This RLi compound with iodine gives the corresponding iodo compound which, when coupled by copper, yields 2,2′,3,3′,6,6′-hexamethoxybiphenyl. Nitration of the iodo compound gives 2,3,6-trimethoxy-5-nitroiodobenzene which was coupled to 2,2′,3,3′,6,6′-hexamethoxy-5,5′-dinitrobiphenyl. Neither of the polymethoxybiphenyls has yielded any 1,9-dibenzofurans.

AMES, IOWA RECEIVED JANUARY 31, 1944

(7) Kleiderer and Adams, THIS JOURNAL, **55**, 4219 (1933).
(8) VanArendonk, Cupery and Adams, *ibid.*, **55**, 4225 (1933).

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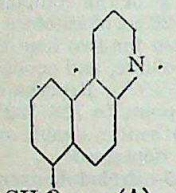
[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

Some Derivatives of 7-Methoxy- and 10-Methoxybenzo(f)quinoline

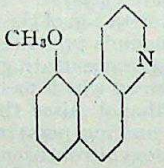
BY ALBERT C. MUELLER[1] AND CLIFF S. HAMILTON

In an earlier paper[2] the preparation of a number of 1-substituted aminobenzo(f)quinolines was described. As a continuation of this work the synthesis of two series of methoxybenzo(f)quinolines with a basic substituent in the 1-position has been undertaken. It was hoped that the presence of the methoxyl would enhance the antimalarial activity of this type of compound. Pharmacological testing of a number of these derivatives is in progress.

The particular isomers chosen for study were 7-methoxybenzo(f)quinoline (A) and 10-methoxybenzo(f)quinoline (B).



(A)



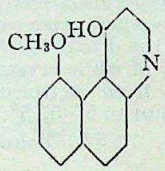
(B)

The starting materials required were 5-methoxy-2-naphthylamine and 8-methoxy-2-naphthylamine. Synthesis of neither of these compounds has been reported in the literature. The aminonaphthols, from which the methyl ethers were prepared, were obtained by the alkali fusion of the appropriate naphthylaminesulfonic acid. To insure efficient conversion of the naphthols to their methyl ethers with dimethyl sulfate, it was necessary to protect the amino groups by acetylation, the acetyl groups being removed by subsequent hydrolysis.

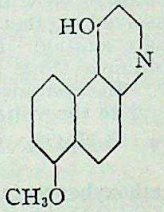
In this investigation the intermediate, 2-acetamido-5-naphthol, was isolated as a stable crystalline hydrate with a melting point higher than that reported by earlier workers.[3,4] Since 8-methoxy-2-naphthylamine was an unstable oil, it was isolated as the hydrochloride.

The conversion of the methoxyamines into the desired methoxybenzo(f)quinolines was accomplished by previously described methods.[2]

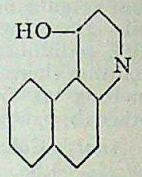
In order to introduce a basic substituent into the 1-position it was necessary to replace the hydroxyl with the more reactive chloro group which, normally, is easily displaced by an amino group. The 7-methoxy isomer reacted smoothly with phosphorus oxychloride to give the desired chloro compound, but all of our attempts to replace the hydroxyl in the 10-methoxy isomer were unsuccessful. It is believed that the group in the 10- or *peri*-position exerts a blocking effect upon the 1-position of the nucleus. Furthermore, IX differed noticeably from XVII and XXI,[2] in other properties, namely, melting point, color and solubility in alkali.



(IX)
m. p. 183°, yellow, insol. in OH^-



(XVII)
m. p. 309°, white, sol. in OH^-



(XXI)
m. p. 288°, white, sol. in OH^-

Two amines, morpholine and piperidine, were condensed with 1-chloro-7-methoxybenzo(f)quinoline yielding the corresponding 1-substituted aminobenzo(f)quinolines.

Experimental

2-Naphthylamine-5-sulfonic acid (I) and 2-naphthylamine-8-sulfonic acid (II) were prepared by the sulfonation of 2-naphthylamine according to the procedure of Green and Vakil.[5]

2-Amino-8-naphthol (III).—A mixture of 83 g. of II and 250 g. of potassium hydroxide was heated in an iron autoclave, equipped with a stirrer, for two and one-half hours at 260°. The fusion melt was cooled and treated with two liters of water. Some insoluble tarry material was removed by filtration and the solution was acidified with concentrated hydrochloric acid. The mixture was filtered again to remove the acid-insoluble portion and the filtrate was neutralized with sodium bicarbonate. The crude product which precipitated was collected on a filter, washed and dried; yield, 44 g. (74%). This was used to prepare the acetyl derivative without further purification. A portion was crystallized from water, then ethanol, yielding pale pink crystals melting at 156–158°; lit.[6] gives 158°.

2-Acetamido-8-naphthol (IV).—Twenty-five grams of III was refluxed briefly in 70 ml. of glacial acetic acid and 30 ml. of acetic anhydride. The mixture was poured into 500 ml. of water and the resulting oil solidified slowly. The crude product was taken up in dilute alkali, filtered and reprecipitated with hydrochloric acid. It was collected by filtration, washed with water and dried; yield, 29 g. (90%). After recrystallization from ethanol it melted at 215–216°. Friedländer and Zinberg reported 210–211°.[7]

2-Acetamido-8-methoxynaphthalene (V).—A solution of 24 g. of IV in 200 ml. of 2 *N* sodium hydroxide was placed in a 500-ml. three-necked flask fitted with a stirrer. Thirty milliliters of dimethyl sulfate was added slowly from a dropping funnel during a period of six hours, the temperature being held at 30°. The product, which precipitated as the reaction proceeded, was collected by filtration, washed with 0.5 *N* alkali and then with water. It was decolorized by charcoal treatment in ethanol and crystallized from ethanol–water solution; yield, 18 g. (70%).

This compound is a white crystalline solid melting at 163–164°. It is soluble in the common organic solvents and sparingly soluble in hot water.

(1) Parke, Davis and Company Fellow.
(2) Mueller and Hamilton, THIS JOURNAL, **65**, 1017 (1943).
(3) Sander, *Ber.*, **58**, 822 (1925).
(4) Bucherer and Wahl, *J. prakt. Chem.*, [2] **103**, 143 (1921).
(5) Green and Vakil, *J. Chem. Soc.*, **113**, 35 (1918).
(6) Newton, English Patent 5148, *J. Soc. Chem. Ind.*, **14**, 264 (1895).
(7) Friedländer and Zinberg, *Ber.*, **29**, 40 (1896).

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Anal. Calcd. for $C_{13}H_{13}O_2N$: C, 72.54; H, 6.09. Found: C, 72.27, 72.40; H, 6.02, 6.15.

8-Methoxy-2-naphthylamine Hydrochloride (VI).—Twenty-three grams of V was refluxed in 200 ml. of ethanol containing 30 ml. of concentrated hydrochloric acid. After three hours the alcohol was removed by distillation and 200 ml. of water was introduced. The resulting solution was treated with charcoal until it was nearly colorless, then concentrated to 100 ml. and cooled slowly. The amine hydrochloride precipitated in long light-pink needles which were collected on a filter. Further concentration of the filtrate yielded additional product; combined yield, 18 g. (81%).

Anal. Calcd. for $C_{11}H_{12}ONCl$: Cl, 16.91. Found: Cl, 16.89, 16.98.

1-Hydroxy-3-carbethoxy-10-methoxybenzo(f)quinoline (VII).—Diethyl sodio-oxalacetate (2 g.) was added to 2 g. of VI in 25 ml. of absolute ethanol. A drop of concentrated hydrochloric acid was introduced and the mixture was shaken intermittently for sixty hours. It was then poured into 70 ml. of water and the alcohol was evaporated. The viscous yellow-brown oil which separated was extracted with ether. The ether was removed *in vacuo*, and the methoxynaphthyliminosuccinate was added slowly to 50 ml. of mineral oil which had been preheated to 260°. After five minutes the mixture was cooled and the crude product separated upon the addition of ether. It was washed with small portions of benzene, decolorized with charcoal and crystallized from ethanol–water mixture yielding 1.7 g. (61%) of pale white crystals; m. p. 181–183°.

Anal. Calcd. for $C_{17}H_{15}O_4N$: C, 68.67; H, 5.09; N, 4.71. Found: C, 68.59; H, 5.15; N, 4.70.

1-Hydroxy-3-carboxy-10-methoxybenzo(f)quinoline (VIII) resulted in quantitative yield when VII was refluxed briefly in 2 *N* alkali and the resulting solution was acidified with dilute hydrochloric acid. The bright-yellow gelatinous product was digested for two hours before it was collected on a filter, washed and dried.

It is a slightly hygroscopic amorphous powder which decomposes at 250–253° with loss of carbon dioxide. It is soluble in basic solutions, but very insoluble in the usual organic solvents.

Anal. Calcd. for $C_{15}H_{11}O_4N$: C, 66.91; H, 4.12. Found: C, 66.79; H, 3.99.

This acid forms a deep-yellow crystalline hydrochloride from 6 *N* hydrochloric acid solution. The salt hydrolyzes readily in water.

Anal. Calcd. for $C_{15}H_{12}O_4NCl$: C, 59.12; H, 3.97. Found: C, 58.77; H, 3.99.

1-Hydroxy-10-methoxybenzo(f)quinoline (IX).—When 2.5 g. of VIII was heated at its decomposition point (250°) until no more gas was evolved, IX was formed in poor yield. The black residue was pulverized, extracted with 100 ml. of boiling ethanol and filtered free of insoluble material. The extract was clarified with charcoal and concentrated to yield 0.6 g. (28%) of bright yellow crystals which were recrystallized from ethanol–water mixture; m. p. 180–182°.

Anal. Calcd. for $C_{14}H_{11}O_2N$: C, 74.65; H, 4.92. Found: C, 74.62, 74.81; H, 4.92, 5.01.

2-Amino-5-naphthol (X) was prepared from I by the same procedure used for making the 2,8 isomer. The product was obtained in yields of 70%; m. p. 198–200°; lit.[4] gives 199.5°.

2-Acetamido-5-naphthol Monohydrate (XI).—Fifty grams of X was treated with 50 ml. of glacial acetic acid and 18 ml. of acetic anhydride. The mixture was refluxed for ten minutes before being poured into 300 ml. of water. The crude product crystallized slowly to yield a gray solid which was reprecipitated from 2 *N* alkali solution with dilute acid. It was decolorized with charcoal and crystallized from ethanol–water solution as nearly white needles; yield (63%); m. p. 117–121°. Sander[3] and Bucherer and Wahl[4] reported 100° and 98–99°, respectively.

This compound contains water of crystallization. Its anhydrous form appeared as an oil and was not obtained in the solid state. It is soluble in alkaline solutions and in the usual organic solvents.

Anal. Calcd. for $C_{12}H_{13}O_3N$: C, 65.74; H, 5.98; H_2O, 8.21. Found: C, 65.63, 65.80; H, 5.83, 6.05; H_2O, 8.17.

2-Acetamido-5-methoxynaphthalene (XII) resulted upon treatment of XI with dimethyl sulfate according to the procedure for making the 8-methoxy isomer. Yields up to 61% were obtained. The product crystallized from methanol–water solution as white platelets, m. p. 151–152°.

Anal. Calcd. for $C_{13}H_{13}O_2N$: C, 72.54; H, 6.09. Found: C, 72.30, 72.39; H, 6.07, 6.08.

5-Methoxy-2-naphthylamine Hydrochloride (XIII).—A suspension of 8 g. of XII in 250 ml. of 5 *N* hydrochloric acid was refluxed for three hours, during which time the solid dissolved. The hot solution was treated with decolorizing charcoal, filtered and slowly cooled. The sparingly soluble hydrochloride precipitated as tiny gray crystals and was collected by filtration. The filtrate was concentrated to yield more product. When recrystallized from hot water the hydrochloride appeared as long white needles; yield 7 g. (95%).

Anal. Calcd. for $C_{11}H_{12}ONCl$: Cl, 16.91. Found: Cl, 16.99, 16.88.

5-Methoxy-2-naphthylamine (XIV).—When XIII was neutralized with cold alcoholic alkali solution, and the alcohol evaporated, the free amine was liberated quantitatively. It crystallized from ethanol–water solution in pink platelets, m. p. 71–72°. Solutions of this compound darken on standing.

Anal. Calcd. for $C_{11}H_{11}ON$: C, 76.27; H, 6.40. Found: C, 75.98, 76.04; H, 6.43, 6.35.

1-Hydroxy-3-carbethoxy-7-methoxybenzo(f)quinoline (XV).—An intimate mixture of XIV (3.5 g.) and diethyl oxalacetate (4 g.) was desiccated over concentrated sulfuric acid for three days with occasional stirring. The viscous brown anil which formed was added with stirring to 100 ml. of preheated (250°) mineral oil. After ten minutes the mixture was cooled, and a light-yellow solid separated. It was removed and washed with benzene, yielding 4 g. (66%) of a light-brown crystalline powder. Repeated crystallizations from ethanol gave nearly white needles, m. p. 256–258°.

Anal. Calcd. for $C_{17}H_{15}O_4N$: C, 68.67; H, 5.09. Found: C, 68.57, 68.75; H, 5.02, 5.07.

1-Hydroxy-3-carboxy-7-methoyxbenzo(f)quinoline (XVI) was formed when XV was heated briefly in 2 *N* alkali and the resulting solution was acidified with dilute hydrochloric acid. The bright-yellow amorphous product was digested on the steam-bath for one hour, collected on a filter, washed and dried. Purification was effected by regenerating the acid from its sodium salt solution after charcoal treatment, m. p. 292–295°, (dec.).

Anal. Calcd. for $C_{15}H_{11}O_4N$: C, 66.91; H, 4.12 Found: C, 66.84, 66.69; H, 4.29. 4.17.

1-Hydroxy-7-methoxybenzo(f)quinoline (XVII).—By means of a molten potassium–sodium nitrate bath, 0.35 g. of XVI was heated carefully to 295°. When the first sign of decomposition was noticed the temperature was lowered and maintained at 280° until the evolution of carbon dioxide had ceased. The brittle residue was extracted with 200 ml. of ethanol and the extract was decolorized with charcoal. The product precipitated when water was added and the mixture was concentrated. It was taken up in 40 ml. of 2 *N* hydrochloric acid and treated again with charcoal, yielding a bright-yellow solution. When made basic with ammonium hydroxide, a white finely-divided crystalline solid precipitated. This was digested on the steam-bath before being collected, dried and weighed, m. p. 308–311°. The yield was 0.14 g. (55%).

Anal. Calcd. for $C_{14}H_{11}O_2N$: C, 74.65; H, 4.92. Found: C, 74.31, 74.44; H, 5.08, 5.09.

1-Chloro-7-methoxybenzo(f)quinoline (XVIII).—A mixture of 10 ml. of phosphorus oxychloride and 0.5 g. of

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XVII was refluxed for four hours. Most of the excess phosphorus oxychloride was removed by distillation and the residue was poured onto 30 g. of ice. The resulting mixture was heated to boiling, treated with charcoal, filtered and cooled. It was made basic with aqueous sodium hydroxide (10%) yielding a white curdy precipitate. The product was crystallized from ethanol–water mixture from which it formed long silky needles, m. p. 118–119°; lit.[8] gives 119°; yield, 0.4 g. (74%).

Anal. Calcd. for $C_{14}H_{10}ONCl$: C, 69.00; H, 4.30. Found: C, 69.08, 69.23; H, 4.28, 4.41.

1-Morpholino-7-methoxybenzo(f)quinoline (XIX) was formed when 0.3 g. of XVIII and 2 ml. of morpholine was refluxed for eight hours. The mixture was poured into 25 ml. of water and a white precipitate formed. The product was treated with charcoal in dilute hydrochloric acid and regenerated by the addition of alkali. A small amount of gummy impurity was removed at *p*H of 6–7. Two crystallizations from ethanol–water, gave tiny white crystals, m. p. 136–137°.

This compound forms a water soluble yellow hydrochloride and is also soluble in the common organic solvents.

Anal. Calcd. for $C_{16}H_{16}O_2N_2$: C, 73.45; H, 6.16. Found: C, 73.54, 73.23; H, 6.16, 6.23.

1-Piperidino-7-methoxybenzo(f)quinoline (XX) was prepared from XVIII and piperidine, similar to the morpholine analog. The product crystallized from acetone–water mixture as white needles, m. p. 116–117°.

Anal. Calcd. for $C_{19}H_{20}ON_2$: C, 78.06; H, 6.90. Found: C, 78.24; H, 7.13.

(8) Carpmael, English Patent 481,874, *Chem. Zentr.*, **109**, II, 117 (1938).

Summary

1. The preparation of the hydrochlorides of 5-methoxy- and 8-methoxy-2-naphthylamine, respectively, from the corresponding aminonaphthols, has been described.

2. These methoxyamines have been converted to benzo(f)quinoline derivatives by condensation with oxalacetic ester and cyclization of the resulting products.

3. 1-Hydroxy-7-methoxybenzo(f)quinoline yielded 1-chloro-7-methoxybenzo(f)quinoline which gave the 1-substituted amino derivatives with morpholine and piperidine.

4. Apparently steric hindrance by the 10-methoxyl in 1-hydroxy-10-methoxybenzo(f)-quinoline prevented replacement of the hydroxyl group by halogen.

LINCOLN, NEBRASKA RECEIVED JANUARY 31, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

The Carbonation and Carbethoxylation of Certain Ketones Using Sodium Triphenylmethide Reagent: β-Keto Ester Synthesis[1,2,3]

BY ERWIN BAUMGARTEN, ROBERT LEVINE AND CHARLES R. HAUSER

Ketones may be converted to β-keto esters by carbethoxylation by means of an alkyl carbonate or by carbonation followed by esterification of the resulting β-keto-acid. Both reactions are brought about by bases. In the present paper, certain examples of these reactions brought about by sodium triphenylmethide are discussed.

Carbethoxylations.—The carbethoxylation of a number of ketones with diethyl carbonate has been effected by means of sodium ethoxide.[4] The reaction has failed, however, with certain ketones in the presence of this base.[4] One of these ketones, di-isobutyl ketone, has now been carbethoxylated with diethyl carbonate by means of the stronger base, sodium triphenylmethide, to form ethyl α-isovalerylisovalerate. Since certain ketones react

$$[(CH_3)_2CHCH_2]_2CO \xrightarrow[\text{by } CO(OC_2H_5)_2]{(C_6H_5)_3CNa \text{ followed}} (CH_3)_2CHCH_2COCH(COOC_2H_5)CH(CH_3)_2$$

with diethyl carbonate in the presence of sodium ethoxide to give an ethyl vinyl carbonate (the "oxygen derivative" of the ketone),[4] instead of the β-keto ester (the "carbon derivative" of the ketone), the β-keto ester obtained in the present case has been characterized not only by the usual ketonic cleavage but also by acidic cleavage. While the regeneration of the original ketone on ketonic cleavage might result from either the β-keto ester or the "oxygen derivative," the formation of isovaleric acid on acidic cleavage could result only from the β-keto ester.

Previous attempts to carbethoxylate methyl ethyl ketone with diethyl carbonate by means of sodium ethoxide[4] or sodium triphenylmethide[5] have failed, presumably because of the ease with which this ketone self-condenses. We have found that the carbethoxylation fails even in the presence of the more reactive carbethoxylating reagent, ethyl 4-phenyl phenyl carbonate, and sodium triphenylmethide.

Carbonations Followed by Esterification.—The carbonation of ketones to form β-keto acids has been carried out previously apparently only with camphor and a few cyclic ketones,[6] sodium amide being used to effect the reaction.

(1) Paper XXIV on "Condensations"; paper XXIII, THIS JOURNAL, **66**, 345 (1944).

(2) Presented at the Pittsburgh meeting of the A. C. S., Sept., 1943.

(3) Supported in part by a grant from the Duke University Research Council.

(4) Wallingford, Homeyer and Jones, THIS JOURNAL, **63**, 2252 (1941).

(5) Abramovitch and Hauser, *ibid.*, **64**, 2271 (1942).

(6) Bredt, *J. prakt. Chem.*, [2] **104**, 9 (1922); [2] **131**, 132 (1932); Gardner, Perkin and Watson, *J. Chem. Soc.*, **97**, 1756 (1910); Koetz and Grethe, *J. prakt. Chem.*, [2] **80**, 473 (1909).

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In the present investigation methyl ethyl, methyl *t*-butyl, di-isopropyl and di-isobutyl ketones have been carbonated using sodim triphenylmethide and the resulting β-keto acids esterified with diazomethane to give, respectively, methyl propionylacetate (37%), methyl γ,γ,γ-trimethylacetylacetate (58%), methyl α-iso-butyrylisobutyrate (56%) and methyl α-isovalerylisovalerate (42%). None of these β-keto esters, or the corresponding ethyl esters, can be prepared satisfactorily by means of sodium alkoxides. The formation of methyl propionylacetate from methyl ethyl ketone, for example, may be represented as follows.

$$C_2H_5COCH_3 \xrightarrow[\text{by } CO_2 \text{ and acid}]{(C_6H_5)_3CNa \text{ followed}} C_2H_5COCH_2COOH \xrightarrow{CH_2N_2} C_2H_5COCH_2COOCH_3$$

Desoxybenzoin appeared to form the corresponding β-keto acid in good yield but it decomposed before it could be esterified. The pronounced instability of this acid has been observed previously.[7]

Methyl propionylacetate has been characterized by several reactive hydrogen and carbonyl group reactions. With phenylhydrazine, methyl propionylacetate gave a pyrazolone, identical with that obtained from authentic ethyl propionylacetate, although the yield of the derivative from the methyl β-keto ester was low. That carbonation occurred at the methyl group of methyl ethyl ketone, rather than at the methylene group, was confirmed by the alkylation of the propionylacetate with *n*-butyl bromide and subsequent ketonic cleavage of the alkylated product to give ethyl *n*-amyl ketone in good yield.

$$C_2H_5COCH_2COOCH_3 \xrightarrow{n\text{-}C_4H_9Br} C_2H_5COCH(C_4H_9)COOCH_3 \longrightarrow C_2H_5COC_5H_{11}$$

Methyl γ,γ,γ-trimethylacetylacetate has been characterized by the formation of a phenylpyrazolone and by ketonic cleavage. Methyl α-isobutylisobutyrate and methyl α-isovalerylisovalerate, which do not exhibit satisfactory reactive hydrogen and carbonyl group reactions, have been characterized by both acidic and ketonic cleavage.

Carbonations *versus* Carbethoxylations Using Sodium Triphenylmethide.—The mechanism of the carbonation of ketones is represented by the ionic[8] equations (1) and (2), while that for the carbethoxylation of ketones (which is similar to that for the acetoacetic ester reaction[9]) is represented in somewhat simplified form by the equations (1), (3) and (4).

(1) $RCOCH_2R' + (C_6H_5)_3C^- \longrightarrow [RCOCHR']^- + (C_6H_5)_3CH$

(2) $[RCOCHR']^- + CO_2 \longrightarrow RCOCHR'COO^-$

(3) $[RCOCHR']^- + CO(OC_2H_5)_2 \longrightarrow RCOCHR'COOC_2H_5 + C_2H_5O^-$

(4) $RCOCHR'COOC_2H_5 + [RCOCHR']^- \longrightarrow [RCOCR'COOC_2H_5]^- + RCOCH_2R'$

One mole of sodium triphenylmethide ion converts one mole of the ketone essentially completely into its anion (1). In the carbonation, the ketone anion condenses with carbon dioxide to form the carboxylate anion (2) which does not appear to react further[10] under the conditions employed; in the carbethoxylation, however, the ketone anion condenses with diethyl carbonate to form a β-keto ester (3) which generally undergoes a rapid proton exchange with unchanged ketone anion regenerating one-half of the original ketone (4). Thus, on the basis of these mechanisms, one mole of sodium triphenylmethide reagent may effect the carbonation of one mole of the ketone, but the carbethoxylation of only one-half mole of ketone.

Actually, per mole of sodium triphenylmethide the yield of α-isovalerylisovaleric ester obtained by the carbonation of di-isobutyl ketone followed by esterification has been much better than that obtained by the carbethoxylation of the same ketone. Similarly, the carbonation of methyl ethyl ketone followed by esterification gave a higher yield of propionylacetic ester per mole of sodium triphenylmethide used than the acylation of ethyl acetate with 4-phenylphenyl propionate,[5] the mechanism of which is similar to a carbethoxylation.

In general, for the synthesis of β-keto esters using sodium triphenylmethide, the method of carbonation of ketones followed by esterification is probably to be preferred to that of the carbethoxylation of ketones or that of the acylation of esters with esters.

Experimental[11]

Preparation of Ketone Anions (Sodium Derivatives).—Sodium triphenylmethide reagent was prepared from one mole of triphenylchloromethane and analyzed.[12,13] By means of the apparatus described elsewhere,[14] approximately two-tenths mole aliquots of the reagent were transferred to one-liter Pyrex bottles. In most cases, the reagent was chilled, air being excluded by an atmosphere of nitrogen. A molecular equivalent of the ketone was added to the reagent with shaking; the ketone anion was formed instantaneously as shown by the discharge of the characteristic color of the reagent. The solution of the ketone anion thus formed was used immediately for the carbonation and carbethoxylation reactions described below.

Ethyl α-Isovalerylisovalerate.—Di-isobutyl ketone (28.4 g., 0.2 mole) was converted to its anion at 0° and the

(7) Beckmann and Paul, *Ann.*, **266**, 1 (1891).

(8) The representation of the reactions of only the anions is simpler and, we believe, adequate for the present purpose, although the positive sodium ion also might play an important role in the detailed mechanism in the ether medium. In this connection, see Morton, Little and Strong, THIS JOURNAL, **65**, 1339 (1943).

(9) See Hauser and Hudson, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1942, Chapter 9.

(10) In certain cases, however, the further carbonation of the carboxylate ion has been observed; see Gilman and Pacewitz, THIS JOURNAL, **62**, 1301 (1940).

(11) Microanalyses by Dr. T. S. Ma, University of Chicago, Chicago, Ill.

(12) Hudson and Hauser, THIS JOURNAL, **63**, 3156 (1941).

(13) Hauser and Hudson, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1943, 2nd Coll. Vol., p. 609 (Note 3).

(14) Baumgarten and Hauser, THIS JOURNAL, **66**, 1037 (1944).

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resulting solution was carbethoxylated with 23.7 g. (0.2 mole) of diethyl carbonate. After seven days at room temperature glacial acetic acid and water were added to the reaction mixture. The ether phase (after extraction with saturated bicarbonate solution) was dried (sodium sulfate followed by "Drierite") and the solvent removed at atmospheric pressure. The residue was distilled *in vacuo* (up to 170° 15 mm.); the distillate gave on redistillation 11 g. (50%) of ethyl α-isovalerylisovalerate, b. p. 118–119.5° (15 mm.).[12]

Ethyl α-isovalerylisovalerate was characterized by ketonic cleavage[15] to di-isobutyl ketone, identified by its semicarbazone, m. p. 121–122°.[16] Acidic cleavage was carried out by refluxing for two hours a solution of 2 g. of ethyl α-isovalerylisovalerate and 0.03 mole of sodium ethoxide in 25 ml. of absolute ethanol, diluting with 5 ml. of water and refluxing for two hours longer. The solvent was evaporated and the solid residue was heated with an excess of thionyl chloride for thirty minutes. The crude acid chloride was converted[17] to isovaleryl anilide, m. p. 109–111°.[18]

Methyl Ethyl Ketone with Ethyl 4-Phenylphenylcarbonate.—The carbethoxylation of the anion of methyl ethyl ketone (0.2 mole, prepared at 0°) with 48.4 g. (0.2 mole) of ethyl 4-phenylphenyl carbonate[19] gave after four and one-half hours at room temperature 9.2 g. of material, b. p. 60–80° (20 mm.) (mainly at 64–69° 20 mm.), consisting presumably of 3-methylheptene-3-one-5 (reported, 66–68°).[5]

Carbonation Followed by Esterification: General Procedure.—The ether solution of the ketone anion, prepared as described above, was transferred onto an approximately ten-fold excess of Dry-Ice by means of a siphon under nitrogen pressure. After the excess of Dry-Ice had evaporated, water and ether were added to the mixture with shaking. The aqueous phase was combined with an ice-cold alkaline extract of the ether phase and acidified with iced mineral acid. The liberated β-keto acid was taken up in ether and the ether solution was dried with sodium sulfate at 0°. Esterification of the β-keto acid was effected with a 10–20% excess of diazomethane[20] (prepared from nitrosomethyl urea), and the excess diazomethane destroyed with glacial acetic acid, which in turn was removed by saturated sodium bicarbonate solution. The ether solution of the β-keto ester was dried over sodium sulfate followed by "Drierite" and the product was isolated by distillation.

Methyl Propionylacetate.—Methyl ethyl ketone (22.4 g., 0.312 mole) was converted at −15° to its anion which was carbonated immediately. Ether and the minimum of water (200 ml.) were added and the ether solution was extracted with 100 ml. of 5% sodium hydroxide solution. The combined aqueous solutions (washed with ether) were acidified with 75 ml. of 12 *N* hydrochloric acid in 100 g. of crushed ice, saturated with sodium chloride and extracted with successive 200-ml. portions of ether until the extract was substantially free from titratable acidity. The combined ether extracts, containing 0.22 equivalent of acid, were dried and esterified as indicated above. Material boiling up to 77° (15 mm.) was redistilled, giving 4.2 g. of a combined fore-run, b. p. 71–73° (16 mm.), and after-run, b. p. 76–78° (16 mm.), and 15.1 g. (37%) of methyl propionylacetate, b. p. 73–76° (16 mm.). A mid-fraction was analyzed:

Anal. Calcd. for $C_6H_{10}O_3$: C, 55.37; H, 7.74. Found: C, 55.04; H, 7.57.

With ammoniacal copper acetate solution, methyl propionylacetate formed a copper salt, m. p. 154–156°, and m. p. 160.3–160.9° after recrystallization from benzene–petroleum ether. With phenylhydrazine in glacial acetic acid solution, the β-keto ester gave, after recrystallization from very dilute ethanol, a low yield of 3-ethyl-1-phenylpyrazolone-5, m. p. and mixed m. p. 97–98° (reported,[21] 100°).

Methyl propionylacetate (26 g., 0.2 mole) was alkylated with an equivalent of sodium methoxide and an excess of *n*-butyl bromide in methanolic solution at 60° for seventy-two hours. Sodium bromide was removed by filtration and the solution concentrated. The reaction mixture was diluted with iced dilute hydrochloric acid and extracted with ether. The ether solution (neutralized with sodium bicarbonate and dried) was distilled, yielding 17.5 g. (47%) of methyl α-butylpropionylacetate, b. p. 108–120° (16 mm.). Redistillation gave 11 g., b. p. 108–112° (16 mm.).

Anal. Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 65.24; H, 9.54.

Ketonic cleavage of 9.3 g. (0.05 mole) of methyl α-butylpropionylacetate in glacial acetatic acid-sulfuric acid mixture[15] gave 4.3 g. (67%) of ethyl *n*-amyl ketone, b. p. 160–166° (mainly 163–165°) (reported, 167–168°).[22] The crude semicarbazone melted at 92–98° and after seven recrystallizations from ether–petroleum ether the pure derivative melted at 116–117°.[23] The 2,4-dinitrophenylhydrazone formed in methanolic hydrochloric acid solution melted at 55–59° (crude) and after two recrystallizations from methanol at 64–65.5°.

Methyl γ,γ,γ-Trimethylacetylacetate.—The anion of pinacolone, prepared at 0° from 19.0 g. (0.19 mole) of pinacolone, was carbonated immediately. γ,γ,γ-Trimethylacetylacetic acid was liberated and esterified as described above. There were obtained 1.6 g. of a fore-run, b. p. 80–82° (17 mm.), and 17 g. (57%) of methyl γ,γ,γ-trimethylacetylacetate, b. p. 82–84° (17 mm.).

Anal. Calcd. for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.94; H, 8.93.

Ketonic cleavage[16] of methyl γ,γ,γ-trimethylacetylacetate gave a 50% yield of pinacolone, b. p. 104–106°. Semicarbazone, m. p. 154.5–156° (reported, 157–158°).[24] Reaction of the β-keto ester with an equivalent of phenylhydrazine gave a 40% yield of 3-*t*-butyl-1-phenylpyrazolone-5, m. p. 110.5–111°.[25]

Methyl α-Isobutyrylisobutyrate.—The anion of di-isopropyl ketone, prepared from 22.8 g. (0.2 mole) of di-isopropyl ketone at 0°, was carbonated. α-Isobutyrylisobutyric acid was liberated and esterified as described. Distillation gave 1.1 g. of fore-run, b. p. 92–94° (26 mm.), 19 g. (55%) of methyl isobutyrylisobutyrate, b. p. 94–96° (26 mm.), and 10 g. of after-run, b. p. 96–98° (26 mm.).

Anal. Calcd. for $C_9H_{16}O_3$: C, 62.76; H, 9.37. Found: C, 62.75; H, 8.96.

Ketonic cleavage[16] of methyl α-isobutyrylisobutyrate gave a 54% yield of di-isopropyl ketone, b. p. 123–124.5°; m. p. of semicarbazone 157–157.5° (reported, 160°).[26] Acidic cleavage gave isobutyric acid, identified by its anilide, m. p. 104–106°.[27]

Methyl α-Isovalerylisovalerate.—The anion of di-isobutyl ketone, prepared at 0° from 28.4 g. (0.2 mole) of di-isobutyl ketone, was carbonated. Isovalerylisovaleric acid was liberated and esterified as described. There were obtained 0.6 g. of fore-run, b. p. 111–114° (19 mm.), 17 g. (42%) of methyl α-isovalerylisovalerate, b. p. 114–116.5° (19 mm.), and 0.4 g. of after-run, b. p. 116.5–118° (19 mm.).[28]

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.58; H, 9.47.

(15) Hudson and Hauser, THIS JOURNAL, **63**, 3163 (1941).
(16) Spielman and Schmidt, *ibid.*, **59**, 2010 (1937).
(17) Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1935, p. 144.
(18) Underwood and Gale, THIS JOURNAL, **56**, 2119 (1934).
(19) Baumgarten, Walker and Hauser, *ibid.*, **66**, 303 (1944).
(20) Arndt, "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1943, 2nd Coll. Vol. p. 166 (Note 3), p. 461.
(21) Blaise, *Compt. rend.*, **132**, 978 (1901).
(22) Bouveault and Locquin, *Bull. soc. chim.*, [3] **31**, 1158 (1904).
(23) Whitmore and Williams, THIS JOURNAL, **55**, 410 (1933).
(24) Gilman and Nelson, *Rec. trav. chim.*, **55**, 529 (1936).
(25) Wahlberg, *Ber.*, **44**, 2072 (1911).
(26) Hauser and Renfrow, THIS JOURNAL, **59**, 1823 (1937).
(27) Fieser and Campbell, *ibid.*, **60**, 168 (1938).
(28) This experiment yielded a relatively large amount of high boiling material. Distillation through a 5" "Vigreux" column gave 6.1 g. of distillate, b. p. 60–130° (5 mm.), without separation.

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Ketonic cleavage[15] of methyl α-isovalerylisovalerate gave a 63% yield of di-isobutyl ketone, b. p. 164–166°. The semicarbazone melted at 121.2–121.8°.[16] Acidic cleavage gave isovaleric acid, identified by its anilide, m. p. 109–111°.[18]

Summary

1. The carbethoxylation of di-isobutyl ketone with diethyl carbonate, which fails in the presence of sodium ethoxide, has been effected by means of sodium triphenylmethide to form ethyl α-isovalerylisovalerate. An attempt to carbethoxylate methyl ethyl ketone using this base in conjunction with ethyl 4-phenylphenyl carbonate has failed.

2. Four ketones, which are not carbethoxylated in the presence of sodium ethoxide, have been carbonated using sodium triphenylmethide and the resulting β-keto acids esterified with diazomethane to form the corresponding methyl β-keto esters.

3. The β-keto esters have been characterized by suitable reactions. The methyl group of methyl ethyl ketone was shown to undergo carbonation.

4. The relative amounts of carbonation and carbethoxylation of ketones that sodium triphenylmethide is capable of effecting is considered in connection with the mechanism of these reactions.

DURHAM, N. C. RECEIVED FEBRUARY 29, 1944

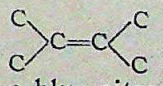
[CONTRIBUTION FROM THE HERCULES EXPERIMENT STATION, HERCULES POWDER COMPANY]

Resin Acids. The Structure of the Lactone of Hydroxytetrahydroabietic Acid[1]

BY RICHARD F. B. COX

The lactonization of dihydroabietic acids derived from abietic and levo-pimaric acids has always led to a single individual lactone melting at 131–132°. No stereoisomeric lactones have yet been produced from these dihydroabietic acids even though acids of rotations −30° to +108° have been investigated. This lactone appears, therefore, to be characteristic of the abietic family of dihydro acids.

Although the lactone has been known for many years[2a] there is very little known about its structure. Hasselstrom[2b] at one time suggested that on the basis of a γ-lactone structure the point of lactonization is probably C-10. Fleck and Palkin[3] then attempted to prove this structure by oxidizing the hydroxytetrahydroabietic acid obtained on saponification of the lactone. Under no conditions were they able to effect an oxidation to a keto acid which would be expected on the basis of Hasselstrom's formula. Moreover, they were unable to esterify the hydroxyl group of the free acid or its methyl ester. They concluded, therefore, that the hydroxyl group must be in a tertiary position which, to fit the molecular models, must be at C-4b.[2a]

It was expected that more concrete evidence in favor of formula I for the lactone might be given by an investigation of the reactions of the dihydroabietic acids produced by dehydration of the hydroxytetrahydroabietic acid. For example, only the Fleck and Palkin formula would be expected to lead to a dihydroabietic acid (4b, 8a) having the  type of double bond which will give a blue nitrosyl chloride derivative.

The stability of the lactone and the ease of lactonization of the hydroxytetrahydroabietic acid under dehydration conditions appeared at first to oppose this method of approach. It was then discovered in the course of our work on resin acids that the lactone underwent a reaction with methylmagnesium iodide which resembled a dehydration in that the product was a mixture of dihydroabietic acids.

The reaction appeared to be an abnormal Grignard reaction as a result of the highly hindered position of the carbonyl group of the lactone. One mechanism to explain the results is shown below.

According to this mechanism, the methylmagnesium iodide first forms a coördination complex (II) with the lactone, as a result of which the carbonyl carbon becomes deficient in electrons. The resulting increased attraction for the oxygen in the bridge then causes the formation of a carbonyl from this oxygen and a shift in the electron deficiency to C-4b. Simultaneously the methyl radical is freed to combine with the activated protons at positions 8a and 5 (III). The end-result of this rearrangement is thus the formation of the dihydroabietic acids as their magnesium salts (IV and V).

Since the gases produced in the reaction included hydrogen, it appears as though the protons at C-5 and C-8a have been displaced completely to combine either with another proton or the methyl radical. Thus the presence of hydrogen leads to the assumption that part of the

(1) Presented before the Division of Organic Chemistry at the 106th meeting of the American Chemical Society, Pittsburgh, Pennsylvania, September 7, 1943.

(2a) Ruzicka and Meyer, *Helv. Chim. Acta*, **5**, 333 (1922); Ruzicka, Waldmann, Meier and Hösli, *ibid.*, **16**, 178 (1933).

(2b) Hasselstrom and McPherson, THIS JOURNAL, **60**, 2340 (1938).

(3) Fleck and Palkin, THIS JOURNAL, **61**, 3197 (1939).

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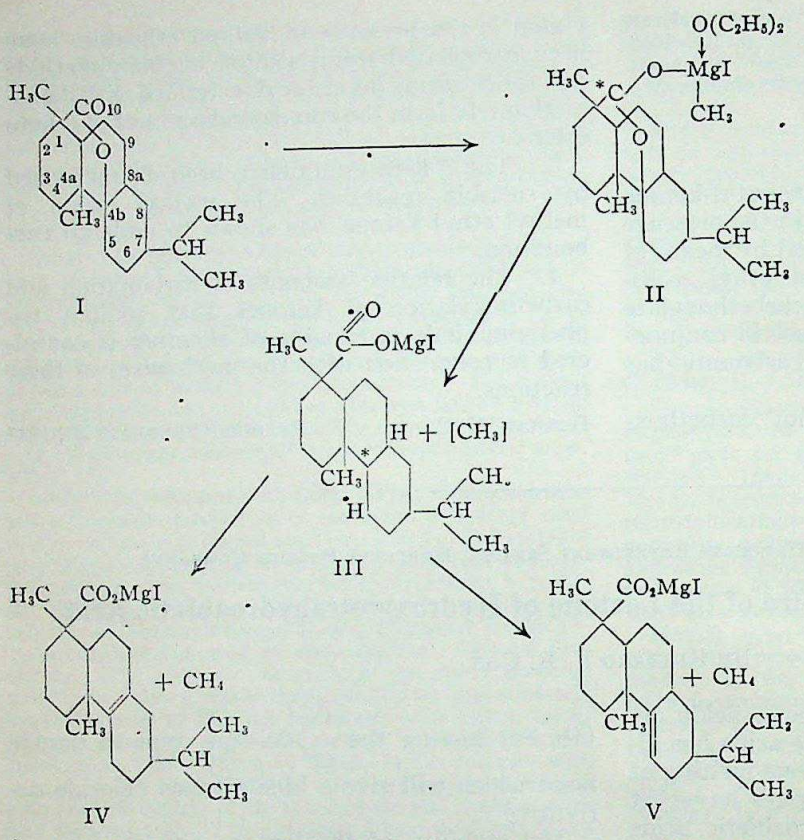

liberated methyl radicals combined to form ethane.

Further study of the reaction showed that the yield of the dihydroabietic acids is consistently about 69% of that expected even though a large excess of the methylmagnesium iodide is used. Likewise the ratio of the dextro to the levo acid remains constant at about 65:35 under varying conditions of reaction and ratios of reactants. Further study of the mechanism of this interesting reaction is not contemplated.

The dihydroabietic acids formed by the reaction of methylmagnesium iodide on the lactone differed sufficiently in crystal size when recrystallized from acetone that they were readily separated from each other by a combination of screening and crystallization. The acid of smaller crystal size melted at 185–186° and had a specific rotation −36°. The other dihydroabietic acid melted at 147–148° and had a specific rotation +68°. The properties of these acids are listed in Table I.

Both of these dihydroabietic acids produced from the lactone were stable in boiling acetic acid but lactonized readily in the presence of a little mineral acid. The lactone produced melted at 131–132° and was the same lactone which is produced from all other dihydroabietic acids. In 7.5% alcoholic hydrochloric acid the lactonization at 75°F. (24°C.) could be followed polarimetrically. The data showing the change in rotation during the course of such a lactonization are given in Table II. While the dextrorotatory acid appeared to lactonize the more readily, these data cannot be interpreted exactly without further knowledge of the products. When the lactonization products were isolated after 430 hours and titrated for unlactonized resin acid, the dextrorotatory acid was shown to have lactonized to the extent of 45% and the levorotatory acid to the extent of 35%. The rotations of the unlactonized acids after separation from the lactone showed that the dextrorotatory acid had undergone isomerization while the levorotatory acid was unchanged in rotation. The change in rotation of the dextrorotatory acid from +68° to acids of rotation +22° indicated the possibility that the isomerized acid mixture was 44% levorotatory acid and 56% dextrorotatory acid which is approximately the ratio of these acids as produced in the reaction between the Grignard reagent and the lactone. Apparently the levorotatory acid is more stable toward isomerization.

In regard to hydrogenation, the dextrorotatory dihydroabietic acid absorbed hydrogen the more readily. The rates of hydrogen absorption (Table III) show that after twenty-seven hours the dextrorotatory acid had absorbed 85% of the theoretical amount of hydrogen while the levorotatory acid had absorbed only 53% of the theoretical amount. Under the influence of reduced platinum oxide catalyst, as in hydrogenation conditions but in the absence of hydrogen, neither acid appeared to isomerize even after 60 hours treatment. In line with slower rates of hydrogenation and the higher melting points of related sterols having a double bond common to two rings, it was therefore expected that the levorotatory dihydroabietic acid might have the double bond in the 4b, 8a position and would give a blue nitroso derivative.

When the levorotatory dihydroabietic acid was treated with nitrosoyl chloride in acetic acid solution, it gave a blue solution from which a blue nitroso compound crystallized on the addition of water. This blue nitroso derivative contained no chlorine and was also formed by reaction with butyl nitrite and any mineral acid. Its neutral character and its analyses indicated that it probably was a nitrosolactone. It melted at 91.5–92° and had the unusually high specific rotation $[\alpha]_D$ −925° (2% in alcohol). Such high rotations are unknown in the resin acid field. The nitrosolactone underwent typical reactions such as hydro-

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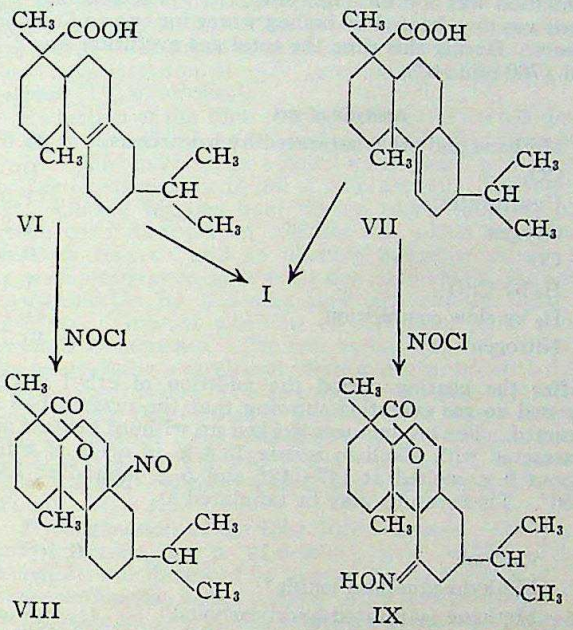
genation to an aminolactone and it lost its nitroso group by hydrolysis in boiling hydrochloric acid with formation of the lactone of hydroxytetrahydroabietic acid, m. p. 131–132°. Based on these characteristics the nitrosolactone is assumed to have formula VIII.

Since the levorotatory dihydroabietic acid is the more stable toward isomerization, has the higher melting point, and gives a blue nitrosyl derivative, it is presumed to be Δ4b,8a-dihydroabietic acid (VI). Support for the Fleck and Palkin formula of the lactone of hydroxytetrahydroabietic acid is thus established.



The dextrorotatory dihydroabietic acid when treated with nitrosyl chloride gave difficultly soluble white crystals in a light-blue mother liquor. These crystals melted at 185–186°, $[\alpha]_D$ −30° (1% in $CHCl_3$) and appeared to be an oximinolactone. Hydrolysis with mineral acids did not remove the oximino group but effected what may have been a Beckman rearrangement.[4] Formula IX has accordingly been assigned to the oximinolactone and Formula VII to the dihydroabietic acid from which it was formed.

Neither the dextro- nor the levo-dihydroabietic acid was found by the nitrosyl chloride reaction to be present in hydrogenated rosin or hydrogenated abietic acid. This is as might be expected in the case of abietic acid because of the position of the double bonds unless hydrogenation were accompanied by isomerization. The specificity of the nitrosyl chloride reaction toward certain dihydroabietic acids also indicates that the nitroso and oximino lactones are probably not the result of isomerization of the resin acids prior to addition of the nitrosyl chloride.

In the case of resin acids with one double bond in the 4b, 5 or 4b, 8a position and another in some other position, the more highly hindered 4b, 5 or 4b, 8a double bonds would be expected to be still present after partial hydrogenation. Thus, if rosin contained such resin acids, hydrogenated rosin would have been expected to give the oximinolactone or nitrosolactone.

Likewise, if abietic acid or levo-pimaric acid contained double bonds in the 4b, 5 or 4b, 8a positions, one of the dihydro acids produced from them would be expected to resemble the new dihydroabietic acids. Since there is no resemblance in physical properties between those dihydro acids reported in the literature and the new dihydroabietic acids, levo-pimaric acid probably does not have Formula X which was favored by Fieser and Campbell,[5] but has instead Formula XI which was favored by Ruzicka.[6]

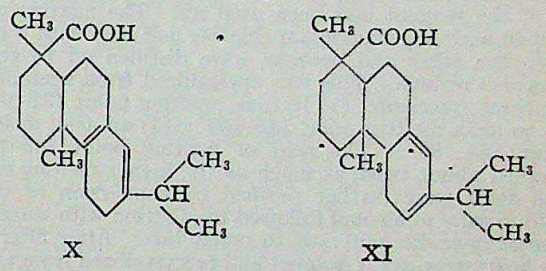


TABLE I

PROPERTIES OF DIHYDROABIETIC ACIDS

Formula assigned		*l*-Dihydroabietic acid VI	*d*-Dihydroabietic acid VII
Melting point, °C.		185–186	147–148
$[\alpha]_D$ (2% in alcohol)		−36°	+68°
Crystal system		Monoclinic	Monoclinic
Sign of double refraction		+	+
Optic axial angle (2*V*)		80° ± 5°	70° ± 5°
Nitrosyl derivative	Melting point, °C.	91.5–92	184–185
	$[\alpha]_D$ (2% solution)	−925° (alc.)	−30° (chloroform)

TABLE II

ISOMERIZATION OF DIHYDROABIETIC ACIDS

Time, min.	*d*-Dihydroabietic $[\alpha]_D$	*l*-Dihydroabietic $[\alpha]_D$
0	+68	−37
20	+59	−37
30	+57	−37
45	+54	−37
70	+41	−37
100	+40	−35
190	+33	−32
235	+29	−25
285	+19	−26
380	+ 8	−27
430	+ 9	−26

Experimental

Reaction of Lactone of Hydroxytetrahydroabietic Acid with CH_3MgI.—(a) One mole of methylmagnesium iodide was prepared from 24 g. of magnesium and 145 g. of methyl iodide in 750 ml. of ether. To the reagent was slowly added 304 g. of the lactone of hydroxytetrahydroabietic acid, melting point 131–132° in 1000 ml. of dry benzene. A small amount of heat was given off in the reaction. After standing for one hour, the mixture was warmed on

(4) Investigation not yet completed.

(5) Fieser and Campbell, THIS JOURNAL, 60, 159 (1938).

(6) Ruzicka and Kaufmau, *Helv. Chim. Acta*, 23, 1346–1356 (1940).

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TABLE III

HYDROGENATION OF DIHYDROABIETIC ACIDS

Time, min.	Hydrogen absorbed by 0.450-g. samples Acid $[\alpha]_D$ −36°, ml.	Acid $[\alpha]_D$ +68°, ml.
0	0	0
72	8.1	16.6
96	8.8	19.2
160	10.8	22.2
205	12.1	23.5
253	12.6	23.4
301	13.2	24.0
349	13.7	24.1
1330	18.1	27.0
1655	17.9	27.2

the steam-bath under reflux for sixteen hours, during which time much of the ether was lost. At the end of this time all of the reagent had been used up. The mixture was washed with 5% ammonium chloride and then with water. Then the ether and benzene were distilled off to get a brownish residue. This was crystallized from acetone to get three fractions: (1) lactone, melting point 131–132°; (2) an acid, melting point 145–150°; (3) an acid, melting point 185–186°. The acid of melting point 145–150° weighed about twice as much as the higher melting acid. The acids were further purified by conversion to their sodium salts in alcohol followed by dilution with water to allow non-acidic materials to precipitate. After filtering, the acids were again isolated and recrystallized from ethyl acetate. The purified low melting acid melted at 147–148° and had a specific rotation (2% in alcohol) +68.00°. *Anal.* Calcd. for $C_{20}H_{32}O_2$: C, 79.0; H, 10.6; equiv. wt., 304. Found: C, 78.7, 78.9; H, 10.45, 10.47, neut. equiv., 305.5. It was unsaturated to $C(NO_2)_4$ and lactonized readily in sulfuric acid to the lactone melting point 131–132°.

The high melting acid was recrystallized from ethyl acetate to a constant rotation. Its melting point was then 185–186° and its specific rotation −36° (2% in alcohol). It was unsaturated as shown by testing with tetranitromethane and lactonized in sulfuric acid to the lactone, melting point 131–132°. Its neutral equivalent was 304, which is the theoretical for a dihydroabietic acid. *Anal.* Calcd. for $C_{20}H_{32}O_2$: C, 79.0; H, 10.6. Found: C, 78.9, 79.0; H, 10.49, 10.52.

In crystallizing these two acids it was found that the large stubby prisms of the lower melting acid could be separated by screening from the small needles of the higher melting acid. In using this method of separation, purification was achieved quite readily, only three cystallizations being necessary to reach the stage where the properties were constant.

(b) One-tenth mole of methylmagnesium iodide was prepared in the usual manner from 15 g. of methyl iodide and 2.3 g. of magnesium using ether as the solvent for the methyl iodide. To this Grignard solution at room temperature was added 30.4 g. of lactone, melting point 131–132°, in dry benzene. When addition was complete, the ether was distilled and the mixture was heated overnight on the steam-bath. The product was then poured into ice water containing 25 g. of ammonium chloride. The benzene layer was then extracted with 2% sodium hydroxide, extract acidified and the acids recovered, dried and weighed: 21.0 g. (69%), N. E., 295 (trace of HCl still remaining), $[\alpha]_D$ +29° (1% in alcohol), bromine no. 74.5; yield calculated from specific rotation, 62.5% $[\alpha]_D$ +68° acid, 37.5% $[\alpha]_D$ −36° acid.

This run was repeated using the same amount of magnesium and methyl iodide but only 15.2 g. of lactone. The same procedure was followed and the acids extracted, dried and weighed; wt. 8.0 (52%), N. E., 295; $[\alpha]_D$ +32° (1% in alcohol); yield calculated from specific rotation, 65% $[\alpha]_D$ +68° acid, 35% $[\alpha]_D$ −36° acid.

Reaction of the Lactone at Room Temperature with CH_3MgI.—The reaction of 0.1 mole of the lactone with 0.1 mole of Grignard reagent described above was repeated exactly except that the reaction mixture was allowed to stand at room temperature overnight instead of being heated overnight. The product, worked up in the usual manner, weighed 29.6 g. It yielded on extraction with alcoholic alkali, 3 g. of acid mixture. This yield of acids is only about one-quarter the yield obtained at the higher temperature.

Quantitative Study of Reaction between Lactone and Methylmagnesium Iodide.—A solution of methylmagnesium iodide was made by combining 2.5 g. of magnesium and 15.6 g. of methyl iodide in 80 ml. of phenetole. To this reagent in a nitrogen atmosphere in a closed vessel fitted with a gas evolution device was added 30.4 g. of lactone in 100 ml. of dry benzene. Some heat was given off and the temperature accidentally rose to 45°. The gas evolution was 305 ml. (760 mm., 0°). The reaction mixture was then heated by boiling water for one and one-half hours. During this time the total gas evolution was 2100 ml. (760 mm., 0°).

Analysis of gas	Sample 1, %
Methane and other saturated hydrocarbons	25.6
CO_2	0.0
Unsaturates	1.0
Oxygen	11.2
CO	0.0
H_2 by CuO	1.4
H_2 by slow combustion	11.1
Nitrogen	49.7

After the heating period the addition of ethyl alcohol caused no gas evolution showing that the reagent had all reacted. The product was worked up without heating and extracted with alkali to isolate 13.4 g. of acids of which about 9 g. melted at 147–148° and 5 g. melted at 185–186°. These results may be tabulated as

	Moles
Lactone	0.100
Methylmagnesium iodide	.109
Methane (saturated hydrocarbons)	.022
Hydrogen	.010
Dihydroabietic acids	.044

If we assume the formation of one mole of ethane for each mole of hydrogen produced, the gases contain 0.012 mole of methane (from 0.012 mole CH_3MgI). Thus 0.032 mole of CH_3MgI is accounted for in the gases formed and 0.044 mole of CH_3MgI in the dihydroabietic acids produced.

Reaction of the Dihydroabietic Acids with Nitrosyl Chloride.—(a) 0.3 g. of dihydroabietic acid, melting point 185–186° $[\alpha]_D$ −36°, was dissolved in 5 ml. of glacial acetic acid containing 0.2 ml. of butyl nitrite. Then 5 ml. of glacial acetic acid containing 0.2 g. of dry hydrogen chloride was added. After standing overnight at 25°, the solution was a dark greenish-blue. About 5 ml. of water was added dropwise to effect crystallization and the resulting light-blue crystals weighing 0.2 g. were filtered out. These crystals melted at 88–88.5° and were recrystallized from a minimum amount of methanol at −70° to raise the melting point to 91.5–92°. The specific rotation $[\alpha]_D$ was −920° (0.2% in alcohol); −925° (2% in alcohol). *Anal.* Calcd. for $C_{20}H_{31}O_3N$: N, 4.2. Found: N, 4.49; Cl, nil.

(b) 0.3 g. of dihydroabietic acid, melting point 147–148°, $[\alpha]_D$ +68°, was dissolved in 5 ml. of glacial acetic acid containing 0.2 ml. of butyl nitrite and 5 ml. of acetic acid containing 0.2 g. of dry hydrogen chloride was added. The mixture turned dark amber but within two hours was light-blue with white crystals in suspension. The crystals were removed by filtration and were washed with alcohol in which they are very insoluble. The yield was 0.1 g., melting point 169–170°. These crystals were recrystallized from a chloroform–methanol mixture to a constant melting point 184–185°; $[\alpha]_D$ −30° (2% in $CHCl_3$). *Anal.* Calcd. for $C_{20}H_{31}O_3N$: N, 4.2. Found: N, 4.33; Cl, nil.

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(c) 42 g. of a mixture of dihydroabietic acids produced by the reaction of methylmagnesium iodide on the lactone of hydroxytetrahydroabietic acid was dissolved in 300 ml. of glacial acetic acid. To this solution was added 30 ml. of butyl nitrite and 450 ml. of glacial acetic acid containing 31 g. of hydrogen chloride. The mixture turned dark and then gradually greenish-blue and crystals separated. The crystals were removed by filtering and were washed once with methanol. They weighed 3 g. and were oximino lactone crystals, melting point 185–186°. The mother liquor was diluted cautiously with water to get 16.3 g. of blue crystals, melting point 91–92°, and 3 g. of white crystals of lactone, melting point 130–131°.

(d) To a solution of 0.3 g. of dihydroabietic acid, melting point 185–186°, $[\alpha]_D$ −36°, in 5 ml. of glacial acetic acid, was added 0.2 ml. of butyl nitrite and then 5 ml. of glacial acetic acid containing 0.2 ml. of concentrated nitric acid (d. 1.42). After two hours at room temperature, water was added to get crystals which were recrystallized from methanol at −70°, melting point 91.5–92°, $[\alpha]_D$ −905° (1% in alcohol).

Reduction of the Blue Nitrosolactone.—To a solution of 2 g. of lactone of hydroxynitrosotetrahydroabietic acid $[\alpha]_D$ −925° in 75 ml. of ethanol was added 2 g. of sodium sulfide (hydrated) in 14 ml. of 70% alcohol. The mixture was refluxed for one hour during which time the blue-green color disappeared. Water was added dropwise to produce crystals and to dissolve inorganic salts. The crystals were taken up in ether and converted to the amine hydrochloride by bubbling hydrogen chloride into the solution. Gradual addition of petroleum ether caused crystals to separate. The free amine was then liberated by neutralizing a methanol solution of the salt with dilute sodium hydroxide. The free amine was then crystallized by diluting the methanol solution with water and was further purified by crystallization from methanol until a melting point of 144–145°, $[\alpha]_D$ ±1° (1.76% in alcohol) was reached. *Anal.* Calcd. for $C_{20}H_{33}O_2N$: N, 4.37. Found: N, 4.27.

Hydrogenation of the Blue Nitrosolactone.—0.268 g. of nitrosolactone, m. p. 91.5–92.5°, $[\alpha]_D$ −925° (2% in ethanol), was dissolved in 10 g. of glacial acetic acid. To this solution was added 0.265 g. of $PtO_2 \cdot H_2O$ (Adams platinum oxide catalyst). The solution was shaken with hydrogen at atmospheric pressure in an apparatus for measuring the volume of hydrogen absorbed. A blank was run on the catalyst in acetic acid at the same time and applied as a correction for the hydrogen absorbed by the catalyst. The corrected volume of hydrogen absorbed was 33.9 ml.

After removal of the catalyst the product was precipitated by adding water. The crystalline aminolactone was then crystallized from methanol. It melted at 146–147° and was shown by mixed melting point to be the same amine which was obtained by reducing the blue nitrosolactone with sodium sulfide.

Hydrolysis of Nitrosolactone —A solution of 1 g. of nitrosolactone, m. p. 91.5–92.5°, in 25 ml. of acetic acid containing 10 ml. of concentrated hydrochloric acid was refluxed. The blue color disappeared in about three hours, but the refluxing was continued forty hours. The product was isolated by adding water and then crystallized from methanol. It amounted to 0.35 g., m. p. 130–131°. It was shown by mixed melting point and microscopic examination to be the lactone of hydroxytetrahydroabietic acid.

Acid Isomerization of Dihydroabietic Acids.—A solution of 0.1000 g. of dihydroabietic acid, melting point 147–148°, $[\alpha]_D$ +68° in 10 ml. of glacial acetic acid was refluxed for thirty minutes. The solvent was evaporated and replaced by 10 ml. of ethanol. The rotation was unchanged by this treatment. Similar treatment of dihydroabietic acid melting point 185–186°, $[\alpha]_D$ −36° did not change the rotation.

A solution of 0.1000 g. of dihydroabietic acid in 5 ml. of ethanol was diluted to 10 ml. with alcoholic hydrogen chloride (15 g. of HCl gas in 100 ml. of solution). The rotation was determined immediately and was followed at 75°F. (29°C.) for twenty days. The change in rotation for both the dextro- and the levo-dihydroabietic acids is given in Table II.

After 430 hours of isomerization, the product was recovered by evaporation and dried over sodium hydroxide pellets *in vacuo*. Titration of these residues indicated that 35% of the levorotatory acid had been converted to the lactone and 45% of the dextrorotatory acid had been converted to the lactone. The lactone was removed from the neutralized solutions by ether extraction and the acids were recovered from the salts. The acid mixture from isomerization of the dextrorotatory acid was +22° indicating the possibility of about 44% levorotatory acid in the mixture. The acid mixture from isomerization of the levorotatory acid was −37° indicating no isomerization to the dextrorotatory acid.

Hydrogenation of Dihydroabietic Acid.—Samples of dihydroabietic acid weighing 0.450 g. were placed in the flasks of a quantitative hydrogenation apparatus, containing 15 ml. of glacial acetic acid. After the resin acid was dissolved, the solution was cooled and 0.401 g. $PtO_2 \cdot H_2O$ catalyst was added. The sample was shaken under a slight pressure of hydrogen for twenty-seven hours. Both dihydroabietic acids $[\alpha]_D$ +68° and $[\alpha]_D$ −36° and a blank on the catalyst were run simultaneously. The data in Table III are corrected for the blank.

After twenty-seven hours, the dextrorotatory acid had absorbed 85% of the theoretical amount of hydrogen and the levorotatory acid had absorbed 53% of the theoretical amount of hydrogen. In both cases the acid mixtures isolated from solution had $[\alpha]_D$ −6°. By lactonizing the remaining dihydroabietic acid and removing the tetrahydroabietic acids, it was found that the tetrahydroabietic acid in each case had zero rotation. By correcting the crude acid mixtures −6° for the rotation of the tetrahydroabietic acid present the unhydrogenated acid from the dextrorotatory acid had $[\alpha]_D$ −40° and that from the levorotatory acid had $[\alpha]_D$ −12°. This is indicative that the hydrogen absorption of the dextrorotatory acid was decreased by isomerization of the original acid to a levorotatory acid.

In order to determine whether the catalyst caused either or both of the acids to isomerize, 0.45-g. samples of each were added to freshly reduced catalyst and acetic acid and were shaken for sixty hours. After this treatment the levorotatory acid had $[\alpha]_D$ −37° and the dextrorotatory acid had $[\alpha]_D$ +66°, which showed no change from the original acid.

Acknowledgment.—The author wishes to acknowledge the skillful assistance of Mr. Thomas F. Sanderson in carrying out the experimental work reported here.

Summary

The lactone of hydroxytetrahydroabietic acid melting at 131–132° has been converted by the reaction with methylmagnesium iodide into two dihydroabietic acids, m. p. 147–148°, $[\alpha]_D$ +68° and m. p. 185–186°, $[\alpha]_D$ −36°, respectively.

Both of these dihydroabietic acids lactonize readily to give only the original lactone, m. p. 131–132°.

The dextrorotatory dihydroabietic acid reacts with nitrosyl chloride to form an oximino lactone. The levorotatory dihydroabietic acid under the same conditions forms a blue nitroso lactone.

The levorotatory dihydroabietic acid absorbs hydrogen in the presence of a platinum catalyst more slowly than does the dextrorotatory acid. In the process of lactonization, the levorotatory acid lactonizes more slowly and does not isomerize while the dextrorotatory acid lactonizes more

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rapidly and at the same time isomerizes to the levorotatory acid.

All of these data support the formula for the lactone of hydroxytetrahydroabietic acid in which the point of lactonization is at C-4b.

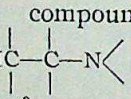
WILMINGTON, DEL. RECEIVED JANUARY 6, 1944

[CONTRIBUTION FROM THE AVERY LABORATORY OF CHEMISTRY OF THE UNIVERSITY OF NEBRASKA]

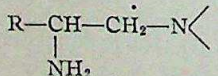
Amino Ketones. II. The Synthesis of α,β-Diamines from α-Amino Ketones*

BY NORMAN H. CROMWELL AND HERMAN HOEKSEMA

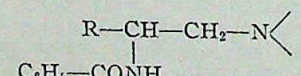
In a previous investigation[1] the synthesis of α,γ-diamines from β-amino ketones was reported. It seemed of interest to investigate similar synthesis of α,β-diamines from α-amino ketones to compare the relative yields in the two series.

Several investigations[2] by other workers have been concerned with the conversion of α-amino ketones to α-amino alcohols in order that the two series of compounds could be studied for their relative values as pressor agents. A similar comparison of the α-amino ketones with their corresponding α,β-diamino compounds should also prove to be interesting. Furthermore, such α,β-diamino compounds might be converted to the benzamides. It has been shown previously that compounds containing the grouping  often possess local anesthetic activity.[3]

Thus a series of diamines (A) and the corresponding benzamides (B) might prove to be of considerable interest, pharmacologically.



(A)

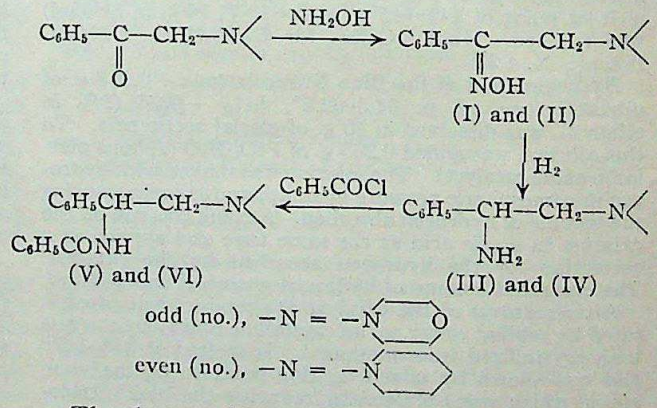


(B)

Attempts were made to obtain in good yields the oximes of ω-N-methylbenzylaminoacetophenone,[4] ω-tetrahydroisoquinolinoacetophenone[5] and ω-tetrahydroquinolinoacetophenone,[6] without success.

The oximes of ω-morpholino-[2b] and ω-piperidinoacetophenone[7] were both obtained in good yields. An extensive investigation was made of the reduction of one of these, (I), to the corresponding α,β-diamine. Sodium and alcohol was found to be the most efficient of the reagents tried. It was interesting to find that α-amino ketoximes are reduced to give better yields of the α,β-diamines by catalytic hydrogen, than were the β-amino ketoximes to give α,γ-diamines.[1] In the latter case it was shown that β-amino ketoximes lost the β-amino group on such treatment, probably because of the tendency to form an α,β-unsaturated ketoxime. The absence of such a tendency with α-amino ketoximes accounts for their greater yields of diamines on catalytic reduction.

The general low yields of α,β-diamines experienced even with sodium and alcohol were caused by condensation of the diamine with itself, through loss of ammonia during distillation. This was shown by the detection of ammonia in the forerun of such distillations and by treating the crude diamine ether solution with benzoyl chloride, and determining the yield of benzamide obtained.



The benzamides (V) and (VI) were readily prepared in good yields from the corresponding α,β-diamines (III) and (IV).

These benzamides have been found to be strong local anesthetics. The various compounds reported in this paper are being fully investigated for various pharmacological activities by L. W. Rowe and others of the Parke, Davis and Company Laboratories. A detailed pharmacological report will be published by them in another journal.

Experimental[8]

ω-Morpholinoacetophenone Oxime (I).—A cooled solution of 200 g. (4.35 mole) of potassium hydroxide in one liter of methanol was mixed with a solution of 61 g. (0.88

* Presented before the Division of Organic Chemistry, American Chemical Society, Cleveland, Ohio, April 4, 1944.

(1) Cromwell, Wiles and Schroeder, THIS JOURNAL, 64, 2432 (1942).

(2) (a) Hartung, *Chem. Rev.*, 9, 435–437 (1931); (b) Rubin and Day, *J. Org. Chem.*, 5, 54 (1940).

(3) (a) Wenker, THIS JOURNAL, 60, 158 (1938); (b) Eisleb, U. S. Patent 2,073,100; *C. A.*, 31, 3211 (1937).

(4) Cromwell and Witt, THIS JOURNAL, 65, 311 (1943).

(5) Allewelt and Day, *J. Org. Chem.*, 6, 384 (1940).

(6) Kunckell, *Ber.*, 30, 576 (1897).

(7) Rabe and Schneider, *ibid.*, 41, 874 (1908).

(8) Micro Dumas analyses for nitrogen and semi-micro analyses for carbon and hydrogen by the Analytical Laboratory, Department of Chemistry, University of Nebraska, under the supervision of H. Armin Pagel.

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mole) of hydroxylamine hydrochloride in 150 ml. of water at 20°. To this basic solution was added a solution of 46 g. (0.19 mole) of ω-morpholinoacetophenone hydrochloride[2b] in 70 ml. of water at 20°. The well-stoppered mixture was allowed to stand at room temperature for two days. The potassium chloride was filtered from the solution and the methyl alcohol evaporated *in vacuo* until only a sirupy residue remained. This residue was then mixed with 150 ml. of water and the solution neutralized with 300 ml. of 6 *N* hydrochloric acid. The white precipitate so obtained was filtered and washed with cold water until no trace of chloride could be detected in the washings. Recrystallization from methanol and water gave soft, white needles, m. p. 147–149°, weighing 38 g. (91% yield).

Anal. Calcd. for $C_{12}H_{16}N_2O_2$: C, 65.43; H, 7.32. Found: C, 65.48; H, 7.42.

This product was soluble in both dilute mineral acids and bases, hot methyl or ethyl alcohol, and warm ether.

ω-Piperidinoacetophenone Oxime (II).—This preparation was carried out in a similar manner to that used for (I), starting with 10 g. (0.043 mole) of ω-piperidinoacetophenone hydrochloride.[7] The white crystalline product weighed 7.9 g. (70% yield), m. p. 111–115°. By fractional crystallization from methyl alcohol, two products were obtained, m. p. 117–118.5° and m. p. 136–138.5°. A mixture of these two isomers melted at 111–115°.

Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.40; H, 8.31. Found: m. p. 118°, C, 71.23; H, 8.40; m. p. 138°, C, 71.08; H, 8.37.

Both of these compounds dissolved readily in dilute mineral acids or bases and were soluble in ether and in methyl and ethyl alcohols.

α-Phenyl-β-morpholinoethylamine (III).—This diamine was obtained by the reduction of the corresponding oxime using various procedures.

A. By Catalytic Hydrogenation: (1) Using Raney Nickel.—Five grams (0.023 mole) of (I) was dissolved in 125 ml. of absolute alcohol and shaken with 1.0 g. of Raney nickel for a short time. The catalyst was filtered off and 1.0 g. of Raney nickel again added to the filtrate and the mixture shaken with hydrogen for six hours under a pressure of 50 lb./sq. in. Removal of the catalyst and evaporation *in vacuo* of the alcohol left a yellow oily residue which was dissolved in ether and washed several times with dilute sodium hydroxide and several times with a saturated salt solution. The ether solution was dried over anhydrous sodium sulfate and evaporated to give an oil which was further dried for several days over solid sodium hydroxide. Distillation gave 0.5 g. (10% yield) of a pale yellow oil, b. p. 134° (2 mm.). Considerable residue remained in the distilling flask and ammonia was detected in the forerun.

Anal. Calcd. for $C_{12}H_{18}N_2O$: C, 69.67; H, 8.74; N, 13.58. Found: C, 69.44; H, 8.90; N, 13.43.

When cooled to 0° this diamine solidified. It is slightly soluble in water and very soluble in quite dilute mineral acids.

Reduction of the oxime was inhibited when a similar reduction mixture, to which had been added 0.374 g. of ammonia, was subjected to the same treatment. Almost one-half of the starting oxime was recovered.

(2) Using Palladium on Charcoal.—Ten grams (0.046 mole) of (I) was dissolved in 50 ml. of glacial acetic acid and one-half gram of 30% palladium on charcoal added. Isolation of the product as in the previous experiment gave 1.4 g. (15% yield), b. p. 134° (2 mm.) and the product solidified on cooling to 0°. A similar experiment with 5 g. of (I) dissolved in 100 ml. of absolute alcohol to which had been added 3.3 g. of dry hydrogen chloride gas gave 0.5 g. (10% yield) of the diamine (III).

B. With Sodium and Alcohol.—Ten grams (0.046 mole) of (I) was dissolved in 120 ml. of absolute alcohol and 13.5 g. (0.59 mole) of cut sodium added over a period of three hours to the refluxing solution. Water (25 ml.) was added to destroy the sodium ethoxide, the solution neutralized with conc. hydrochloric acid at 0°, and the precipitated sodium chloride filtered off. The filtrate was then acidified and the solvent removed by vacuum distillation. The residue was mixed with 50% sodium hydroxide, with cooling, and the precipitated oil separated, purified and distilled as before, b. p. 150–152° (3 mm.), wt. 2.5 g. (26% yield). This product also solidified on cooling to 0°.

α-Phenyl-β-piperidinoethylamine (IV).—This diamine was prepared by a sodium–alcohol reduction of (II). It was necessary to use carefully dried absolute alcohol as the reduction medium. Because this diamine was somewhat soluble in water and dilute sodium hydroxide, 40% alkali was used in the purification step to remove any unchanged oxime. The product was a light yellow oil obtained in 24% yield, b. p. 128° (3 mm.). Considerable residue remained in the distilling flask and ammonia was detected in the forerun. The diamine became very viscous on cooling to 0° but did not solidify.

Anal. Calcd. for $C_{13}H_{20}N_2$: C, 76.45; H, 9.86; N, 13.70. Found: C, 76.62; H, 10.07; N, 13.54.

α-Phenyl-β-morpholino-N-benzoylethylamine (V) and α-Phenyl-β-piperidino-N-benzoylethylamine (VI).—These benzamides were prepared by treating a dry ether solution of the diamine with an equal molar quantity of benzoyl chloride at 0°. After allowing the mixture to stand at 0° for three hours the white hygroscopic hydrochloride was removed and mixed with dilute sodium bicarbonate and allowed to stand for twelve hours more in the ice-chest. The white gummy precipitate was recrystallized from alcohol and water. A 95% yield of (V), m. p. 143–144°, was obtained.

Anal. Calcd. for $C_{19}H_{22}N_2O_2$: C, 73.52; H, 7.15; N, 9.09. Found: C, 73.79; H, 7.42; N, 9.05.

A 94% yield of (VI), m. p. 135–136°, resulted.

Anal. Calcd. for $C_{20}H_{24}N_2O$: C, 77.87; H, 7.85; N, 9.03. Found: C, 77.99; H, 8.20; N, 9.07.

Both (V) and (VI) were soluble in dilute mineral acids and insoluble in water.

The preparation of (VI) was repeated using an ether solution of the undistilled diamine (IV) (theoretically containing 2.15 g.). A yield of 2.0 g. of (VI), m. p. 135–136°, resulted. Assuming a 94% yield on benzoylation, this indicates a 65% yield of the diamine (IV) from the sodium and alcohol reduction of (II).

Summary

1. The conversion of α-amino ketones to the corresponding diamines via the reduction of the oximes of the amino ketones has been investigated.

2. Some interesting α,β-diamines and their corresponding benzamides have been prepared.

LINCOLN, NEBRASKA RECEIVED JANUARY 24, 1944

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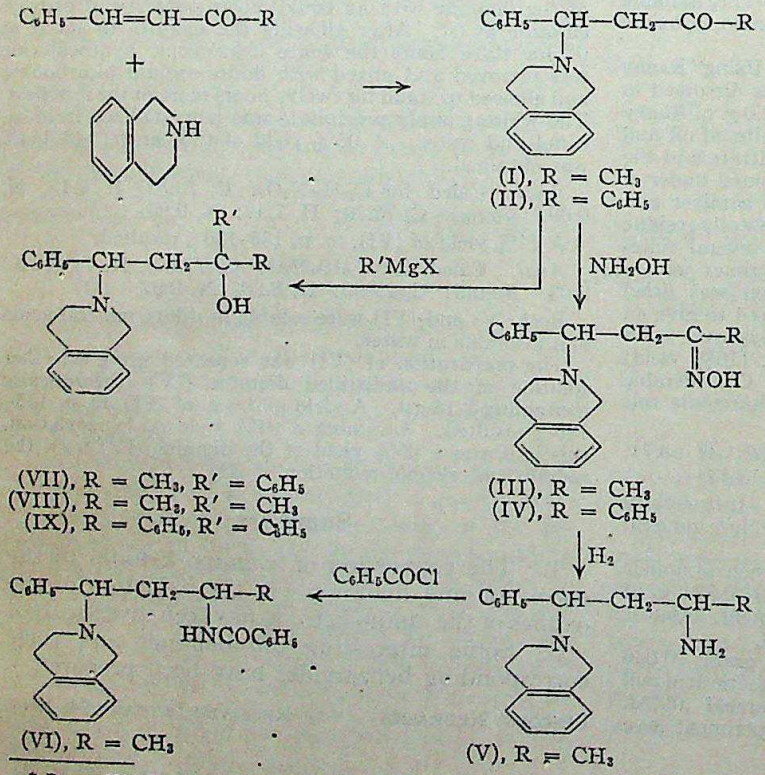
Amino Ketones. III.* β-Tetrahydroisoquinolino Ketones and Derivatives. Reaction with Grignard Reagents[1]

BY NORMAN H. CROMWELL AND JOHN S. BURCH

While extending our investigations of the chemistry of β-amino ketones,[2] it seemed important to introduce the interesting base tetrahydroisoquinoline into these molecules. Buck and Ide[3] reported N-alkyl tetrahydroisoquinolines to show slight depressor action and to be strong sympatholytics. Allewelt and Day[4] reported that 1-phenyl-2-tetrahydroisoquinolino ethanol hydrochloride showed mild local anesthetic activity.

Tetrahydroisoquinoline was found to add readily to benzalacetone and benzalacetophenone to give the β-amino ketones (I) and (II), respectively. The oxime (III) of (I) was reduced with sodium and alcohol to 1-phenyl-1-tetrahydroisoquinolino-3-aminobutane, (V). This reduction was accompanied by some cleavage of the tetrahydroisoquinolino nitrogen to β-carbon bond, thereby reducing the yield of diamine. (V) reacted with benzoyl chloride to give low yields of 1-phenyl-1-tetrahydroisoquinolino-3-benzamidobutane (VI).



Apparently the only previous study of the reaction of a β-amino ketone with a Grignard reagent is the addition of methylmagnesium iodide to diacetone amine, reported by Kohn.[5] Since the β-amino ketones (I) and (II) could be obtained in a pure dry state it was of interest to compare their reactivities with Grignard reagents. Moreover, the resulting amino alcohols should be of interest pharmacologically.

Phenylmagnesium bromide and methylmagnesium iodide both added readily to (I) to give good yields of the corresponding amino alcohols (VII) and (VIII), respectively. Only a very slow and incomplete reaction was experienced in adding phenylmagnesium bromide to (II). This might be expected because of the hindering and electron attracting effect of the phenyl group attached to the carbonyl group, along with the similar effect of the tetrahydroisoquinolino group in the beta position. However, methylmagnesium iodide added readily to this same amino ketone (II) to give a good yield of the amino alcohol (VII).

The pharmacological investigations of these compounds will be reported elsewhere.

Experimental[6]

β-Tetrahydroisoquinolinobenzylacetone (I).—To a solution of 60.8 g. (0.416 mole) of benzalacetone in 100 ml. of 95% ethyl alcohol was added 58.2 g. (0.437 mole) of tetrahydroisoquinoline.[7] This solution was heated to boiling and then allowed to stand at room temperature for two days and in an ice-chest four days. The white crystalline product was filtered and washed with a 70% alcohol solution; yield 69.0 g. (59%); m. p. 71–72°. Recrystallization from low boiling petroleum ether or methyl alcohol and water solutions did not change the melting point of the white product.

Anal. Calcd. for $C_{19}H_{21}NO$: C, 81.68; H, 7.58. Found: C, 81.70; H, 7.83.

Attempts to prepare this amino ketone in a petroleum ether solution gave a mixed product that resisted purification.

β-Tetrahydroisoquinolinobenzylacetone Oxime (III).—To a solution of 11.2 g. (0.162 mole) of hydroxylamine hydrochloride and 16.6 g. (0.202 mole) of sodium acetate in 180 ml. of methyl alcohol and 40 ml. of water was added 29.0 g. (0.104 mole) of (I), dissolved in 300 ml. of methanol. This mix-

* Paper II: Cromwell and Hoeksema, THIS JOURNAL, 66, 870 (1944).

(1) Presented before a session of the Division of Organic Chemistry, 107th Meeting of the American Chemical Society, Cleveland, Ohio, April 4, 1944.

(2) Cromwell, Wiles and Schroeder, *ibid.*, 64, 2432 (1942).

(3) Buck and Ide, *ibid.*, 60, 2101 (1938).

(4) Allewelt and Day, *J. Org. Chem.*, 6, 385 (1941).

(5) Kohn, *Sitzungsber.*, 116[2b], 953 (1907).

(6) Micro-Dumas analyses for nitrogen and semi-micro analyses for carbon and hydrogen by the Analytical Laboratory, Department of Chemistry, University of Nebraska, under the supervision of H. Armin Pagel.

(7) Cromwell and Cram, THIS JOURNAL, 65, 301 (1943).

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ture was heated to boiling and allowed to stand one day at room temperature and two days in the ice-chest. The white, needle-shaped crystals were filtered and washed with 50% methyl alcohol and recrystallized from 95% alcohol, wt. 25.8 g. (84% yield), m. p. 155–157°.

Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.51; H, 7.53. Found: C, 77.52; H, 7.68.

β-Tetrahydroisoquinolinobenzylacetophenone (II).—To 100 ml. of 95% alcohol were added 26.8 g. (0.129 mole) of benzalacetophenone and 17.8 g. (0.134 mole) of tetrahydroisoquinoline. Using the same procedure as with (I), the yield was 36.7 g. (83%), recrystallized from an alcohol-ether mixture, m. p. 90–91°.

Anal. Calcd. for $C_{24}H_{23}NO$: C, 84.42; H, 6.79. Found: C, 84.24; H, 7.04.

The oxime (IV) of (II) was prepared by the procedure used for (III); yield 10%, recrystallized from absolute alcohol, m. p. 173–175°.

Anal. Calcd. for $C_{24}H_{24}N_2O$: C, 80.86; H, 6.79. Found: C, 80.82; H, 6.87.

1-Phenyl-1-tetrahydroisoquinolino-3-aminobutane (V).—The oxime (III) was reduced in boiling ethanol with sodium and the diamine isolated by the method outlined in the first paper of this series.[2] The product was a thick, pale-green oil that flowed only when warm and refused to solidify or crystallize, b. p. 178–180° (1 mm.), yield 32%.

Anal. Calcd. for $C_{19}H_{24}N_2$: C, 81.38; H, 8.63; N, 9.99. Found: C, 80.95; H, 8.73; N, 10.06.

From this reduction mixture was also isolated tetrahydroisoquinoline identified as its benzene sulfonamide, m. p. 154°,[8] benzalacetone oxime, m. p. 113–116°,[9] and benzylacetone oxime, m. p. 85–88°.[10]

The benzamide (VI) of (V) was prepared by the method outlined in the first paper in this series.[2] The yield was comparatively low, however (30%); recrystallized from 95% alcohol, m. p. 159–161°.

Anal. Calcd. for $C_{26}H_{28}N_2O$: C, 81.21; H, 7.34. Found: C, 80.89; H, 7.32.

4-Tetrahydroisoquinolino-2,4-diphenylbutanol-2 (VII).—To an ethereal solution of phenylmagnesium bromide, prepared from 3.5 g. (0.144 mole) of magnesium, was added as rapidly as possible, a solution of 10 g. (0.036 mole) of (I) in 75 ml. of dry ether. The solution was stirred during addition and refluxed for four hours thereafter, a white precipitate forming during this time. The reaction mixture was decomposed by pouring it onto ice and 10 g. of ammonium chloride. The product was separated from the water layer with ether–benzene extractions. This ether–benzene layer was washed with four 50-ml. portions of 0.03 *N* hydrochloric acid to remove any free tetrahydroisoquinoline.

Evaporation of the solvent and recrystallization of the residual oil from low boiling petroleum ether gave 5.5 g. (43% yield) of white crystals, m. p. 115–116°.

Anal. Calcd. for $C_{25}H_{27}NO$: C, 83.99; H, 7.61. Found: C, 83.94; H, 7.64.

This same amino alcohol (VII) was obtained in 45% yields by adding methylmagnesium iodide to the β-amino ketone (II).

4-Tetrahydroisoquinolino-2-methyl-4-phenylbutanol-2 (VIII).—This carbinol was prepared from (I) by the method outlined for (VII), using methylmagnesium iodide. The mixture was refluxed for three hours even though an addition product had precipitated in ten minutes. The ether–benzene extractions containing the product were freed of tetrahydroisoquinoline by adding a small amount of acetic anhydride. After standing at room temperature for twelve hours this acetic anhydride reaction mixture was extracted with ten 60-ml. portions of 0.2 *N* hydrochloric acid. The combined acid extracts were made basic with sodium hydroxide and the liberated amino alcohol extracted with benzene. Evaporation of the benzene left a brown oil which was crystallized from low-boiling petroleum ether, yield 46%, m. p. 95–96°. This product was considerably more soluble in dilute hydrochloric acid than was (VII).

Anal. Calcd. for $C_{20}H_{25}NO$: C, 81.31; H, 8.53. Found: C, 81.25; H, 8.60.

3-Tetrahydroisoquinolino-1,1,3-triphenylpropanol-1 (IX).—The amino ketone (II) was refluxed for seven hours with phenylmagnesium bromide. Only a small amount of white addition product was precipitated. The product was isolated in the manner outlined for (VII). Only a small amount of the amino alcohol was obtained (5% yield), recrystallized from absolute alcohol, m. p. 78–80°. A mixed melting point experiment with (II) gave m. p. 73–78°.

Anal. Calcd. for $C_{30}H_{29}NO$: C, 85.88; H, 6.97. Found: C, 85.82; H, 7.20.

Summary

1. β-Tetrahydroisoquinolinobenzylacetone and the corresponding benzylacetophenone have been prepared and their reactions with Grignard reagents compared.

2. 1-Phenyl-1-tetrahydroisoquinolino-3-aminobutane and the benzamide have been prepared starting with the β-amino ketone.

Lincoln, Nebraska Received January 24, 1944

(8) Von Braun, *Ber.*, **57B**, 910 (1924).
(9) Zelinsky, *ibid.*, **20**, 923 (1887).
(10) Vavon, *Compt. rend.*, **154**, 1706 (1912).

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Sulfides and Sulfones Derived from *p*-Mercaptophenylarsonic Acid[1]

BY JACK F. MORGAN AND CLIFF S. HAMILTON

Although numerous ethers derived from *p*-hydroxyphenylarsonic acid have been described in the literature, very little is known of the corresponding thioethers or sulfides derived from *p*-mercaptophenylarsonic acid. Only four such compounds, *p*-methyl-,[2a,b] *p*-ethyl-,[3] *p*-benzylmercaptophenylarsonic acid[4] and *p*-arsonophenylmercaptoacetic acid,[2] are described in the literature. In each case they were prepared by means of the Bart[5] or Scheller[6] reactions. *p*-Arsonophenylmercaptoacetic acid has also been produced from diazotized arsanilic acid by treatment with potassium xanthate followed by basic hydrolysis and reaction with monochloroacetic acid.[7]

In the present work one sulfide, *p*-β-hydroxyethylmercaptophenylarsonic acid, was prepared by means of the Bart reaction. Several other sulfides containing substituted aliphatic, heterocyclic and aromatic groups attached to the sulfur atom of *p*-mercaptophenylarsonic acid were synthesized by a more convenient method. *p*-Thiocyanophenylarsonic acid was obtained in 30–45% yields by the method of Barber.[8] Basic hydrolysis of the thiocyano derivative gave an intermediate acid. This intermediate was readily condensed with active aliphatic, heterocyclic and aromatic halides in basic solution to form the desired sulfides. The intermediate is apparently either composed principally of *p*-mercaptophenylarsonic acid or readily yields this arsonic acid when dissolved in alkaline solution.

In general, sulfones are obtained readily from organic sulfides by oxidation with hydrogen peroxide. In this manner both *p*-methyl-[2a] and *p*-ethylsulfonylphenylarsonic acid[3] have been prepared. In addition *p*-methylsulfonylphenylarsonic acid has been synthesized by means of the Bart reaction on *p*-aminophenylmethylsulfone.[9] No other mention is made in the literature of sulfones derived from *p*-sulfophenylarsonic acid.

Ten sulfides derived from *p*-mercaptophenylarsonic acid were, with one exception, readily converted to the corresponding sulfones by treatment with hydrogen peroxide. 2′-Amino-4′-pyrimidyl-4-arsonophenylsulfide decomposed when warmed in perhydrol.

(1) Original manuscript received October 16, 1943.

(2) (a) Doak, Steinman and Eagle, THIS JOURNAL, **62**, 3012 (1940); (b) Streitwolf, Fehrle, Herrmann and Hilmer, German Patent, 536,996 (1930) [*Chem. Zentr.*, **103**, [I] 254 (1932)].

(3) Cherline and Iacoubovitch, *Bull. soc. chim.*, [5] **1**, 1367 (1934).

(4) Takahashi, *J. Pharm. Soc.* Japan, **55**, 875 (1935); *Chem. Abs.*, **30**, 721 (1936).

(5) Bart, *Ann.*, **429**, 55 (1922).

(6) Scheller, British Patent, 261,026 (1925); German Patent, 522,892 (1926).

(7) Lucius and Bruning, German Patent, 216,270 (1908); British Patent, 4246 (1908) [*Chem. Zentr.*, **80** [IV] 2105 (1909)].

(8) Barber, *J. Chem. Soc.*, 2727 (1930).

(9) Barber, *ibid.*, 2047 (1930).

Experimental

***p*-Aminophenyl-β-hydroxyethylsulfide (I).**—*p*-Nitrophenyl-β-hydroxyethylsulfide was prepared by the method of Waldron and Reid.[10] By means of hydrogen and Raney nickel, 100 g. of the nitro compound was reduced in acetone solution. Removal of the acetone yielded (I) (84 g., 99%), m. p. 43–44°, b. p. 232–235° (38 mm.) (dec.). The product consisted of a light tan wax-like crystalline mass, soluble in the usual organic solvents and hot water, but almost insoluble in cold water. For analysis a sample of the amine was converted to its hydrochloride.

***p*-Aminophenyl-β-hydroxyethylsulfide Hydrochloride (II).**—An ether solution of (I) was treated with dry hydrogen chloride. The precipitated hydrochloride (II) was removed by filtration, washed with ether and recrystallized from ethanol–petroleum ether, m. p. 170°.

Anal. Calcd. for $C_8H_{12}ClNOS$: N, 6.81; Cl, 17.24. Found: N, 6.61; Cl, 16.92.

***p*-β-Hydroxyethylmercaptophenylarsonic Acid (III).**—This arsonic acid was readily prepared in yields of 46–48% from the corresponding amine by the method of Bart.[5] The compound was purified by two recrystallizations from water. The white dimorphous solid may be obtained either as leaflets melting at 120.5–121° or as needles melting at 132–133°. Either crystalline form could be obtained from aqueous solution by seeding with the appropriate crystals.

Anal. Calcd. for $C_8H_{11}AsO_4S$: As, 26.93. Found: needles, As, 26.93; leaflets, As, 26.90.

***p*-Thiocyanophenylarsonic acid** was prepared by the method of Barber[8] in 30–45% yields.

Intermediate Acid (IV).—A solution of *p*-thiocyanophenylarsonic acid (50 g.) in 500 ml. of 10% sodium hydroxide was refluxed for six hours, cooled and slowly treated with 4 *N* hydrochloric acid. The small amount of red gum, which first separated, was removed and the acidification continued (congo red) to obtain a nearly white precipitate of (IV); yield, 35 g. (78% calcd. as *p*-mercaptophenylarsonic acid). This product does not melt below 250°, is insoluble in boiling water but readily dissolves in dilute sodium hydroxide.

Sulfides Derived from (IV).—The intermediate acid (IV) (11.7 g., 0.05 mole calcd. as *p*-mercaptophenylarsonic acid) and dissolved in an aqueous or dilute alcohol solution of sodium hydroxide (6 g., 0.15 mole) and treated with the appropriate halide (0.1 mole). The mixture was refluxed for a period of four to sixty hours depending on the reactivity of the halide. The crude product which separated on acidification (congo red) was purified by two recrystallizations from water, the hot solution being treated with activated charcoal.

Dilute ethanol (25–30%) was used as solvent when halides of low solubility were employed, *i. e.*, ethyl chloroacetate, *p*-nitrochlorobenzene or 2-amino-4-chloropyrimidine. Because *p*-[β-(β′-hydroxyethoxy)-ethylmercapto]-phenylarsonic acid existed as an oil it was isolated as its sodium salt from ethanol solution.

Sulfones.—The appropriate sulfide (2 g.) was treated with 10 ml. of 27.5% hydrogen peroxide solution and warmed a short time. The resulting solution was allowed to stand overnight and cooled in the refrigerator for several hours. The white crystalline sulfone was removed by filtration, washed with a small amount of water and dried. In a few cases no solid separated and the compounds were isolated by slow evaporation of the peroxide solutions at room temperature. Some of the sulfones were further purified by recrystallization from water.

(10) Waldron and Reid, THIS JOURNAL, **45**, 2399 (1923).

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TABLE I

SULFIDES

	Name	Yield, %	M. p., °C.	Formula	As analyses, %[11] Calcd.	Found
1	*p*-β-Hydroxyethylmercaptophenylarsonic acid[a] (III)	46–48	120.5–121 132 –133	$C_8H_{11}AsO_4S$	26.93	26.90 26.93
2	*p*-γ-Hydroxypropylmercaptophenylarsonic acid	31	116.3–117.5	$C_9H_{13}AsO_4S$	25.64	25.74
3	*p*-β-Ethoxyethylmercaptophenylarsonic acid	52	121 –122	$C_{10}H_{15}AsO_4S$	24.47	24.65
4	Sodium *p*[-β-(β′-hydroxyethoxy)-ethylmercapto]-phenylarsonate	54	>250	$C_{10}H_{14}AsNaO_5S$	21.77	21.67
5	*p*-Acetonylmercaptophenylarsonic acid	18	172.5	$C_9H_{11}AsO_4S$	25.82	26.05
6	*p*-Arsonophenylmercaptoacetic acid[b]	55	192	$C_8H_9AsO_5S$	25.64	25.65
7	Ethyl *p*-arsonophenylmercaptoacetate[c]	19	123	$C_{10}H_{13}AsO_5S$	23.40	23.56
8	2′-Amino-4′-pyrimidyl-4-arsonophenylsulfide	39	131.5–132	$C_{10}H_{10}AsN_3O_3S$	22.90	22.87
9	4′-Nitro-4-arsonodiphenylsulfide	52	183	$C_{12}H_{10}AsNO_5S$	21.09	21.17
10	4′-Amino-4-arsonodiphenylsulfide[d]	31	211.5 (dec.)	$C_{12}H_{21}AsNO_3S$	23.04	23.07

[a] Prepared by the Bart reaction (specific preparation is given). [b] Previously reported as melting at 187° (ref. 7) and 248–250° (ref. 2b). [c] Also isolate a 27% yield of *p*-arsonophenylmercaptoacetic acid (6) melting at 192°. [d] Prepared by the reduction of (9) with hydrogen and Raney nickel in aqueous sodium bicarbonate.

TABLE II

SULFONES

	Name	Yield, %	M. p., °C.	Formula	As analyses, % Calcd.	Found
1	*p*-β-Hydroxyethylsulfonylphenylarsonic acid	59	177	$C_8H_{11}AsO_6S$	24.15	24.30
2	*p*-γ-Hydroxypropylsulfonylphenylarsonic acid	78	160.5	$C_9H_{13}AsO_6S$	23.11	23.33
3	*p*-β-Ethoxyethylsulfonylphenylarsonic acid	89	182.5–184.5	$C_{10}H_{15}AsO_6S$	22.15	22.36
4	Sodium *p*-[β-(β′-hydroxyethoxy)-ethylsulfonyl]-[a] phenyl arsonate	83	180.5	$C_{10}H_{14}AsNaO_7S$	19.91	20.00
5	*p*-Acetonylsulfonylphenylarsonic acid	30	202.5–203.5	$C_9H_{11}AsO_6S$	23.25	23.70
6	*p*-Arsonophenylsulfonylacetic acid[a]	91	188 –189	$C_8H_9AsO_7S$	23.11	22.91
7	Ethyl *p*-arsonophenylsulfonylacetate	59	165 –166	$C_{10}H_{13}AsO_7S$	21.27	21.47
8	4′-Nitro-4-arsonodiphenylsulfone	40	>250	$C_{12}H_{10}AsNO_7S$	19.35	19.25
9	4′-Amino-4-arsonodiphenylsulfone[b]	52	229–230 (dec.)	$C_{12}H_{12}AsNO_5S$	20.97	21.00

[a] Isolated by evaporation because of high solubility. [b] Prepared by reduction of (8) with hydrogen and Raney nickel in aqueous sodium bicarbonate.

Melting Point Determination.—Organic arsonic acids normally are converted to their anhydrides by heat; the temperature and time required to complete the dehydration depends on the acid involved and may be a function of the relative acidity of that acid. The dehydration is illustrated by the equation

$$RAsO_3H_2 \xrightarrow{\Delta} RAsO_2 + H_2O$$

If an arsonic acid is heated slowly to its normal melting point, any of three observations may be made depending on the ease of dehydration of the compound. These observations will be: for no dehydration, the normal melting point; partial dehydration, lowered melting point or partial melting; complete dehydration, no melting until melting point of anhydride is reached. In general the anhydrides melt at considerably higher temperatures than the corresponding arsonic acids and frequently decompose at temperatures above 250° without melting.

Melting points of the compounds described in this paper were accurately determined by inserting a sample in a preheated bath at a temperature which was 0–5° below the melting point and slowly raising the temperature of the bath. The shortened time allowed for dehydration allows the observation of melting points which otherwise might be overlooked.

A Bureau of Standards certified thermometer was used in all melting point determinations and stem corrections were calculated to obtain corrected readings.

(11) Cislak and Hamilton, THIS JOURNAL, **52**, 638 (1930).

Summary

1. Two general methods were used to synthesize a number of new sulfides derived from *p*-mercaptophenylarsonic acid.

2. *p*-β-Hydroxyethylmercaptophenylarsonic acid was prepared from the corresponding amine by means of the Bart reaction.

3. *p*-Thiocyanophenylarsonic acid was hydrolyzed in alkaline solution to yield an intermediate acid. This intermediate was readily condensed with substituted aliphatic, heterocyclic and aromatic halides to yield sulfides derived from *p*-mercaptophenylarsonic acid.

4. Sulfides derived from *p*-mercaptophenylarsonic acid were oxidized with hydrogen peroxide to obtain eight new sulfones.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF WINTHROP CHEMICAL COMPANY, INC.]

Hydrogenation of Basic Nitriles with Raney Nickel

BY WOLFGANG HUBER

According to von Braun[1] the hydrogenation of a nitrile is expressed by the following series of reactions

$$RCN + H_2 \longrightarrow RCH{=}NH \quad (1)$$

$$RCH{=}NH + H_2 \longrightarrow RCH_2NH_2 \quad (2)$$

$$RCH{=}NH + RCH_2NH_2 \longrightarrow RCH(NH_2)NHCH_2R \quad (3)$$

$$RCH(NH_2)NHCH_2R + H_2 \longrightarrow RCH_2NHCH_2R + NH_3 \quad (4)$$

Numerous procedures have been described in the literature to minimize the formation of secondary amines according to equations 3 and 4. Thus, Carothers[2] hydrogenated benzonitrile to benzylamine with platinum oxide in good yields using acetic anhydride as solvent, and attributed the high yield to the fact that the primary amine is quickly acetylated and therefore protected against interaction with the intermediate imine. Hartung[3] used alcohol containing one mole of hydrochloric acid and palladized charcoal in the hydrogenation of aromatic nitriles, and Kindler[4] used glacial acetic acid containing one mole of concentrated sulfuric acid and palladium sponge to hydrogenate nitriles to the corresponding β-arylethylamines. The high yield of primary amines in these reactions is attributed to the removal of the base from the reaction equilibrium by salt formation, thus preventing the possible interaction with the intermediary imine according to equation 3.

In connection with other work it was of interest to develop a method for the reduction of basic heterocyclic nitriles to the corresponding primary amines exclusively. It was found that such nitriles, and for that matter basic nitriles in general, cannot be hydrogenated in good yields to the corresponding primary amines by any of the aforesaid methods. It is obvious that basic nitriles in the presence of acids or acetic anhydride will undergo salt formation or acetylation, the latter products being considerably less soluble than the parent nitriles in the non-aqueous solvents generally used in hydrogenations. The resulting heterogeneous reaction mixture slows the hydrogenation speed and the subsequent coating of undissolved nitrile salt with primary amine salt, precipitating from the solution, tends to slow further and eventually inhibit the reduction. The poisoning effect of anhydrous mineral acids on catalysts such as platinum oxide, palladized charcoal and palladium on zirconium oxide is an additional factor which tends to slow the smooth and speedy reduction of basic nitriles.

(1) von Braun, Blessing and Zobel, *Ber.*, **56**, 1988 (1923).
(2) Carothers and Jones, THIS JOURNAL, **47**, 3051 (1925).
(3) Hartung, *ibid.*, **50**, 3370 (1928).
(4) Kindler, Peschke and Brandt, *Ber.*, **68**, 2241 (1935).

In the hydrogenation of 2-methyl-4-aminopyrimidine-5-nitrile with either one of the aforesaid catalysts the formation of secondary amine is thus always considerable or even predominant, the reduction time is markedly increased and often, due to catalyst poisoning, the hydrogenation is incomplete. Data illustrating this behavior are listed in Table I.

The hydrogenation of basic nitriles to the corresponding primary amines, however, can be carried out smoothly and with excellent yields with Raney nickel in organic solvents and in the presence of ammonia. Schwoegler and Adkins[5] were the first to use Raney nickel and ammonia in the hydrogenation of aliphatic nitriles, thus obtaining *n*-pentyl- and *n*-heptylamine in excellent yields. The results of this study seem to confirm their assumption that it is the ammonia rather than the primary amine which will react with the imine formed according to equation 1 of the von Braun scheme, thus giving rise to the formation of additional primary amine according to the equations

$$RCH{=}NH + NH_3 \longrightarrow RCH(NH_2)_2 \quad (5)$$

$$RCH(NH_2)_2 + H_2 \longrightarrow RCH_2NH_2 + NH_3$$

The yields, in all reactions studied, were found to be nearly quantitative. Secondary amines, if found at all, were rarely present in excess of 5%. The presence of ammonia, however, is essential since reduction with Raney nickel alone always leads to the formation of large amounts of secondary amines. Indeed, a rather high concentration of ammonia is desirable; generally 3-4 moles of ammonia were used per mole of nitrile. Using less than 2.5 moles of ammonia per mole of nitrile seems to cause a competitive reaction between ammonia-imine and primary amine-imine in equation 5, thus increasing the formation of secondary amine. With all compounds investigated, the reduction proceeded smoothly at room temperature with hydrogen pressures ranging from 60 to 200 lb./sq. in. Vigorous shaking of the autoclave seems to be essential for a smooth reduction at these pressures, since it was found that in slowly shaking autoclaves considerably higher hydrogen pressures were necessary to insure a smooth hydrogenation. A variety of organic solvents has been used including methanol, ethanol, 2-propanol, butanol, dioxane, *n*-butyl ether and formamide. For all practical purposes methanol was found to be an excellent solvent, whereas in water or in aqueous solvents the amounts of secondary amines present were always considerable. The hydrogenation proceeds very quickly, the average time for 0.5 mole

(5) Schwoegler and Adkins, THIS JOURNAL, **61**, 3499 (1939).

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TABLE I

HYDROGENATION OF 2-METHYL-4-AMINOPYRIMIDINE-5-NITRILE[6] WITH VARIOUS SOLVENTS AND CATALYSTS

Size of batch, mole	Catalyst	Solvent	Pressure, lb.	Temp., °C.	Reduction time, hours	Primary[a] amine, % yield	Secondary[b] amine, % yield	Uptake of[c] hydrogen, % of theory
0.1	Palladium on zirconium oxide[d]	Ac_2O	60	28	18	47	49	96
.1	Palladium on zicronium oxide[d]	EtOH–HCl	60	28	9.5	74	24.5	100
1.0	Palladium on zirconium oxide[d]	EtOH–HCl	60	55	37	32	60	88
0.1	Palladium on zirconium oxide[d]	EtOH–H_2SO_4	55	29	11.5	38	30	74
.1	Palladium on zirconium oxide[d]	AcOH–HCl	80	55	8.5	70	29	102
.1	Palladium on zirconium oxide[d]	AcOH–H_2SO_4	80	26	13	62	36.5	99
.1	Palladized charcoal	Ac_2O	60	25	14.5	42	41	86
.1	Palladized charcoal	EtOH–HCl	80	25	11	58	36	96
.4	Palladized charcoal	EtOH–HCl	80	55	26	34	50	85
.05	Palladized charcoal	EtOH–H_2SO_4	80	31	6.5	64	34	104
.1	Palladized charcoal	AcOH–HCl	80	29	10	61	30	94
.1	Pt_2O Adams catalyst	Ac_2O	80	55	9.5	69	30	100
.1	Pt_2O Adams catalyst	EtOH–HCl	60	29	9.5	52	46	107
.1	Pt_2O Adams catalyst	EtOH–H_2SO_4	60	29	14	44	43	87

[a] The % of primary amine present was determined by condensation of the free base wtih potassium dithioformate (see Huber, THIS JOURNAL, 65, 2225 (1943)) and subsequent weighing of the precipitated 2-methyl-4-amino-5-thioformylaminomethylpyrimidine. [b] The % of secondary amine present was determined from the weight of the 2-methyl-4-amino-5-hydroxymethylpyrimidine obtained by the treatment of the secondary amine salt with dilute alkali. For details see experimental part. [c] In the case of very slow hydrogen uptake fresh catalyst was always added; generally, however this had no lasting beneficiary effect. [d] Addition of small amounts of a 5% aqueous $PdCl_2$ solution did not improve the rate or the speed of the hydrogenation.

TABLE II

HYDROGENATION OF BASIC NITRILES

Nitrile	Product	B. p., °C. (mm.)	M. p., °C.	Yield, %	Reduction time, min.	Batch size, mole	Average pressure, lb.	Amount of catalyst, g.
2-Methyl-4-aminopyrimidine-5-nitrile[7]	2-Methyl-4-amino-5-aminomethylpyrimidine.[7] As Dihydrochloride.		262, dec.	93.3	80	2.0	125	50
	Di-(2-methyl-4-amino-5-pyrimethyl) amine.[a]			4.2	80	2.0	125	50
2,4-Diaminopyrimidine-5-nitrile[8]	2,4-Diamino-5-aminomethyl-pyrimidine.[8] As dihydrochloride		258, dec.	94.0	50	.5	200	25
	Di-(2,4-diamino-5-pyrimethyl)amine[a]			4.1	50	.5	200	25
N-Benzyl-4-phenylpiperidine-4-nitrile[9]	N-Benzyl-4-phenyl-4-aminomethylpiperidine	224–26 (1)	71–72	91	90	.5	125	29
Pyridine-3-nitrile	3-pyridylmethylamine	98–99 (12)		89	55	.5	100	25
	Di-(3-pyridylmethyl)-amine			8	55	.5	100	25
4-Methyl-5-cyanomethylthiazole[10]	4-Methyl-5-β-aminoethylthiazole[10]	79–80 (1)		92	80	.5	125	29
4-Diethylaminobutyronitrile[11]	4-Diethylamino-butylamine[12]			97	65	2.0	100	55
	Di-(4-diethylaminobutyl)-amine			2	65	2.0	100	55
Furan-2-nitrile[b]	2-Furyl-methylamine	49–50 (10)		84	76	1.0	125	45
	Di-(2-furylmethyl)-amine	126–28 (10)		11	76	1.0	125	45

[a] Determined as 2-methyl-4-amino-5-oxymethylpyrimidine. [b] Although not a basic nitrile, this method gave excellent yields of the primary amine which were considerably in excess of those reported in the literature.[5,13]

batches being from thirty to eighty minutes. Compounds hydrogenated include pyrimidine, piperidine, pyridine, thiazole, furan and aliphatic basic nitriles. In each reduction the corresponding primary amine was obtained in excellent yields. A summary of the results is found in Table II. The description of the apparatus and a detailed procedure are given in the experimental part.

It is believed that in the preparation of primary amines from basic nitriles in general and from heterocyclic basic nitriles in particular the hydrogenation with Raney nickel in the presence of ammonia will often suggest itself as the method of choice.

(6) Grewe, *Z. physiol. Chem.*, **242**, 89 (1936).
(7) Grewe, *ibid.*, **242**, 89 (1936).
(8) Huber, THIS JOURNAL, **65**, 2222 (1943).
(9) Eisleb, *Ber.*, **74**, 1433 (1941).
(10) Price and Pickel, THIS JOURNAL, **63**, 1069 (1941).
(11) Strukov, *Khim. Farm. Prom.*, 332 (1933).
(12) von Braun and Lemke, *Ber.*, **55**, 3634 (1922).
(13) Paul, *Bull. soc. chim.*, [5] **4**, 1121 (1937).

Experimental

Apparatus.—The reduction vessel was an ordinary steel cylinder, 9 × 6 inches with rounded bottom and flanged top with lead gasket. A pressure gage and an inlet valve were welded onto the side wall of the vessel, the valve being connected with a copper spiral to a hydrogen tank. The necessary agitation was provided by a Schaerr type shaker into which the reduction vessel was placed. The total capacity of the vessel was 4 liters. After calibration the hydrogen consumption was measured by the pressure drop as indicated by the pressure gage. The copper spiral between reduction vessel and hydrogen tank was made flexible enough to stay on during the shaking to facilitate quick recharging in cases where the size of the batch required hydrogen in excess of the volume available.

Method.—Average pressures as given in Table II were calculated as the mean between highest and lowest pressure

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as indicated by the side wall gage. For example, if the pressure at the beginning of the hydrogenation was 200 lb./sq. in. and dropped during the course of the reduction to 150 lb./sq. in., to be recharged then to 200 lb./sq. in. again, the average pressure was taken as 175 lb./sq. in.

The Raney nickel was prepared according to the method of Covert and Adkins.[14] The catalyst was washed with water till free of alkali, the water replaced by methanol and the catalyst kept under methanol till ready for use. In none of the experiments had the Raney nickel been stored for more than three weeks. Although the same catalyst can be used several times, it is better to use fresh Raney nickel each time in order to insure a good reduction speed.

The hydrogen was the ordinary commercial product which gave satisfactory results without purification.

The nitriles, prepared according to the literature, were purified until their physical characteristics were constant.

In a typical experiment anhydrous ammonia (4 moles) was incorporated with cooling into anhydrous methanol (35 moles) and the solution filled into the reduction vessel. Nitrile (1 mole) and Raney nickel (1.5 moles)[15] were then added with final attachment of gasket and flange to give a pressure tight seal. The size of the reaction vessel and the volume of the charge were adjusted so that a pressure drop of 50 lb. was equivalent to an uptake of 0.33 mole of hydrogen. The vessel was charged with hydrogen to the maximum pressure necessary and shaking started thereafter. After the uptake of hydrogen equivalent to a 50 lb. pressure drop, fresh hydrogen was charged up to the initial pressure level. This operation was repeated until the calculated amount of hydrogen had been consumed. In all the experiments in this study the hydrogenation stopped after two moles of hydrogen had been consumed, indicating that reduction under these conditions is limited to the nitrile group. The spent catalyst was removed by filtration, washed with methanol and the filtrate decolorized with charcoal, if necessary. After removal of the solvent the residue was freed from unchanged nitrile, if any, and the primary amine purified by distillation, recrystallization, or via its salts. Secondary amine, when present, was isolated by fractional distillation or crystallization.

N-Benzyl-4-phenyl-4-(aminomethyl)-piperidine.—One hundred thirty-one grams of N-benzyl-4-phenylpiperidine-4-nitrile[16] in 560 cc. of methanol containing 34 g. of anhydrous ammonia and 29 g. of Raney nickel took up the calculated amount of hydrogen in ninety minutes at an average pressure of 125 lb./sq. in. From the oily residue, obtained after removal of the solvent, N-benzyl-4-phenyl-4-(aminomethyl)-piperidine was secured by vacuum distillation; b. p. 224–26° (1 mm.); yield, 121 g. or 91%; m. p. 71–72°.

Anal. Calcd. for $C_{19}H_{24}N_2$: N, 10.00. Found: N, 9.84.

On titration the base consumed two moles of hydrochloric acid. The dihydrochloride was recrystallized from acetone–ethanol; m. p. 202–204° (dec.).

Anal. Calcd. for $C_{19}H_{24}N_2Cl_2$: Cl, 20.11. Found: Cl, 19.68.

The dipicrate melts at 229–30°.

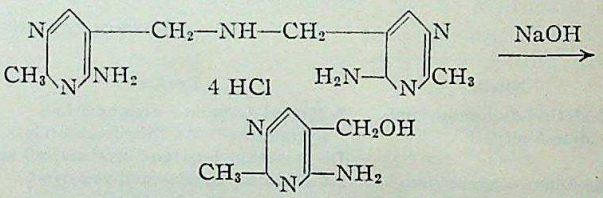
Di-(2-methyl-4-amino-5-pyrimethyl)-amine.—Seven grams of 2-methyl-4-aminopyrimidine-5-nitrile was dissolved in 150 cc. of water containing two mols of hydrochloric acid and 100 mg. of moderately active palladized charcoal. The reduction was performed in a Parr–Burgess hydrogenator and the theoretical amount of hydrogen had been taken up after sixteen hours of shaking at room temperature under a pressure of 60 lb./sq. in. After removal of the catalyst, the filtrate was concentrated to a small volume and the reduction product precipitated with excess ethanol containing some hydrochloric acid. The di-(2-methyl-4-amino-5-pyrimethyl)-amine tetrahydrochloride thus obtained was purified by recrystallization from 85% ethanol. Small amounts of 2-methyl-4-amino-5-aminomethylpyrimidine dihydrochloride which were present stayed in solution due to the greater solubility of this compound in 85% ethanol. The tetrahydrochloride melted at 357° (dec.).

Anal. Calcd. for $C_{12}H_{21}N_7Cl_4$: N, 24.19; Cl, 35.06. Found: N, 24.25; Cl, 35.20.

The picrate as obtained from the hydrochloride crystallizes from water; m. p. 269–70° dec.

The free secondary amine is unstable. Even on addition of the calculated amount of dilute alkali to a chilled solution of the tetrahydrochloride the carbon–nitrogen bond is broken with evolution of ammonia and formation of 2-methyl-4-amino-5-hydroxymethylpyrimidine. The latter proved to be identical in all respects with an authentic sample prepared according to the literature.[17] Table III shows the respective data of the two specimens and their derivatives. This instability of the carbon–nitrogen linkage to hydrolysis is not uncommon[18] and accounts also for the fact that the small amounts of di-(2-methyl-4-amino-5-pyrimethyl)-amine formed during the reduction of 2-methyl-4-aminopyrimidine-5-nitrile with Raney nickel in the presence of ammonia are often not found as such but in the form of 2-methyl-4-amino-5-(hydroxymethyl)-pyrimidine.

TABLE III



	M. p., °C.	M. p. (lit.), °C.	Mixed m. p., °C.
Alcohol	192–193	194	191–193
Hydrochloride	220–222	224	223–224
Picrate	194–195	194–196	194–196

Anal. Calcd. for $C_6H_{10}ON_3Cl$: N, 23.93; Cl, 20.22. Found: N, 23.76; Cl, 20.37.

Di-(4-diethylaminobutyl)-amine.—This secondary amine was obtained by vacuum fractionation of the still foots from the preparation of 4-diethylaminobutylamine. If the primary amine is prepared by the reduction of the corresponding nitrile with Raney nickel in the presence of ammonia the amount of secondary amine does not usually exceed 2–3%; b. p. 125–26° (2 mm.).

Anal. Calcd. for $C_{16}H_{37}N_3$: N, 15.49. Found: N, 15.36.

The hydrochloride as obtained with ethanolic hydrogen chloride and precipitated with ether is very hygroscopic and cannot be conveniently purified.

A crystalline, non-hygroscopic picrate was obtained from an alcoholic solution of the base with alcoholic picric acid in the presence of two moles of hydrochloric acid, m. p. 90–93°.

Anal. Calcd. for $C_{24}H_{43}O_{14}N_9$: C, 42.27; H, 6.36. Found: C, 42.51; H, 6.19.

Summary

Basic nitriles cannot be hydrogenated to the

(14) Covert and Adkins, THIS JOURNAL, **54**, 4116 (1932).

(15) In large batches considerably less Raney nickel is necessary.

(16) Eisleb, *Ber.*, **74**, 1433 (1941); *C. A.*, **36**, 5465 (1942). The nitrile and the N-benzyl-4-phenyl-4-(aminomethyl)-piperidine dihydrochloride were kindly prepared by Dr. C. E. Kwartler of this Laboratory.

(17) Andersag and Westphal, *Ber.*, **70**, 2035 (1937).

(18) Kharasch and Howard, THIS JOURNAL, **56**, 1370 (1934); Huber, *ibid.*, **65**, 2222 (1943). For a summary, see Houben-Weyl, "Die Methoden der organischen Chemie," second ed., 1924, Vol. 4, pp. 446–469.

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corresponding primary amines in good yields by methods involving the use of acidic solvents and palladium or platinum type catalysts.

The hydrogenation with Raney nickel in the presence of ammonia, however, results in the formation of primary amines in nearly quantitative yields. Compounds hydrogenated include pyrimidine, piperidine, pyridine, thiazole and aliphatic basic nitriles.

RENSSELAER, N. Y. RECEIVED FEBRUARY 28, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF RICHMOND]

Tris-(hydroxymethyl)-aminomethane Derivatives. I. Polyhydroxyamines[1,2]

BY J. STANTON PIERCE AND JOHN WOTIZ[3]

Polyfunctional compounds are of particular interest as they afford opportunities for the synthesis of substances with varied properties, many of which are of practical importance. The ethanolamines have been found to be particularly useful, due to their solubility properties, ease of preparation and low cost. A large and interesting field for the synthesis of more highly polar amino alcohols than the ethanolamines was opened by the recent commercial synthesis of tris-(hydroxymethyl)-aminomethane, $(HOCH_2)_3CNH_2$,[4] (A). In 1897, Piloty and Ruff[5] prepared (A) by the reduction of tris-(hydroxymethyl)-nitromethane which had been prepared two years previously by Henry,[6] by the reaction of nitromethane and formaldehyde.

Various investigators have combined two primary or secondary amino groups by reaction with epichlorohydrin,[7] α,ω-dihalohydrins[8] or α,ω-dihalogenalkanes.[9] This paper takes up the synthesis of polyhydroxyamines by the union of two molecules of (A), mainly through methylene or methylene and hydroxymethylene groups, by the union of (A) with other amino alcohols through methylene and hydroxymethylene groups, and by the alkylation of (A) with chlorohydrins. A subsequent paper will take up the preparation of alkyl and alkaryl derivatives of (A).

The symmetrical polyhydroxydisecondary amines described in this paper usually were prepared by heating (A) with an α,ω-dihalide, in most cases the bromide. The reactions were carried out under reflux, with no solvent or with alcohol as solvent, and in sealed tubes, with alcohol as solvent. The asymmetrical diamines, all of which are derivatives of 2-propanol, were prepared by treating a secondary amine with epichlorohydrin at a temperature not exceeding 30° and by the reaction of the product thus formed with (A) at elevated temperature, with alcohol as solvent. Also, two molecules of (A) reacted with epichlorohydrin, to form a symmetrical derivative. Monoalkylation products of (A) were prepared by reaction with halohydrins.

The greatest difficulty in the preparation of the polyhydroxyamines described in this paper was their isolation and purification. Since the free bases, as obtained, showed no tendency to crystallize, they were converted to hydrobromides or hydrochlorides for identification and analysis. A typical mixture in the preparation of a symmetrical disecondary amine likely contained dihalide, (A), the monoalkylation product of (A) and the desired disecondary amine, the latter three compounds being present both as the free bases and as the halogen acid salts. Usually, excess halogen acid was added to convert all of the free bases to their salts. The unreacted alkylene dihalide was removed by evaporation or extraction with ether. Finally, purification was effected by fractional crystallization or by selective extraction with two solvents, evaporation of the solvent, if necessary, and trituration of the oily residue with alcohol or acetone or a mixture of the two solvents. Since this purification involved so much loss of material, the yield is given only in the case of 1,3-bis-[tris-(hydroxymethyl)-methylamino]-2-propanol, the compound which was studied most fully.

The polyhydroxyamines described in this paper are characterized by their very high water solubility, both as the free bases and in the form of their salts with hydrochloric or hydrobromic acid. Some of these derivatives of (A) have a great tendency to hold ferric hydroxide, bismuth hydroxide and some other metallic hydroxides in solution. The solubilizing action of the derivatives of (A) is being studied with the view to technical and pharmaceutical applications and will be reported elsewhere. Each of these compounds has one or two secondary amino groups. The high proportion of hydroxyl groups and likely their spatial arrangement makes difficult some of the reactions

(1) Acknowledgment is made to Dr. E. Emmet Reid, Research Adviser to the Chemistry Department of the University of Richmond, for his advice in this work.

(2) This research was assisted by a grant from Chas. C. Haskell and Co., Inc., Richmond, Va.

(3) Taken from the thesis submitted by John Wotiz in partial fulfillment for the degree of Master of Science. Present address, Department of Chemistry, The Ohio State University, Columbus, Ohio.

(4) C. L. Gabriel, *Ind. Eng. Chem.*, **32**, 891 (1940).

(5) O. Piloty and O. Ruff, *Ber.*, **30**, 1665, 2062 (1897).

(6) Henry, *Bull. soc. chim.*, [3] **13**, 1001 (1895).

(7) O. Eisleb, U. S. Patent 1,790,042 (1931); Groggins and Stirton, *Ind. Eng. Chem.*, **29**, 1359 (1937).

(8) J. F. Olin, U. S. Patent 2,042,621 (1936); V. Kartaschoff, U. S. Patent 2,149,527 (1939).

(9) I. G. Farbenindustrie A. G., British Patent 459,746 (1937).

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of amino nitrogens. However, in some cases it is possible to get an amino group to react and a study is being made to utilize these polyhydroxyamines for the preparation of various polyfunctional compounds.

Experimental

1,3-Bis-[-tris-(hydroxymethyl)-methylamino]-propane Dihydrobromide, $(HOCH_2)_3CNHCH_2CH_2CH_2NHC(CH_2OH)_3 \cdot 2HBr$.—A solution of 24 g. of (A) (0.2 mole) and 10 g. of trimethylene bromide (0.05 mole) in 150 ml. of alcohol was heated under reflux on a water-bath for six hours. On standing overnight, needle-like crystals of (A)·HBr were formed. These crystals were filtered off and the filtrate was made distinctly acidic with hydrobromic acid. The acidic solution was evaporated to low volume to remove most of the water. The gummy residue was dissolved in hot absolute alcohol and the solution was treated with an equal volume of anhydrous acetone. Two layers were formed. The lower layer was separated and triturated with a mixture of equal volumes of absolute alcohol and anhydrous acetone, until crystalline. The solid, 1,3-bis-[tris-(hydroxymethyl)-methylamino]-propane dihydrobromide, on three recrystallizations from alcohol, melted at 170–171°.

1,2-Bis-[tris-(hydroxymethyl)-methylamino]-ethane Dihydrobromide, $(HOCH_2)_3CNHCH_2CH_2NHC(CH_2OH)_3 \cdot 2HBr$.—This product was made and purified by practically the same procedure as the compound above.

1,6-Bis-[tris-(hydroxymethyl)-methylamino]-hexane Dihydrobromide, $(HOCH_2)_3CNH(CH_2)_6NHC(CH_2OH)_3 \cdot 2HBr$.—A mixture of 48.4 g. of (A) (0.4 mole) and 24.4 g. of hexamethylene bromide (0.1 mole) was refluxed with mechanical stirring until a homogeneous mixture was obtained. The brown glue thus formed was dissolved by refluxing with 300 ml. of 95% alcohol. The alcoholic solution was made strongly acidic with hydrobromic acid and most of the alcohol was evaporated. The residue was treated with absolute alcohol and anhydrous acetone to yield crystals of impure (A)·HBr, melting at 128–132°. The filtrate was treated with three volumes of anhydrous acetone. An oily layer was formed. This lower layer was triturated with absolute alcohol and anhydrous acetone, yielding a solid melting at 150–155°. On recrystallization from 95% alcohol and anhydrous acetone, the product melted at 160.5–162°.

1,3-Bis-[tris-(hydroxymethyl)-methylamino]-2-propanol Dihydrochloride, $(HOCH_2)_3CNHCH_2CHOHCH_2NHC(CH_2OH)_3 \cdot 2HCl$.—Glyceroldichlorohydrin was heated with two molar quantities of (A) at 100° for three hours with no solvent and with frequent stirring. The yellow glue formed was dissolved in hot alcohol and the solution was acidified with hydrochloric acid. The precipitate which formed, on cooling, was recrystallized from aqueous alcohol.

Better results were obtained by the following procedure: 242 g. of (A) (2.0 moles) and 92.5 g. of epichlorohydrin (1.0 mole) were mixed with 200 ml. of alcohol and heated on a boiling water-bath under reflux for five hours. The viscous brown liquid was treated with 100 ml. (appreciable excess) of concentrated hydrochloric acid, with stirring. The reaction mixture was cooled and filtered with suction. On one recrystallization from an alcohol–water solution, there was obtained 190 g. (51%) of the dihydrochloride of 1,3-bis-[tris-(hydroxymethyl)-methylamino]-2-propanol, m. p. 185–187°.

1,3-Bis-[tris-(hydroxymethyl)-methylamino]-2-propanol, $(HOCH_2)_3CNHCH_2CHOHCH_2NHC(CH_2OH)_3$.—The free base, mixed with a little sodium chloride, was prepared by treatment of the dihydrochloride, in methyl alcohol, with the calculated quantity of sodium methylate, refluxing, filtering and evaporating the methyl alcohol solution. Also, the free base, free of inorganic impurities, was obtained from the dihydrochloride by prolonged heating of an aqueous solution with excess silver carbonate, removal of dissolved silver with hydrogen sulfide and removal of colored impurities by repeated solution in absolute alcohol and treatment with anhydrous acetone. Finally, by evaporation of the oily lower layer, the free base was obtained as an oil. Calcd. for $C_{11}H_{27}O_7N_2$: nitrogen, 9.40. Found: N, 9.41.

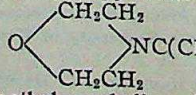
1-Diethanolamino-3-tris-(hydroxymethyl)-methylamino-2-propanol Dihydrochloride, $(HOCH_2CH_2)_2NCH_2CHOHCH_2NHC(CH_2OH)_3 \cdot 2HCl$.—A mixture of 10.5 g. of diethanolamine (0.1 mole) and 9.5 g. of epichlorohydrin (0.1 mole) was stirred well, the temperature being kept around 30°. After the initial exothermic reaction ceased, the mixture was left overnight at room temperature. The clear viscous liquid was extracted with ether. The ether insoluble product was added to 12 g. of (A) (0.1 mole) and 50 ml. of alcohol and the mixture was heated under reflux for six hours on a water-bath. The reaction mixture was acidified with concentrated hydrochloric acid. An oil was thrown out by the addition of absolute alcohol, acetone and ether. This oil was converted to a semi-solid by solution in aqueous alcohol, treatment with anhydrous acetone and by allowing the lower layer, after evaporation, to stand in a vacuum desiccator. Finally, purification was effected by extraction with hot absolute alcohol.

1,3-Di-(diethanolamino)-2-propanol Dihydrochloride, $(HOCH_2CH_2)_2NCH_2CHOHCH_2N(CH_2CH_2OH)_2 \cdot 2HCl$.—The condensation product of diethanolamine and epichlorohydrin was prepared to compare it with the product formed by the reaction of epichlorohydrin with one molecule each of diethanolamine and (A).

10.5 g. of diethanolamine (0.1 mole) and 9.3 g. of epichlorohydrin (0.1 mole) were mixed by shaking and cooling below 30°. After the exothermic reaction ceased, a clear viscous liquid resulted. An additional 10.5 g. of diethanolamine was added and the liquid was heated on a water-bath for eight hours. The product then was acidified with concentrated hydrochloric acid and was extracted with acetone. The lower layer was recrystallized from absolute alcohol.

1-Ethylethanolamino-3-tris-(hydroxymethyl)-methylamino-2-propanol Dihydrochloride, $HOCH_2CH_2(C_2H_5)NCH_2CHOHCH_2NHC(CH_2OH)_3 \cdot 2HCl$.—Ethylaminoethanol was treated with an equimolar quantity of epichlorohydrin at a temperature below 30°. After the exothermic reaction ceased, the viscous liquid was left at room temperature overnight. The condensation product thus formed was heated with an equimolar amount of (A) for eight hours on a water-bath and the mixture was acidified with hydrochloric acid. Repeated attempts to recrystallize from alcohol failed to yield a solid but the light pink colored glue analyzed satisfactorily.

γ,γ′-Bis-[tris-(hydroxymethyl)-methylamino]-propyl Ether Dihydrochloride, $(HOCH_2)_3CNHCH_2CH_2CH_2OCH_2CH_2CH_2NHC(CH_2OH)_3 \cdot 2HCl$.—A mixture of 17 g. of γ,γ′-dichloropropyl ether (0.1 mole) and 24 g. of (A) (0.2 mole) in 100 ml. of alcohol was heated in a sealed tube overnight at 110°. The alcoholic solution was acidified with hydrochloric acid and the precipitated (A)·HCl was filtered off. Repeated evaporations, solution in absolute alcohol, treatments with anhydrous acetone and finally treatments with anhydrous ether were necessary to remove all of the (A)·HCl. The oil finally obtained analyzed slightly low for γ,γ′-bis-[tris-(hydroxymethyl)-methylamino]-propyl ether dihydrochloride.



$NC(CH_2OH)_3 \cdot HCl$, **4-Tris-(hydroxymethyl)-methylmorpholine Hydrochloride.**—Fourteen grams of β,β′-dichloroethyl ether (0.1 mole) and 24 g. of (A) (0.2 mole) were heated with 100 ml. of alcohol in a sealed tube overnight at 150°. On cooling, snow-white crystals of (A)·HCl were formed. The crystals were filtered off and the filtrate was acidified with hydrochloric acid. On partial evaporation, a solid was obtained. On recrystallization from alcohol, the 4-tris-(hydroxymethyl)-methylmorpholine hydrochloride melted at 184–185°. Calcd. for $C_8H_{18}O_4NCl$: Cl, 15.57. Found: Cl, 15.59.

A further concentration of the original filtrate yielded other crops of crystals, likely mainly (A)·HCl, judging

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TABLE I

POLYHYDROXYAMINE HYDROHALIDES

Compounds	Empirical formula	M. p., °C. uncor.	Halogen analyses, % Calcd.	Found[b]
$(HOCH_2)_3CNH_2\cdot HCl$[a]	$C_4H_{12}O_3ClN$	149–150	22.50	22.58
$(HOCH_2)_3CNH_2\cdot HBr$[a]	$C_4H_{12}O_3BrN$	133–134	39.55	39.52
$(HOCH_2)_3CNHCH_2CH_2NHC(CH_2OH_3)\cdot 2HBr$	$C_{10}H_{26}O_6Br_2N_2$	205–206	37.16	37.09
$(HOCH_2)_3CNH(CH_2)_3NHC(CH_2OH)_3\cdot 2HBr$	$C_{11}H_{28}O_6Br_2N_2$	170–171	35.98	35.25
$(HOCH_2)_3CNH(CH_2)_6NHC(CH_2OH)_3\cdot 2HBr$	$C_{14}H_{34}O_6Br_2N_2$	160.5–162	32.87	32.10
$(HOCH_2)_3CNHCH_2CHOHCH_2NHC(CH_2OH)_3\cdot 2HCl$	$C_{11}H_{28}O_7Cl_2N_2$	186–188	19.10	19.07
$(HOCH_2)_3CNHCH_2CHOHCH_2NHC(CH_2OH)_3\cdot 2HBr$	$C_{11}H_{28}O_7Br_2N_2$	160–162	34.73	34.67
$(HOCH_2CH_2)_2NCH_2CHOHCH_2N(CH_2CH_2OH)_2\cdot 2HCl$	$C_{11}H_{28}O_5Cl_2N_2$	98–100	20.90	20.97
$(HOCH_2CH_2)_2NCH_2CHOHCH_2NHC(CH_2OH)_3\cdot 2HCl$	$C_{11}H_{28}O_6Cl_2N_2$	139–141	19.96	19.55
$(HOCH_2CH_2)(C_2H_5)NCH_2CHOHCH_2NH(CH_2OH)_3\cdot 2HCl$	$C_{11}H_{28}O_5Cl_2N_2$	Sirup	20.90	19.74
$HOCH_2CHOHCH_2NHC(CH_2OH)_3\cdot HCl$	$C_7H_{18}O_5ClN$	Sirup	15.31	14.90
$HOCH_2CH_2NHC(CH_2OH)_3\cdot HCl$	$C_6H_{16}O_4ClN$	Sirup	17.58	17.30
$HOCH_2CH_2CH_2NHC(CH_2OH)_3\cdot HBr$	$C_7H_{18}O_4BrN$	Sirup	30.72	30.18
$(HOCH_2)_3CNH(CH_2)_3O(CH_2)_3NHC(CH_2OH)_3\cdot 2HCl$	$C_{14}H_{34}O_7Cl_2N_2$	Sirup	17.16	16.30

[a] Compounds given for reference. [b] We are indebted to E. E. Bowden and Walter W. Haden for most of the halogen analyses in this work.

from the melting points. No β,β'-bis-[tris-(hydroxymethyl)-methylamino]-ethyl ether was isolated.

1,2-Dihydroxy-3-tris-(hydroxymethyl)-methylaminopropane Hydrochloride, $HOCH_2CHOHCH_2NHC(CH_2OH)_3\cdot HCl$.—A mixture of 24 g. of (A) (0.2 mole) and 11 g. of glycerol monochlorohydrin (0.1 mole) was heated under reflux with 50 ml. of alcohol for five hours. The resulting liquid was acidified with hydrochloric acid, while hot. On cooling, crystals of (A)·HCl were obtained and filtered off. More (A)·HCl was obtained by concentration of the filtrate and treatment with dry acetone. This process was repeated until no crystals were obtained. The solution then was concentrated to a sirup which was completely miscible with absolute alcohol and dry acetone. The sirup, while hot, was placed in a vacuum desiccator. After two days of drying, a satisfactory analysis for chloride was obtained.

Similar procedures were used for the reaction of ethylene chlorohydrin and trimethylene bromohydrin with (A) and for purification of the products formed.

Summary

A series of highly polar polyhydroxyamines have been made from tris-(hydroxymethyl)-aminomethane.

RICHMOND, VA. RECEIVED JANUARY 18, 1944

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF BRYN MAWR COLLEGE]

The Cleavage of (Dialkylvinyl)-alkylcyanoacetic Esters by Sodium Alkoxides[1]

BY ELIZABETH M. OSMAN AND ARTHUR C. COPE

More or less extensive cleavage of (dialkylvinyl)-alkylcyanoacetic esters to unsaturated nitriles has been observed to occur as a side reaction during condensation of the esters with urea in the presence of sodium alkoxides.[2] This paper reports an investigation of the cleavage reaction, and its use in the preparation of certain α,β-unsaturated nitriles. The hydrolysis of the nitriles to acids has also been studied.

The products of cleavage are ethyl carbonate and an α,β-unsaturated nitrile

$$R''CH{=}C(R')\underset{R}{\overset{CN}{\underset{|}{C}}}\underset{I}{\overset{}{}}COOC_2H_5 + C_2H_5OH \xrightarrow{NaOC_2H_5} CO(OC_2H_5)_2 + R''CH_2C(R'){=}C(R)CN$$

Similar cleavage of other cyanoacetic and malonic ester derivatives has been observed by several investigators.[3] The reaction proceeds readily at moderate temperature with disubstituted esters such as I which contain an α,β-unsaturated (electron attracting, or negative) group. Malonic ester derivatives which are not labilized by electron attracting substituents are cleaved in a similar manner at higher temperatures.[3c]

Kandiah and Linstead[4] have proposed a reaction mechanism for the cleavage in which the carbethoxyl group is removed by combination with ethoxide ion as ethyl carbonate, forming the anion of the nitrile. This ion acquires a proton from the solvent alcohol, producing the nitrile and reforming ethoxide ion. α,β- and β,γ-unsaturated nitriles are equilibrated rapidly in the presence of sodium ethoxide,[4] so that

(1) Abstracted from a dissertation presented to the Faculty of the Graduate School of Bryn Mawr College by Elizabeth M. Osman in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) Cope and Hancock, THIS JOURNAL, 61, 776 (1939).

(3) *Cf.* (a) Rogerson and Thorpe, *J. Chem. Soc.*, 87, 1702 (1905); Thole and Thorpe, *ibid.*, 99, 2191 (1911); Ingold and Thorpe, *ibid.*, 115, 143 (1919); Birch, Kon and Norris, *ibid.*, 123, 1369 (1923); Birch and Kon, *ibid.*, 123, 2440 (1923); (b) Kon and Nilayanan, *ibid.*, 1536 (1927); (c) Cope and McElvain, THIS JOURNAL, 54, 4311, 4319 (1932).

(4) Kandiah and Linstead, *J. Chem. Soc.*, 2139 (1929).

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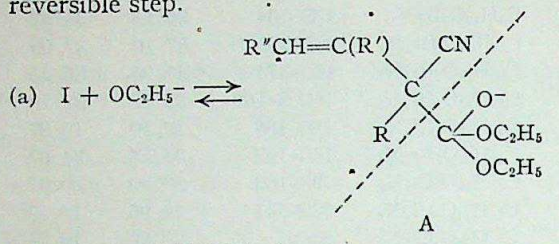
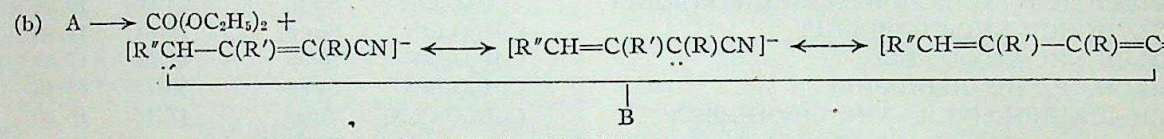
either form or an equilibrium mixture can be the final product. Our results are in accord with this mechanism, which we would expand to include the addition of ethoxide ion as a discrete, reversible step.



(a) $I + OC_2H_5^- \rightleftharpoons A$



(b) $A \longrightarrow CO(OC_2H_5)_2 + [R''CH{-}C(R')=C(R)CN]^- \longleftrightarrow [R''CH=C(R')C(R)CN]^- \longleftrightarrow [R''CH=C(R')-C(R)=C=N:]^-$

B

(c) $B + C_2H_5OH \longrightarrow OC_2H_5^- + R''CH_2C(R')=C(R)CN$

The relative ease with which a number of ethyl (dialkylvinyl)-alkylcyanoacetates are cleaved was determined as follows. The esters (Table I, also ref. 5) were treated with a molecular equivalent of sodium ethoxide in absolute alcohol for one-half hour at a constant temperature. Temperatures were chosen at which partial cleavage occurred. The extent of the reaction was determined in each case by fractional distillation and determination of the yield of ethyl carbonate, unsaturated nitrile, and recovered ester. The data obtained are summarized in Table II.

The susceptibility to cleavage of four esters with the structure $C_2H_5CH=C(CH_3)C(R)(CN)COOC_2H_5$ decreased in the following order: R = methyl > ethyl and *n*-propyl > isopropyl (esters 2, 7, 8 and 9, Table II). This is the order of increasing size and capacity for electron release of the alkyl groups. The relative rates of cleavage of six esters in which R in general formula I was methyl, while the substituted vinyl group was varied, were also determined (esters 1 to 6, Table II). All of these esters were cleaved to a similar extent, 35 to 49%, on treatment with one molar equivalent of alcoholic sodium ethoxide at 30° for thirty minutes.

The reason for the unusual ease with which (substituted vinyl)-alkylcyanoacetic esters are cleaved, according to the sequence of reactions outlined above, is the electron attraction of the substituted vinyl group. Esters are known to undergo ester interchange (step a) in the presence of sodium alkoxides. In this case the intermediate adduct, A, contains the electron attracting nitrile and substituted vinyl groups, while the carbethoxyl group has acquired an integral negative charge from the ethoxide ion and has become electron repelling. If the central methylene carbon atom acquires the electron pair corresponding to the bond at the point of the dotted line in formula A as a result of these forces, ethyl carbonate is formed and process (b) is completed. The normal reaction under mild conditions for esters in which the α-carbon atom is not attached to electron attracting groups is the reversal of (a). Large or branched alkyl groups on the central methylene carbon atom (R in formula I) would be expected to slow the cleavage by steric hindrance to the addition step (a), and by electron release opposed to the cleavage step (b). Modification of R′ and R″ would produce relatively minor effects, since the influence of the substituted vinyl group is due primarily to its unsaturation.

Much more drastic conditions were required to produce partial cleavage of similarly substituted malonic ester and malononitrile derivatives (10 and 11, Table II). Treatment with an equivalent quantity of alcoholic sodium ethoxide for thirty hours at 80° resulted in approximately 30% cleavage of the malonate, while the malononitrile was cleaved to the extent of 50% in one hundred and twenty hours at about 90°. The relatively slow cleavage of the malonate (10) compared to the corresponding cyanoacetate (1) is explained by the fact that the carbethoxyl is less electron attracting than the nitrile group. Consequently, there is less tendency for the cleavage step (b) to occur in the malonic ester series. The substituted malononitrile (11) apparently is converted by addition of an ethoxide ion into an iminoether derivative, $CH_3CH=C(C_2H_5)C(CH_3)(CN)C(OC_2H_5)=NH$, which resists cleavage.

The cleavage of alkyl (1-methyl-1-butenyl)-ethylcyanoacetates, $C_2H_5CH=C(CH_3)C(C_2H_5)(CN)COOR$, by solutions of sodium in methyl, ethyl, isopropyl and *n*-butyl alcohols was also investigated, to determine the relation of the nature of the alkoxide ion to the rate of cleavage. The data obtained are listed in Table III. The cleavages proceeded at approximately equal rates in each of the alcohols except methanol. Cleavage was somewhat slower in methyl alcohol, and it was possible to convert the ethyl ester into the methyl ester by treatment with sodium methoxide in methyl alcohol at a temperature (50°) too low to produce cleavage. Previous investigation[5] of the alkylation of alkylidene cyanoacetic esters has shown that much poorer yields are obtained when the esters are converted into their enolates by sodium methoxide in methyl alcohol than when sodium ethoxide or sodium isopropoxide is employed. According to the present results, the defects of methanol as an alkylation medium cannot be explained by rapid cleavage of the products by methoxide ion. They probably are due to the higher acidity of methyl alcohol, which could lead to an unfavorable

(5) Cope and Hancock, THIS JOURNAL, 60, 2903 (1938).

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TABLE I

SUBSTITUTED VINYLALKYLCYANOACETIC ESTERS[a]

Substituted vinyl group	Alkyl group	Yield, %	B. p., °C.	Mm.	$n^{25}D$	d^{25}_{25}	Molecular refraction Calcd.	Found	Formula[a]	Nitrogen, % Calcd.	Found
1-Methyl-1-propenyl	Methyl[d]	65	106–108	11	1.4450	0.9728	49.40	49.58	$C_{10}H_{15}O_2N$	7.73	7.60
1-Methyl-1-butenyl	Ethyl[b,e]	17	114–116	8	1.4519	.9780	54.02	54.01	$C_{11}H_{17}O_2N$[b]	7.17	7.21
1-Methyl-1-butenyl	Ethyl[c,f]	73	139–142	23	1.4414	.9332	63.26	63.38	$C_{13}H_{21}O_2N$[c]	6.28	6.35
1,3-Dimethyl-1-butenyl	Methyl[d]	79	129–133	20	1.4427	.9403	58.64	59.14	$C_{12}H_{15}O_2N$	6.69	6.54
1-Propyl-1-butenyl	Methyl[d]	81	128–129	12	1.4478	.9421	63.26	63.62	$C_{13}H_{21}O_2N$	6.28	6.39
1-Methyl-1-hexenyl	Methyl[d]	62	132–136	12	1.4477	.9403	63.26	63.37	$C_{13}H_{21}O_2N$	6.28	6.18

[a] Ethyl esters except for the following: [b] Methyl ester. [c] Isopropyl ester. [d] The alkylating agent was methyl iodide. [e] The alkylating agent was ethyl iodide. [f] The alkylating agent was ethyl sulfate.

equilibrium in the ester-ester enolate conversion.

$$RCH_2C(R)=C(CN)COOR + RONa \rightleftharpoons [RCH=C(R)C(CN)COOR]^-Na^+ + ROH$$

Completion of the cleavage of (substituted vinyl)-alkylcyanoacetic esters by refluxing with alcoholic sodium ethoxide affords a good synthesis for certain α,β-unsaturated nitriles. The properties of a number of nitriles which were prepared by this method are summarized in Table IV. An equilibrium mixture of α,β- and β,γ-unsaturated nitriles should be formed under the conditions of cleavage. The exaltation in molecular refraction of each of the nitriles, and the results of ozonization of two of them (outlined in the Experimental Part) indicate that they are very largely or completely in the α,β-unsaturated form.

The inert character and in particular the resistance to hydrolysis of conjugated unsaturated nitriles has been noted by many investigators.[3b,6] It was found to be possible to hydrolyze the nitriles listed in Table IV by employing drastic conditions. The nitriles were refluxed for forty-eight hours with a solution of potassium hydroxide in diethylene glycol containing a small amount of water. Unsaturated acids were obtained in this manner in yields of 49 to 81% (Table V). The available evidence (see the Experimental Part) indicates that the acids obtained were mixtures of the α,β- and β,γ-unsaturated isomers. The conditions of hydrolysis favor the establishment of equilibrium between the two forms.

One reaction in addition to hydrolysis which was completed successfully with 2-ethyl-3-methyl-2-hexenenitrile was conversion into the amidine by reaction with sodamide. The amidine was not very stable, and decomposed on standing into ammonia and the original nitrile. It was characterized by analysis and conversion into the picrate.

Experimental Part[7]

Substituted Vinylalkylcyanoacetic Esters.—Alkylidene cyanoacetic esters were prepared by the methods described recently.[8] They were alkylated in the alcohol corresponding to the ester alkoxyl group, to prevent ester interchange, by a general procedure previously employed for preparing homologous esters.[5] The yields and properties of esters not previously described in ref. 5 are recorded in Table I.

(1-Ethylpropenyl)-methylmalononitrile.—1-Ethylpropylidene malononitrile (40.2 g.) was added to a solution of 6.9 g. of sodium in 300 cc. of dry isopropyl alcohol and treated with 51 g. of methyl iodide under conditions used for synthesis of the ethyl homolog.[9] After purification by distillation, shaking with sodium bisulfite solution and redistillation, the alkylation product was obtained in yield of 41.6 g. (93%); b. p. 105–108° (17–18 mm.); $n^{25}D$ 1.4458; d^{25}_{25} 0.9182; MD calcd. 42.95; found 43.15.

Anal. Calcd. for $C_8H_{12}N_2$: N, 18.90. Found: N, 18.83.

Cleavages in Ethyl Alcohol: Substituted Vinylalkylcyanoacetic Esters.—Each of the esters was treated with an equivalent quantity of sodium ethoxide in alcohol solution for exactly thirty minutes at 30, 50, or 80 ± 2°. The data in Table II show the extent of cleavage in each case. The following typical example is cited to illustrate the experimental procedure.

Sodium (4.6 g., 0.2 mole) was dissolved in 100 cc. of absolute alcohol in a 500-cc. three-necked flask equipped with a stirrer, a reflux condenser connected through a drying tube to a source of nitrogen, a dropping funnel and a thermometer. A nitrogen atmosphere under slight positive pressure was maintained throughout the reaction. The solution of sodium ethoxide was cooled to 30°, and ethyl (1-methyl-1-hexenyl)-methylcyanoacetate (44.7 g., 0.2 mole) was forced into the flask from the dropping funnel. The mixture was stirred at 30 ± 2° for thirty minutes, and then poured, with stirring, into a mixture of 40 cc. of 6 *N* hydrochloric acid and 100 g. of ice. The non-aqueous layer was removed, and the aqueous layer was extracted with three 50-cc. portions of benzene, which were combined with the non-aqueous layer and washed once with 30 cc. of water. The benzene was distilled through a small Widmer column at atmospheric pressure, and the residue was fractionated slowly and carefully through the column. The following fractions were separated: 3.5 g., b. p. 90–112°, $n^{25}D$ 1.4080; 2.2 g. (9.3%) of ethyl carbonate, b. p. 112–115°, $n^{25}D$ 1.3842; 1.3 g. of intermediate (5.5% calculated as ethyl carbonate), b. p. 115 (atm. p.)–100° (14 mm.), $n^{25}D$ 1.3969; 9.9 g. (32.7%) of 2,3-dimethyl-2-octenenitrile, b. p. 100–110° (14 mm.), $n^{25}D$ 1.4521; 1.3 g. intermediate (4.3% calculated as nitrile), b. p. 110–125° (13 mm.), $n^{25}D$ 1.4510; 23.9 g. (53.7%) of the original ester, b. p. 125–133° (11 mm.), $n^{25}D$ 1.4484; 3.0 g. (6.7% calculated as recovered ester) obtained by evacuating the column to a pressure of 1 mm., $n^{25}D$ 1.4512. The object of the distillation was to provide as accurate an analysis as possible of the reaction mixture; physical properties of the pure esters and nitriles are recorded elsewhere (ref. 5 and Table I and IV). The same molar concentrations of reactants were employed in each cleavage.

Ethyl (1-Methyl-1-propenyl)-methylmalonate.—This ester[10] was treated with a molecular equivalent of alcoholic sodium ethoxide for thirty minutes in the manner outlined

(6) *Cf.* Heyl and Meyer, *Ber.*, **28**, 1798 (1895); Meyer, *ibid.*, **28**, 3197 (1895); Kohler and Corson, THIS JOURNAL, **45**, 1975 (1923).

(7) All melting and boiling points are uncorrected.

(8) Cope, Hofmann, Wyckoff and Hardenbergh, THIS JOURNAL, **63**, 3452 (1941).

(9) Cope and Hoyle, *ibid.*, **63**, 733 (1941).

(10) Cope and Hancock, *ibid.*, **60**, 2902 (1938).

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TABLE II

CLEAVAGE OF (DIALKYLVINYL)-ALKYLCYANOACETIC ESTERS[a] BY ALCOHOLIC SODIUM ETHOXIDE

No.	Ester	Formula	Conditions of cleavage Time, hours	Temp., °C.	Ethyl carbonate yield, %[b]	Nitrile formed by cleavage, yield, %[b]	Ester recovered, %[b]
1	Ethyl (1-methyl-1-propenyl)-methylcyanoacetate	$CH_3CH{=}C(CH_3)C(CH_3)(CN)COOC_2H_5$	0.5	30	31	42 (43)	41 (54)
2	Ethyl (1-methyl-1-butenyl)-methylcyanoacetate	$C_2H_5CH{=}C(CH_3)C(CH_3)(CN)COOC_2H_5$	.5	30	29[c]	41 (44)[c]	47 (55)[c]
			.5	50	46 (59)	73 (90)	0
3	Ethyl (1-ethyl-1-propenyl)-methylcyanoacetate	$CH_3CH{=}C(C_2H_5)C(CH_3)(CN)COOC_2H_5$	.5	30	23 (25)	34 (35)	55 (65)
			.5	50	78 (79)	91 (104)	0
4	Ethyl (1,3-dimethyl-1-butenyl)-methylcyanoacetate	$i\text{-}C_3H_7CH{=}C(CH_3)C(CH_3)(CN)COOC_2H_5$	.5	30	19 (25)	46 (49)	44 (49)
5	Ethyl (1-methyl-1-hexenyl)-methylcyanoacetate	$n\text{-}C_4H_9CH{=}C(CH_3)C(CH_3)(CN)COOC_2H_5$	.5	30	9 (15)	33 (37)	54 (61)
6	Ethyl (1-propyl-1-butenyl)-methylcyanoacetate	$C_2H_5CH{=}C(n\text{-}C_3H_7)C(CH_3)(CN)COOC_2H_5$	.5	30	23 (27)[c]	41 (45)[c]	51 (57)[c]
7	Ethyl (1-methyl-1-butenyl)-ethylcyanoacetate	$C_2H_5CH{=}C(CH_3)C(C_2H_5)(CN)COOC_2H_5$	.5	50	25	38 (46)	36 (45)
8	Ethyl (1-methyl-1-butenyl)-propylcyanoacetate	$C_2H_5CH{=}C(CH_3)C(n\text{-}C_3H_7)(CN)COOC_2H_5$	.5	50	40 (44)	54 (60)	27 (37)
9	Ethyl (1-methyl-1-butenyl)-isopropylcyanoacetate	$C_2H_5CH{=}C(CH_3)C(i\text{-}C_3H_7)(CN)COOC_2H_5$	.5	50	0	0	87 (98)
			.5	80	42 (45)	71 (72)	17 (25)
10	Ethyl (1-methyl-1-propenyl)-methylmalonate	$CH_3CH{=}C(CH_3)C(CH_3)(COOC_2H_5)_2$	30	80	14	22 (32)	52 (64)
11	(1-Ethyl-1-propenyl)-methylmalononitrile	$CH_3CH{=}C(C_2H_5)C(CH_3)(CN)_2$	120	94–87		50 (51)	0

[a] A related malonic ester and malononitrile derivative are included in the table. [b] The first figures in each case represent the purest fraction, while the figures in parentheses include the intermediate fractions in the manner indicated in the detailed example in the Experimental Part. [c] Average from two similar cleavages in which the deviation in yield averaged 4% and the extreme deviation was 7%.

above at temperatures of 30, 50 and 80°, and also for five hours at 80°. In each case no monocarboxylic ester could be isolated, and 84 to 98% of the original ester was recovered. When the reaction mixture was kept at 80° for thirty hours, partial cleavage occurred as indicated in Table II. In order to identify the cleavage product, the fractions resulting from partial cleavage were combined and refluxed with alcoholic sodium ethoxide for seven days. This treatment resulted in complete cleavage. The properties of the monocarboxylic ester fraction were: b. p. 69–75° (16 mm.); $n^{25}D$ 1.4355. This index of refraction lies between the values ($n^{20}D$) of 1.4453 and 1.4298 given by Kon, Linstead and Maclennan[11] for ethyl 2,3-dimethyl-2-pentenoate and ethyl 2,3-dimethyl-3-pentenoate, respectively. An equilibrium mixture of these two esters should be formed in the presence of sodium ethoxide.

(1-Ethyl-1-propenyl)-methylmalononitrile.—No appreciable cleavage resulted from treatment of this malononitrile derivative (0.2 mole) with an equivalent quantity of alcoholic sodium ethoxide for thirty hours at 80°. Approximately 25% of the malononitrile derivative was recovered, while a higher boiling fraction was obtained, which according to analytical evidence was composed principally of $CH_3CH{=}C(C_2H_5)C(CH_3)(CN)C(OC_2H_5){=}NH$, the corresponding imino-ether (25 g., 64% calculated as the imino-ether, b. p. 120–129° (16 mm.), $n^{25}D$ 1.4560). Repetition of this experiment with a reaction time of one hundred and twenty hours at the boiling point (which dropped from 94 to 87° during this time) gave 50% cleavage to 3-ethyl-2-methyl-2-pentenenitrile, as indicated in Table II. Nitrogen and ethoxyl determinations on the higher boiling fraction were in accord with values for a mixture of the malononitrile derivative, the imino-ether formulated above, and the cyanoacetic ester derivative which could be formed from the latter in the process of isolation.[12]

(11) Kon, Linstead and Maclennan, *J. Chem. Soc.*, 2459 (1932).

(12) Similar mixtures have been obtained previously by reaction of malononitrile derivatives with sodium alkoxides; see ref. 9 and references cited therein.

Cleavages in Methyl, Isopropyl and *n*-Butyl Alcohols.—Ethyl (1-methyl-1-butenyl)-ethylcyanoacetate (0.2 mole) was added to a solution of 4.6 g. of sodium in 200 cc. of each of the anhydrous alcohols named above, and allowed to react for exactly thirty minutes at a constant temperature. More dilute solutions were employed than in the cleavages in ethyl alcohol in order to avoid crystallization of the least soluble sodium alkoxides. The cleavage of

TABLE III

CLEAVAGE BY SODIUM ALKOXIDES OF ALKYL (1-METHYL-1-BUTENYL)-ETHYLCYANOACETATES, $C_2H_5CH{=}C(CH_3)C(C_2H_5)(CN)COOR$

Alcohol[a]	R of ester alkoxyl group	Cleavage temp., °C.	Nitrile formed by cleavage, yield, %[b]	Ester recovered, %[b,d]
Ethyl	Ethyl	50	10 (13)[c]	71 (80)[e]
Ethyl	Ethyl	69	37	48 (58)
Ethyl	Ethyl	80	65 (70)[e]	23 (26)[e]
Ethyl	Isopropyl	50	14 (16)	68 (76)
Isopropyl	Ethyl	80	67 (70)	19 (24)
Isopropyl	Isopropyl	80	55	28 (35)
n-Butyl	Ethyl	50	26	70 (74)
Methyl	Ethyl	50	0	82 (94)[e]
Methyl	Ethyl	69	7 (12)	62 (80)[e]
Methyl	Methyl	69	11 (16)	71 (79)

[a] The alcohol used as the medium for cleavage. [b] The first figures in each case represent the purest fraction, while the figures in parentheses include the intermediate fractions. [c] Average from two similar cleavages in which the deviation in yield averaged 3% and the extreme deviation was 8%. [d] The recovered ester is calculated as the original ester except where otherwise indicated. Mixed esters were actually produced in the reaction mixtures in which the ester and alcohol alkoxyl groups were dissimilar. [e] The ester recovered was practically pure methyl ester formed by ester interchange; $n^{25}D$ 1.4516 to 1.4512, b. p. 112–116° (8 mm.).

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TABLE IV

UNSATURATED NITRILES

Compound	B. p., °C.	Mm.	$n^{25}D$	d^{25}_{25}	Molecular refraction Calcd.	Found	Exaltation	Formula	Nitrogen, % Calcd.	Found[a]
2,3-Dimethyl-2-pentenenitrile	64	17	1.4469	0.8427	33.96	34.71	0.75	$C_7H_{11}N$	12.83	12.76
3-Ethyl-2-methyl-2-pentenenitrile	74–76	17	1.4500	.8442	38.58	39.33	.75	$C_8H_{13}N$	11.37	11.18
2,3-Dimethyl-2-hexenenitrile	73–77	14–16	1.4491	.8413	38.58	39.40	.82	$C_8H_{13}N$	11.37	11.35[b]
2-Ethyl-3-methyl-2-hexenenitrile	76–78	8	1.4512	.8394	43.20	44.16	.96	$C_9H_{15}N$	10.21	10.15
3-Methyl-2-propyl-2-hexenitrile	98	14	1.4531	.8404	47.82	48.80	.98	$C_{10}H_{17}N$	9.26	9.12
2-Isopropyl-3-methyl-2-hexenenitrile	81–84	9	1.4494	.8366	47.82	48.67	.85	$C_{10}H_{17}N$	9.26	9.04
2,3,5-Trimethyl-2-hexenenitrile	74–76	9	1.4503	.8371	43.20	44.21	1.01	$C_9H_{15}N$	10.21	10.03
2-Methyl-3-propyl-2-hexenenitrile	88–90	8	1.4542	.8415	47.82	48.84	1.02	$C_{10}H_{17}N$	9.26	9.12
2,3-Dimethyl-2-octenenitrile	96–98	9	1.4532	.8405	47.82	48.80	0.98	$C_{10}H_{17}N$	9.26	9.26[b]

[a] By the semi-micro Kjeldahl method unless otherwise indicated. The reason for the consistently low values is believed to be the stability and volatility of the compounds. [b] Micro-Dumas analysis by the Arlington Laboratories. Kjeldahl analyses were low.

this ester with sodium ethoxide in ethyl alcohol was repeated at the same concentration in order to obtain directly comparable data. In isolating the products, the reaction mixtures were poured into 40 cc. of 6 *N* hydrochloric acid and 200 g. of ice. After adding 200 cc. of water, the non-aqueous layer was separated and the aqueous layer was extracted with three 80-cc. portions of benzene. Two 40-cc. portions of sodium chloride solution were used to wash the combined extracts. Otherwise, the conditions of reaction and the method of separating the products corresponded to the procedure outlined for cleavages in ethyl alcohol. The corresponding isopropyl ester was also subjected to cleavage in ethyl and isopropyl alcohol under these conditions, and the methyl ester was treated with sodium methoxide in methyl alcohol, in order to determine the effect of the ester alkoxyl group on the rate of cleavage. Table III contains the data obtained. The yields of alkyl carbonates are not included, since mixtures were formed in the instances where the ester and alcohol alkoxyl groups were different.

A cleavage of the ethyl ester in methyl alcohol in which the quantities and concentrations of the reactants cited above were used was completed by refluxing the mixture for eight hours. The yield of 2-ethyl-3-methyl-2-hexenenitrile was 24.1 g. (88%).

Preparation and Characterization of Nitriles Produced by Cleavage.—The nitriles which are described in Table IV were prepared by completing the cleavages summarized in Table II. The products of partial cleavage were combined with any of the ester which was available and refluxed with an equivalent quantity or slight excess of sodium ethoxide in absolute alcohol for one to five hours. For example: sodium (10 g., 0.43 mole) was dissolved in 200 cc. of absolute alcohol. Ethyl (1,3-dimethyl-1-butenyl)-methylcyanoacetate (44 g., 0.2 mole) and the products from partial cleavage of 0.2 mole of this ester were added, and the solution was refluxed for one hour. The mixture was cooled, poured into ice and hydrochloric acid, extracted and distilled as described above. The yield of 2,3,5-trimethyl-2-hexenenitrile (Table IV) was 50.3 g. (89%). Yields were approximately 90% in the case of each nitrile prepared.

The carbon skeleton of 2-ethyl-3-methyl-2-hexenenitrile, chosen as representative of the nitriles listed in Table IV, was confirmed by hydrogenation followed by hydrolysis to a known derivative. The nitrile (27.4 g.) in alcohol solution absorbed a molar equivalent of hydrogen on shaking at room temperature in the presence of 1 g. of palladinized charcoal for sixty hours. After removal of the solvent, the product was washed with dilute hydrochloric acid to remove basic by-products and distilled through a small Widmer column. The yield of 2-ethyl-3-methylhexanenitrile was 16 g., b. p. 71–72° (7 mm.); $n^{25}D$ 1.4232; d^{25}_{25} 0.8181; MD calcd. 43.60, found 43.48.

Anal. Calcd. for $C_9H_{17}N$: N, 10.06. Found: N, 9.95.

The above nitrile (6.5 g.) was hydrolyzed by refluxing for twelve hours with a solution of 2.8 g. of potassium hydroxide in 40 cc. of ethylene glycol and approximately 1 cc. of water. The mixture was poured into water, extracted with ether, and separated into acidic and neutral fractions by reëxtraction with sodium hydroxide. The acid fraction on distillation yielded 1.9 g. of 2-ethyl-3-methylhexanoic acid,[30] b. p. 230°, $n^{25}D$ 1.4332. The neutral fraction was steam distilled, and yielded as a volatile fraction 0.5 g. of the original nitrile. A solid (3.6 g.) was obtained from the residue, and on recrystallization yielded 3.4 g. of 2-ethyl-3-methylhexaneamide, m. p. 96–97°.[13]

The exaltation in molecular refraction exhibited by the group of nitriles in Table IV (0.75 to 1.02 units) is good evidence that each of the compounds is α,β-unsaturated, although small amounts of the β,γ-unsaturated isomers could be present. von Auwers[14] observed exaltations of 0.9 to 1.0 for conjugated unsaturated nitriles. Two of the unsaturated nitriles were cleaved by ozonization, following a procedure outlined previously.[10] The volatile product obtained by hydrolysis of the ozonide from 2-ethyl-3-methyl-2-hexenenitrile was methyl propyl ketone, identified as the 2,4-dinitrophenylhydrazone, m. p. and mixed m. p. with a known sample 143–144°. 2,3-Dimethyl-2-pentenenitrile yielded methyl ethyl ketone, m. p. and mixed m. p. of the 2,4-dinitrophenylhydrazone with a known sample 114–115°. These ketones are the products expected from the α,β-unsaturated structures in each case.

Hydrolysis of Unsaturated Nitriles.—The nitriles listed in Table IV were hydrolyzed by a general procedure which is illustrated by the following example. 2,3-Dimethyl-2-octenenitrile (17.8 g., 0.12 mole) was added to a solution of potassium hydroxide pellets (13.4 g.) and water (2.4 cc.) in 60 cc. of diethylene glycol. The solution was boiled under reflux for forty-eight hours, cooled and diluted with 120 cc. of water. The solution was extracted three times with benzene, acidified with 60 cc. of 6 *N* hydrochloric acid, and again extracted with three 50-cc. portions of benzene. The benzene extracts of the acid solution were washed with dilute sodium chloride solution and distilled through a small Widmer column, yielding 12 g. of 2,3-dimethyloctenoic acid (Table V). The acids obtained by hydrolysis have the properties of mixtures of the α,β- and β,γ-unsaturated isomers. The indices of refraction of 2,3-dimethylpentenoic acid, 3-ethyl-2-methylpentenoic acid and 2-ethyl-3-methylhexenoic acid lie between the values reported by Kon, Linstead, *et al.*, for the pure α,β- and β,γ-unsaturated forms (see footnotes to Table V). Two of the acids, 2-methyl-3-propylhexenoic acid and 2,3,5-trimethylhexenoic acid, were ozonized. Only products derived from the β,γ-unsaturated forms of these acids could be isolated, indicating that this form probably predominated in each case. From the former the 2,4-dinitrophenylhydrazone of ethyl propyl ketone was isolated, m. p. 145–146°, and from the latter the 2,4-dinitrophenylhydrazone of methyl ethyl ketone, m. p. 110–111°.

Ethyl (1-Methylbutylidene)-acetamidine.—2-Ethyl-3-methyl-2-hexenenitrile (41.9 g.) was added slowly to a

(13) Volwiler and Tabern, THIS JOURNAL, 58, 1352 (1936).

(14) von Auwers, *Ber.*, 56, 1172 (1923).

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TABLE V

UNSATURATED ACIDS

Acid	Yield, %	B. p., °C.	Mm.	$n^{25}D$	d^{25}_{25}	Molecular refraction, Calcd.	Observed	Exaltation	Formula	Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found
2,3-Dimethylpentenoic[a]	50	118–120	20	1.4529	0.9681	35.60	35.88	+0.28	$C_7H_{12}O_2$	65.59	65.63	9.44	9.41
3-Ethyl-2-methylpentenoic[b]	62	116–117.5	10	1.4548	.9571	40.22	40.41	.19	$C_8H_{14}O_2$	67.57	67.41	9.92	9.88
2,3-Dimethylhexenoic	53	115–118	10	1.4540	.9497	40.22	40.67	.45	$C_8H_{14}O_2$	67.57	67.52	9.92	9.96
2-Ethyl-3-methylhexenoic[c]	56	120–123	9	1.4514	.9358	44.84	45.11	.27	$C_9H_{16}O_2$	69.19	69.05	10.32	10.26
3-Methyl-2-propylhexenoic	49	131–133	10	1.4520	.9271	49.46	49.68	.22	$C_{10}H_{18}O_2$	70.55	70.52	10.66	10.72
2,3,5-Trimethylhexenoic	79	132–140	20	1.4520	.9274	44.84	45.58	.74	$C_9H_{16}O_2$	69.19	69.33	10.32	10.25
2-Methyl-3-propylhexenoic	81	129–133	9	1.4568	.9299	49.46	49.99	.53	$C_{10}H_{18}O_2$	70.55	70.43	10.66	10.84
2,3-Dimethyloctenoic	59	137–140	10	1.4560	.9289	49.46	49.96	.50	$C_{10}H_{18}O_2$	70.55	70.40	10.66	10.69

[a] Pure α,β- and β,γ-forms prepared by Abbott, Kon and Satchell, *J. Chem. Soc.*, 2519 (1928); α,β-unsaturated acid, b. p. 116° (18 mm.), $n^{17.5}D$ 1.45952; β,γ-unsaturated acid, b. p. 116° (20 mm.), $n^{18.2}D$ 1.4498. [b] Pure α,β- and β,γ-forms prepared by Kon, Leton, Linstead and Parsons, *J. Chem. Soc.*, 1416 (1931); α,β-unsaturated acid, b. p. 122° (12 mm.), $n^{20.5}D$ 1.47183; β,γ-unsaturated acid, b. p. 116–117° (14 mm.), $n^{20.3}D$ 1.45003. [c] α,β-unsaturated acid, b. p. 127° (12 mm.), $n^{20}D$ 1.46916; β,γ-unsaturated acid, b. p. 90° (14 mm.), $n^{19.5}D$ 1.43568 (same ref. as footnote *b*).

suspension of sodamide (freshly prepared from 6.9 g. of sodium) in 100 cc. of dry boiling benzene in a 500-cc. three-necked flask, with stirring. After the exothermic reaction subsided, the mixture was refluxed for one-half hour. It was cooled to room temperature, and poured, with stirring, into 100 cc. of concd. hydrochloric acid and 100 g. of ice. The benzene layer was separated and washed with a little water, and the combined aqueous layers were washed twice with ether. The aqueous solution was covered with ether, cooled in an ice-bath and made alkaline by the slow addition from a dropping funnel of 180 cc. of 25% sodium hydroxide, with stirring. The ether layer was separated and the aqueous layer was extracted twice with small volumes of ether. The combined ether layers were washed once with water and distilled through a small Widmer column. Ethyl (1-methylbutylidene)-acetamidine was obtained in yield of 12.5–24.4 g. (27–53%); b. p. 99–101° (1 mm.); $n^{25}D$ 1.4932; d^{25}_{25} 0.9050; MD calcd. 48.68; found 49.70 (exaltation 1.02).

Anal. Calcd. for $C_9H_{18}N_2$: N, 18.16. Found: N, 18.09.

It was necessary to analyze the amidine derivative immediately after distillation, because of fairly rapid decomposition into the original nitrile and ammonia, each of which could be detected by odor. Nitrogen analyses made after three hours or more were approximately 0.5% low.

Ethyl (1-methylbutylidene)-acetamidine was converted into the picrate by reaction with an equivalent quantity of picric acid in boiling alcohol. It was precipitated by the addition of water and recrystallized from dilute alcohol; m. p. 136.5–137.5°.

Anal. Calcd. for $C_{15}H_{21}O_7N_5$: N, 18.27. Found: N, 18.14.

Summary

The cleavage of a number of (dialkylvinyl)-alkylcyanoacetic esters by sodium alkoxides has been investigated from the standpoint of the relation of structure to ease of cleavage, and also as a synthetic method for α,β-unsaturated nitriles. The hydrolysis of these nitriles to acids also has been studied.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

A Simultaneous Condensation–Reduction Method for the Preparation of Ethyl Monoalkylcyanoacetates

BY ELLIOT R. ALEXANDER AND ARTHUR C. COPE

A method for condensing aliphatic and aromatic ketones with ethyl cyanoacetate was described recently[1] in which the reactants are refluxed in benzene solution with an ammonium acetate and acetic acid catalyst. The equilibrium reaction

$$R_2CO + CH_2(CN)COOC_2H_5 \rightleftharpoons R_2C{=}C(CN)COOC_2H_5 + H_2O$$

is displaced to the right by removing the water formed during the condensation with a constant water separator. Another possible method of displacing this equilibrium is to remove the unsaturated ester as it is formed by catalytic hydrogenation. This possibility has been investigated and experimental conditions have been developed for a practical synthetic method for condensing a number of aldehydes and ketones with ethyl cyanoacetate and simultaneously reducing the products to the corresponding ethyl monoalkylcyanoacetates.

In addition to the reduction of alkylidene cyanoacetic esters in the presence of palladinized charcoal[1] and with aluminum amalgam,[2] there are two general methods of preparing ethyl alkylcyanoacetates directly: the sodium enolate of ethyl cyanoacetate may be alkylated with alkyl halides, or ethyl carbonate may be condensed with nitriles in the presence of sodium ethoxide.[3] Both of these methods give poor yields of the lower members of the series of monoalkylcyanoacetates.

(1) Cope, Hofmann, Wyckoff and Hardenbergh, THIS JOURNAL, 63, 3452 (1941).

(2) Cowan and Vogel, *J. Chem. Soc.*, 1529 (1940).

(3) Wallingford, Jones and Holmeyer, THIS JOURNAL, 64, 576 (1942).

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TABLE I

ETHYL MONOALKYLCYANOACETATES, $RCH(CN)COOC_2H_5$

Alkyl group, R	Ketone or aldehyde used in preparation[a]	Time of condensation–reduction, hours	Yield,[b] %	B. p. °C.	Mm.	$n^{25}D$	d^{25}_4	Molecular refraction Calcd.[c]	Found
Ethyl[e]	Acetaldehyde	2.5	80–85 A	84–85	7	1.4163	0.9836	36.01	36.02
n-Propyl[f]	Propionaldehyde	3	94 A	95–96	8	1.4200	.9650	40.63	40.70
n-Butyl[g]	Butyraldehyde	1.3	94–96 A	108–109	8	1.4242	.9537	45.25	45.27
Isobutyl[h]	Isobutyraldehyde	4	98 B	98–99	7	1.4232	.9499	45.25	45.35
Isoamyl[f]	Isovaleraldehyde	4	95 B	113–114	7	1.4279	.9427	49.87	49.97
n-Heptyl[i]	Heptaldehyde	4	71 B	111–113	1	1.4337	.9284	59.11	59.24
Benzyl[e]	Benzaldehyde	16[d]	63 B	118–122	0.4	1.5033	1.0762	55.89	55.50
Isopropyl[h]	Acetone	5–6	90–93 C	89–91	8	1.4203	0.9662	40.63	40.67
s-Butyl[h]	Methyl ethyl ketone	4.5–6	79–81 C	99–100	7	1.4267	.9615	45.25	45.11
1-Methylbutyl[h]	Methyl propyl ketone	11	63 C	111–112	8	1.4300	.9496	49.87	49.85
Cyclohexyl[h]	Cyclohexanone	4–6	91–98 C	138–139	8	1.4574	1.0154	52.29	52.41
1,3-Dimethylbutyl[j]	Methyl isobutyl ketone	8–11	41–63 C	117–119	8	1.4316	0.9360	54.49	54.62
1-Methylhexyl[k]	Methyl amyl ketone	9	71 C	135–137	8	1.4340	.9305	59.11	59.14
4-Heptyl[h]	Dipropyl ketone	7–22	39 C	131–132	7	1.4378	.9407	59.11	58.94
1-Methylhexyl[l]	Methyl hexyl ketone	5–6	73–81 C	112–115	1.0	1.4359	.9286	63.73	63.43

[a] Freshly distilled commercial products were used. [b] Capital letters refer to condensation–reduction methods designated by these letters in the Experimental Part. [c] The value 3.12 was used for the atomic refraction of nitrogen; see Eisenlohr, *Z. physik. Chem.*, **79**, 142 (1912). [d] Heated to 60° during the hydrogenation. [e] Hessler, *Am. Chem. J.*, 22, 175 (1889). [f] Darapsky, *J. prakt. Chem.*, **146**, 253 (1936). [g] Ref. 4. [h] Ref. 2. [i] Calcd. for $C_{12}H_{21}O_2N$: C, 68.26; H, 10.00; N, 6.7. Found: C, 68.60; H, 10.00; N, 6.8. [j] Calcd. for $C_{11}H_{19}O_2N$: C, 67.10; H, 9.70. Found: C, 67.20; H, 9.71. [k] Calcd. for $C_{12}H_{21}O_2N$: C, 68.26; H, 10.00. Found: C, 68.32; H, 10.19. [l] Calcd. for $C_{13}H_{23}O_2N$: C, 69.40; H, 10.30. Found: C, 69.16; H, 10.45.

In the alkylation procedure it is impossible to prevent dialkylation, and the lower molecular weight monoalkylcyanoacetates are difficult to separate from the dialkylcyanoacetates by distillation.[4] Pure products have been obtained in good yield by the condensation–reduction method described in this paper. All of the reactants are commercially available and it is unnecessary to prepare intermediate halides or nitriles, or to work in an anhydrous medium with sodium ethoxide or metallic sodium.

The optimum experimental conditions for the reaction vary slightly according to the type of carbonyl compound used. Piperidine acetate and acetic acid were employed as the condensing agents with aldehydes, and ammonium acetate and acetic acid with ketones. Alcohol was found to be the most satisfactory solvent for the condensation–reduction of ethyl cyanoacetate and ketones; dioxane for higher aldehydes (isobutyraldehyde, isovaleraldehyde, heptaldehyde and benzaldehyde); and glacial acetic acid for low molecular weight aldehydes (acetaldehyde, propionaldehyde, and butyraldehyde). The preferred procedure for carrying out the reaction for each of the three classes is given in the Experimental Part. Palladinized charcoal was found to be a suitable hydrogenation catalyst under these conditions. In the presence of platinum oxide partial reduction of the nitrile group occurred, while Raney nickel was deactivated by the acetic acid present in the reaction mixture. The properties and yields of ethyl monoalkylcyanoacetates prepared by the condensation–reduction procedure are listed in Table I.

(4) Hessler, *Am. Chem. J.*, **22**, 169 (1899).

The method seems particularly well adapted for use with aldehydes and methyl ketones not branched at the α-carbon atom, which gave yields ranging from 63 to 98% of ethyl monoalkylcyanoacetates. When dipropyl ketone was used the yield dropped to 39%, and a pure product could not be isolated from the reaction with diisobutyl ketone.

Condensation–reduction of acetophenone and propiophenone with ethyl cyanoacetate in alcohol or dioxane solution at temperatures up to 90° in the presence of ammonium acetate, acetic acid, and palladinized charcoal yielded mixtures, apparently due to incomplete hydrogenation of the condensation products. Under similar conditions, a pure sample of ethyl (1-phenylethylidene)-cyanoacetate[1] was not completely hydrogenated. When aldol was employed in the reaction, the product proved to be ethyl *n*-butylcyanoacetate.

Ethyl alkylmalonates could not be prepared by the condensation–reduction of butyraldehyde, isobutyraldehyde, or benzaldehyde with ethyl malonate in dioxane solution in the presence of ammonium acetate, acetic acid, and palladinized charcoal at temperatures up to 100°. No hydrogen was absorbed and the starting materials were recovered. Similar results were obtained with butyraldehyde and ethyl malonate in glacial acetic acid.

Experimental[5]

The following methods were used to prepare the compounds listed in Table I:

(5) All melting and boiling points are uncorrected. We are indebted to Mr. Saul Gottlieb for microanalyses.

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A. Lower Molecular Weight Aliphatic Aldehydes with Ethyl Cyanoacetate.—A mixture of ethyl cyanoacetate[6] (56.6 g., 0.5 mole), the freshly distilled aldehyde (0.6 mole), 1.0 g. of palladinized charcoal[7] and 80 ml. of glacial acetic acid was placed in a 500-ml. Pyrex bottle later to be used for the reduction. To this was added a solution of piperidine (2.0 ml., 0.02 mole) in 20 ml. of glacial acetic acid and hydrogenation at a pressure of 1 to 2 atmospheres was begun immediately.[8] Reduction was rapid and exothermic. In one to three hours the theoretical amount of hydrogen (0.5 mole) was taken up, and absorption ceased.

The ethyl alkylcyanoacetates were purified readily by distillation. The reaction mixture was filtered, 50 ml. of benzene was added, and the solution was washed with two 50-ml. portions of 10% sodium chloride solution followed by three 25-ml. portions of water. If emulsions were formed at this point, they were broken by the addition of a few ml. of ether. The washings were extracted with two small portions of benzene and the combined benzene solutions were distilled through a Widmer column under reduced pressure. No ethyl cyanoacetate was recovered in the forerun, and only a small distillation residue remained.

When aldol was the aldehyde used, 0.7 mole of hydrogen was absorbed (calcd., 0.5 mole) and 55.5 g. (66%) of ethyl *n*-butylcyanoacetate was obtained. The identity of this ester was established by analysis (*Anal.* Calcd. for $C_9H_{15}O_2N$: C, 63.98; H, 8.94. Found: C, 64.29; H, 8.88), and conversion into the amide, m. p. and mixed m. p. with a known sample 125.5–126.5°.[9]

B. Branched Chain, Higher Molecular Weight Aliphatic Aldehydes, and Benzaldehyde.—A mixture of ethyl cyanoacetate (56.6 g., 0.5 mole), the aldehyde (0.6 mole), glacial acetic acid (6.0 g., 0.05 mole) and 150 ml. of dioxane[10] was placed in a 500-ml. Pyrex bottle later to be used for the reduction and cooled in an ice–salt mixture to 4°. Piperidine (2.0 ml., 0.02 mole) was added dropwise to this solution during approximately ten minutes with occasional swirling. The temperature rose to 20° and the solution became turbid. When the addition was complete, 1.0 g. of palladinized charcoal was added and the mixture was hydrogenated as before. With the aliphatic aldehydes, heat was evolved and reduction was complete in about four hours. With benzaldehyde, hydrogen absorption was very slow even when the reaction was carried out at 60°. The esters were purified as in method A. In the reactions employing aliphatic aldehydes, no ethyl cyanoacetate was recovered and only small distillation residues were left. With benzaldehyde there was a forerun of ethyl cyanoacetate (8.0 g.) and considerable residue (35 g.).

C. Aliphatic Ketones with Ethyl Cyanoacetate.—Ethyl cyanoacetate (56.6 g., 0.5 mole), the ketone (0.55 mole), ammonium acetate (3.9 g., 0.05 mole), glacial acetic acid (6.0 g., 0.1 mole), 100 ml. of 95% ethanol and 1.0 g. of palladinized charcoal were placed in a 500-ml. Pyrex bottle and hydrogenated as before. These reductions were exothermic but to a lesser degree than those mentioned under methods A and B. The esters were purified as in method A.

Summary

Experimental conditions are described whereby a number of aldehydes and aliphatic ketones can be condensed with ethyl cyanoacetate and simultaneously hydrogenated in the presence of palladinized charcoal to obtain pure ethyl monoalkylcyanoacetates in good yield. Ammonium acetate and acetic acid were employed as the condensing agents with ketones, and piperidine acetate and acetic acid with aldehydes.

(6) Obtained from the Dow Chemical Company, Midland, Michigan.

(7) Hartung, THIS JOURNAL, **50**, 3372 (1928), subsequently modified by Dr. Hartung as follows. Ten ml. of a commercial palladium chloride solution containing 0.1 g. of palladium and approximately 0.05 g. of hydrogen chloride per ml. (obtained from the J. Bishop Company, Malvern, Pennsylvania) is added to a solution of 27 g. of sodium acetate trihydrate in 100 ml. of water. Norite (9 g.) is added and the mixture is hydrogenated until absorption ceases. The catalyst (10 g.) is filtered on a Büchner funnel, washed with water, dried by drawing air through the funnel for about thirty minutes and stored in a desiccator over calcium chloride.

(8) With propionaldehyde the yield of ethyl *n*-propylcyanoacetate dropped from 94 to 61% when the solution was allowed to stand for one hour before reduction was commenced. The yield of ethyl *n*-butylcyanoacetate was 87% when the reaction mixture stood for three hours before hydrogenating.

(9) Guareschi, *Atti Accad. sci. Torino*, **37**, 15 (1901); *Chem. Zentr.*, **73**, II, 700 (1902).

(10) Purified by boiling over sodium for forty-eight hours and redistilling.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

Some Derivatives of Phenothiazine

BY HENRY GILMAN AND DAVID A. SHIRLEY

The first attempt to apply a phenothiazine derivative as an antimalarial agent was made by Guttman and Ehrlich[1] in 1891, when they showed that methylene blue was an active chemotherapeutic agent against human malaria, and later work[2,3] substantiated this claim. As a part of the extensive antimalarial research carried out by the I. G. Farbenindustrie, Schuleman[4] modified the structure of methylene blue by replacing an N-methyl group with alkylaminoalkyl groupings. More recently Holcomb and Hamilton[5] prepared 3,7-di-(6′-methoxy-2′-methyl-4′-quinolyl)-thionine as a possible antimalarial, but no report is available of its pharmacological value.

These prior studies have been concerned with the oxidized or methylene blue types of phenothiazine. It seemed of interest to prepare some appropriately substituted, non-oxidized phenothiazines for testing in avian malaria. Phenothiazine and some of its simple derivatives have a significantly low toxicity for animals. The toxicity is still further reduced by the introduction of

(1) Guttman and Ehrlich, *Berlin klin. Wochschr.*, **28**, 953 (1891).

(2) Couto, *Arch. Schiffs- u. Tropen-Hyg.*, **30**, 275 (1926).

(3) Fourneau, Trefouel, Bovet and Benoit, *Ann. inst. Pasteur*, **46**, 520 (1931).

(4) Schuleman, *Proc. Roy. Soc. Med.*, **25**, 897 (1932); German Patent 588,945 [*C. A.*, **24**, 2242 (1930)]; German Patent 490,275 [*C. A.*, **24**, 2241 (1930)].

(5) Holcomb and Hamilton, THIS JOURNAL, **64**, 1309 (1942).

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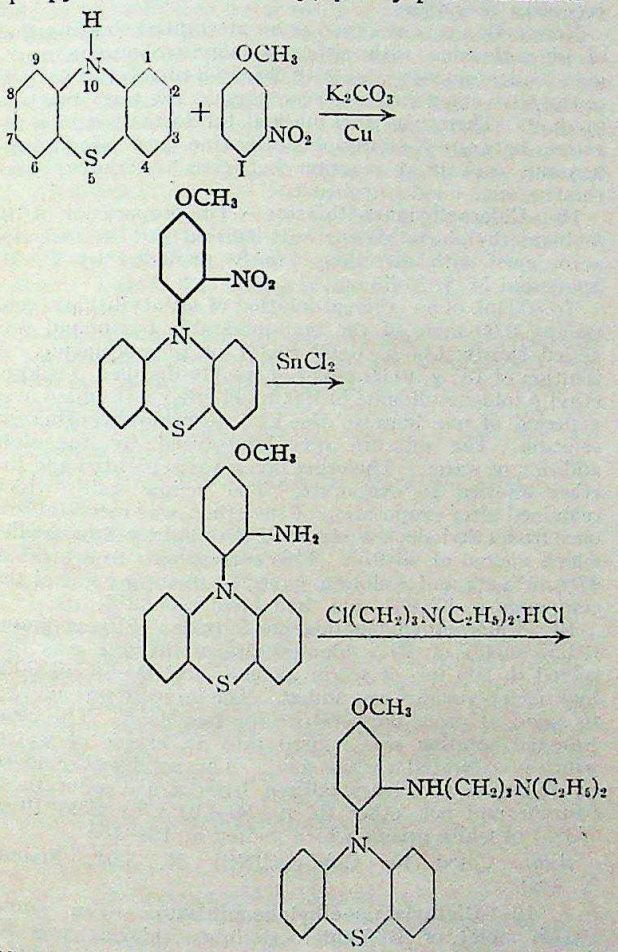
substituents in the 10-position.[6] For this reason, and also because of the opportunity of introducing some nuclear substituents like chlorine and methoxy groups which are present in atabrine, some substituted 10-phenylphenothiazine derivatives were prepared. Some of these had the generally desirable dialkylaminoalkylamino group, and the following typical series of reactions illustrates the synthesis of 10-(2′-γ-diethylaminopropylamino-4′-methoxy)-phenylphenothiazine



None of these compounds showed antimalarial activity with the exception of 10-(4′-γ-diethylaminopropylamino)-phenylphenothiazine, which had a doubtful activity at a daily dosage of twelve and one-half milligrams.

A series of phenothiazine derivatives was prepared which contained a basic alkylaminoalkyl group attached to the nitrogen of phenothiazine. These compounds were prepared by the following reactions in which the synthesis of 10-γ-diethylaminopropylphenothiazine is an illustration (RN- is the phenothiazyl radical).

$$\text{RNH} \xrightarrow[\text{(2) } p\text{-}CH_3C_6H_4SO_3(CH_2)_3Cl]{\text{(1) } n\text{-}C_4H_9Li} \xrightarrow[\text{(3) } H_2O]{} \text{RN—}(CH_2)_3Cl \xrightarrow{(C_2H_5)_2NH} \text{RN—}(CH_2)_3N(C_2H_5)_2$$

(6) Schaffer, Haller and Fink, *J. Econ. Entomol.*, **30**, 361 (1937).

There were also prepared two derivatives of this type which contained a methoxyl group in the 3-position. These compounds were prepared by the same series of reactions shown above, starting with 3-methoxyphenothiazine which was prepared from 4-methoxydiphenylamine by ring closure with sulfur. None of these derivatives showed any activity.

In addition, tests were carried out on a miscellany of phenothiazine derivatives which were prepared either during the course of the investigation on the metalation of phenothiazine[7] or as intermediates in the synthesis of the compounds containing groups likely to impart or increase antimalarial action. This group of compounds, listed in the Experimental Part, was also without activity.

Experimental

10-(2′-Nitro)-phenylphenothiazine.—Twenty grams (0.1 mole) of phenothiazine, 37 g. (0.15 mole) of *o*-iodonitrobenzene, 100 ml. of xylene, 15 g. of potassium carbonate, and 1 g. of copper bronze were refluxed with stirring for ten hours. The mixture was cooled, filtered and the residue extracted with water. The residue was recrystallized from a mixture of benzene and petroleum ether (b. p. 80–110°) to give 14 g. (44%) of yellow-brown prisms which melted at 156–157°.

Anal. Calcd. for $C_{18}H_{12}O_2N_2S$: N, 8.75. Found: N, 8.66.

10-(2′-Amino)-phenylphenothiazine.—Five grams (0.015 mole) of 10-(2′-nitro)-phenylphenothiazine, 10 g. of granulated tin, and 20 ml. of water were stirred and refluxed for one-half hour during which 75 ml. of concd. hydrochloric acid was added. The mixture was stirred and heated for an additional one-half hour. The organic matter was removed by filtration and recrystallized from alcohol. Another recrystallization from petroleum ether (b. p. 80–110°) gave 4.5 g. (95%) of light yellow needles melting at 139–139.5°.

Anal. Calcd. for $C_{18}H_{14}N_2S$: N, 9.65. Found: N, 9.66.

γ-Diethylaminopropyl Chloride Hydrochloride.—The general procedure for the preparation of γ-diethylaminopropyl chloride hydrochloride was kindly furnished by Dr. R. R. Burtner and represents a modification of the procedure of Slotta and Behnisch.[8]

A mixture of 1200 ml. of chloroform and 290 g. (2.43 moles) of thionyl chloride was immersed in an ice-bath, and to this was added (one hour) a solution of 157 g. (1.20 moles) of γ-diethylaminopropanol in 260 ml. of chloroform. The mixture was refluxed for three hours, after which the solvent and excess thionyl chloride were removed by distillation. The residue was treated cautiously with 300 ml. of 40% sodium hydroxide solution and extracted with 2 liters of ether. The ethereal solution was dried over anhydrous sodium sulfate and then evaporatively distilled. The residue distilled as a colorless oil at 73–75° (20 mm.). The yield was 131 g. (73%).

The hydrochloride is a white, extremely hygroscopic powder which melts at 66–68°. Magidson and Strukov[9] reported the compound to melt at 62–64°.

10-(2′-γ-Diethylaminopropylamino)-phenylphenothiazine.—Four grams (0.013 mole) of 10-(2′-amino)-phenylphenothiazine and 2.5 g. (0.014 mole) of γ-diethylaminopropyl chloride hydrochloride were heated for fifteen hours in a test-tube immersed in a metal bath at 130–140°. The dark red viscous product was extracted with hot 2% hydrochloric acid. The acidic extracts were made alkaline

(7) Gilman, Shirley and Van Ess, THIS JOURNAL, **66**, 625 (1944); Gilman, Van Ess and Shirley, *ibid.*, **66**, in press (1944).

(8) Slotta and Behnisch, *Ber.*, **68**, 754 (1935).

(9) Magidson and Strukov, *Arch. Pharm.*, **271**, 569 (1933).

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with concentrated sodium hydroxide solution and extracted with ether. The ethereal extract was dried over anhydrous sodium sulfate and evaporatively distilled. The residual oil was distilled at less than 0.5 mm. pressure. It boiled at 215–230° and was a yellow-green, fluorescent, highly viscous oil. The yield was 2.7 g. or 49%.

Anal. Calcd. for $C_{25}H_{29}N_3S$: N, 10.41. Found: N, 10.54.

TABLE I

10-(γ-DIETHYLAMINOPROPYLAMINO)-PHENYLPHENOTHIAZINES AND THEIR PRECURSORS

10-Substituent	M. p., °C.	Yield, %	N Analyses, % Calcd.	Found
-(4′-nitro)-phenyl-[a]	157	33	8.75	8.77
-(4′-amino)-phenyl-[b]	132–133	85	9.65	9.41
-(4′-γ-diethylaminopropyl amino)-phenyl	[c]	42	10.41	10.50
-(2′-nitro-4′-methyl)-phenyl-[d]	179.5–180	36	8.40	8.47
-(2′-amino-4′-methyl)-phenyl-[e]	140–140.5	81	9.20	9.45
-(2′-γ-diethylaminopropyl-amino-4′-methyl)-phenyl	[f]	45	10.08	10.09
-(2′ nitro-4′-methoxy)-phenyl-[g]	184–186	26	8.00	7.85
-(2′-amino-4′-methoxy)-phenyl[h]	180–181	57	8.75	8.74
(2′-γ-diethylaminopropyl-amino-4′-methoxy)-phenyl	[i]	47	9.70	9.60
-(2′-methoxy-4′-nitro)-phenyl-[j]	159–160	36	8.00	8.06
(2′-nitro-4′-chloro)-phenyl-[k]	185–186.5	21	7.90	8.10
-(2′-amino-4′-chloro)-phenyl-[l]	125.5–126	38	8.65	8.45
-(2′-γ-diethylaminopropyl-amino-4′-chloro)-phenyl-	[m]	47	9.61	9.62

[a] Prepared from phenothiazine (0.1 mole) and *p*-iodonitrobenzene (0.15 mole); crystallized first from ethanol, then from benzene; yellow prisms. [b] The nitro compound was reduced by tin and hydrochloric acid. Crystallization from petroleum ether (b. p., 80–110°) gave yellow prisms; yield in first run was 46%. [c] The product was distilled at less than 0.5 mm. with a bath temperature of 350°, and was a yellow "glass." [d] Prepared from phenothiazine (0.1 mole) and 3-nitro-4-iodotoluene (0.12 mole). The 3-nitro-4-iodotoluene was prepared in 88% yield by treating the diazotized 3-nitro-4-aminotoluene with potassium iodide in accordance with some general directions of Beilstein and Kuhlberg, *Ann.*, **158**, 344 (1872). The brownish crystals of the product were obtained from glacial acetic acid, and a mixed m. p. with phenothiazine (m. p. 180–181°) was below 150°. [e] Reduction was effected by adding a hot solution of stannous chloride in concd. hydrochloric acid to a hot glacial acetic acid suspension of the nitro compound. Crystallization was from petroleum ether (b. p., 80–110°). [f] The product distilled at a bath temp. of 270° under a pressure of less than 0.5 mm., and was a yellow oil with a green fluorescence. [g] Prepared (first in 24% and then in 26% yield) from phenothiazine (0.1 mole) and 3-nitro-4-iodoanisole (0.12 mole). The latter was prepared in 92% yield from diazotized 3-nitro-4-aminoanisole in general accordance with the directions of Reverdin, *Ber.*, **29**, 2595 (1896). [h] Reduction was effected by stannous chloride and concd. hydrochloric acid; the yield in a first preparation was 53%. Crystallization from benzene gave small olive-green prisms. [i] The product distilled at 220–235° at a pressure less than 0.5 mm., and was a yellow-red oil. [j] Prepared from phenothiazine (0.1 mole) and 2-iodo-5-nitroanisole (0.15 mole). The orange-red plates were obtained by first crystallizing from acetic acid and then from a mixture of benzene and petroleum ether (b. p., 80–110°). The m. p. of 5-nitro-2-iodoanisole (prepared by diazotization) was 130–131° instead of 127–128° reported previously by Meldola and Eyre, *Proc. Chem. Soc.*, **17**, 131 (1901). An attempted reduction of 10-(2′-methoxy-4′-nitro)-phenylphenothiazine by stannous chloride gave a mixture which has not been resolved by crystallization. [k] Prepared from phenothiazine (0.1 mole) and 2-nitro-4-chloroiodobenzene (0.125 mole). Crystallization from acetic acid gave brown prisms. The 2-nitro-4-chloroiodobenzene was obtained in 96% by the procedure of Körner, *Gazz. chim. ital.*, **4**, 381 (1874). [l] Reduction was by stannous chloride, and there was appreciable tar formation. Crystallization was from benzene and then from pet. ether (b. p., 80–110°). [m] The product distilled over the range 270–280° (2 mm.) as a yellow oil.

Preparation of 10-(γ-Diethylaminopropylamino)-phenylphenothiazines.—The nitro-, the amino- and the γ-diethylaminopropylamino-phenylphenothiazines described in Table I were prepared in general accordance with the directions just given for the preparation of 10-(2′-γ-diethylaminopropylamino)-phenylphenothiazine and its necessary precursors.

No reaction was observed in an attempted condensation of phenothiazine with either *m*-iodonitrobenzene or 2-iodo-5-nitrotoluene; and with 2-iodo-3-nitrotoluene, 24% of the nitro compound was recovered in the tarry reaction product. There was also marked tar formation in a reaction between 3-methylphenothiazine and *o*-iodonitrobenzene, and in a reaction between 3-methoxyphenothiazine and *o*-iodonitrobenzene.

10-β-Chloroethylphenothiazine.—The preparation of 10-β-chloroethylphenothiazine was carried out in essential accordance with directions kindly provided by S. M. Spatz and M. J. Kolbezen.

To 600 ml. of an ethereal solution of *n*-butyllithium containing 0.69 mole of the organometallic compound was added slowly 137 g. (0.69 mole) of phenothiazine. A solution of 151 g. (0.69 mole) of freshly distilled β-chloroethyl *p*-toluenesulfonate in 100 ml. of ether was added over a period of one hour to the iced 10-lithiophenothiazine solution. The mixture was hydrolyzed by the slow addition of water. The ether layer was separated and the ether allowed to evaporate. The yellow solid, which remained after evaporation of the ether, was recrystallized once from ethyl alcohol to give 85 g. of light yellow needles which melted at 96–97°. This corresponds to a yield of 47%. Spatz and Kolbezen gave the melting point of the compound as 97–98°, and their yield was 62%.

10-β-Chloroethylphenothiazine-5-oxide.—Fifteen grams (0.057 mole) of 10-β-chloroethylphenothiazine was dissolved in 500 ml. of warm alcohol, and 50 ml. of 30% hydrogen peroxide[10] was added. The mixture was allowed to stand at room temperature for two days. The clear wine-red solution was poured into an excess of water, which precipitated a white solid. This solid was removed by filtration and recrystallized from a 1:1 mixture of benzene and pet. ether (b. p., 80–110°) to yield 10 g. (63%) of white prisms which melted at 154–155°.

Anal. Calcd. for $C_{14}H_{12}OClNS$: N, 5.04. Found: N, 4.80.

10-β-Diethylaminoethylphenothiazine.—Ten grams (0.038 mole) of 10-β-chloroethylphenothiazine was refluxed with 30 ml. of diethylamine in the presence of 1.0 g. of copper bronze for sixty hours. The reaction mixture was dissolved in dilute hydrochloric acid and this solution was made strongly alkaline with sodium hydroxide. The mixture was extracted with ether and the combined extracts dried over sodium sulfate. Evaporative distillation of the dried ethereal solution followed by a vacuum distillation of the residue gave a yellow oil boiling at 161–165° at a pressure of less than 0.5 mm. The yield was 7.6 g. (67%).

Anal. Calcd. for $C_{18}H_{22}N_2S$: N, 9.40. Found: N, 9.46.

Table II lists other 10-β-aminoethylphenothiazines prepared in an analogous manner.

The condensation of β-chloroethylphenothiazine (0.038 mole) and 8-amino-6-methoxyquinoline (0.114 mole) was effected by heating with 1.0 g. of copper powder for five hours in a nitrogen atmosphere at 140–150°.

10-γ-Chloropropylphenothiazine.—10-γ-Chloropropylphenothiazine was prepared in a manner analogous to the preparation of 10-β-chloroethylphenothiazine from 10-lithiophenothiazine and γ-chloropropyl *p*-toluenesulfonate.

(10) Kehrmann and Diserens, *Ber.*, **48**, 318 (1915).

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TABLE II

10-(β-AMINOETHYLPHENOTHIAZINES)

10-Substituent	B. p., °C.	Yield, %	N Analyses, % Calcd.	Found
-β-dipropylaminoethyl-[a]	225–230 (1 mm.)	77	8.59	8.50
-β-morpholinoethyl-[b]	198–201 (< 0.5 mm.)	71	8.97	8.95
-β-(6′-methoxy-8′-quinolyl)-aminoethyl-	[c]	12	10.53	10.82

[a] The product was a light yellow oil. [b] The light yellow, viscous oil solidified to a white crystalline mass which melted at 74.5–75.5°. [c] The red, viscous oil distilled over the range 310–330° at a pressure less than 0.5 mm. This oil was extracted several times with pet. ether (b. p., 80–110°), and evaporation of the solvent gave a mixture of oil and yellow crystals. Recrystallization from a mixture of benzene and pet. ether, and then from pet. ether (b. p., 80–110°), gave light yellow prisms melting at 118.5–119.5°.

The product crystallized from methanol in the form of white prisms melting at 60°. The yield was 32%.

Anal. Calcd. for $C_{15}H_{14}ClNS$: N, 5.08. Found: N, 5.23.

10-γ-Diethylaminopropylphenothiazine.—The reaction of 10-γ-chloropropylphenothiazine and diethylamine was carried out as previously described under the preparation of 10-β-diethylaminoethylphenothiazine. The product was a yellow oil boiling at 170–182°/< 0.5 mm. and was obtained in a yield of 68%.

Anal. Calcd. for $C_{19}H_{24}N_2S$: N, 8.97. Found: N, 9.18.

The *dipicrate* derivative separated from the alcohol as yellow prisms which melted at 103–104°.

Anal. Calcd. for $C_{31}H_{30}O_{14}N_8S$: N, 14.56. Found: N, 14.80.

It was attempted to prepare 10-γ-diethylaminopropylphenothiazine by the condensation of γ-diethylaminopropyl chloride or its hydrochloride with phenothiazine, but only unchanged phenothiazine or tarry product was isolated in two attempts. Also unsuccessful was an attempt to use γ-diethylaminopropyl bromide hydrobromide in the preparation of this compound.

Table III lists other 10-γ-aminopropylphenothiazines prepared by a corresponding procedure.

TABLE III

10-(γ-AMINOPROPYLPHENOTHIAZINES)

10-Substituent	B. p., °C.	Mm.	Yield, %	N Analyses, % Calcd.	Found
-γ-dipropylaminopropyl-[a]	257–262	2	57	8.25	8.17
-γ-diallylaminopropyl-[b]	245–260	1	53	8.34	8.57
γ-piperidylpropyl-[c]	255–265	1–2	33	8.65	8.90

[a] Reaction was effected by refluxing, in the presence of copper powder, for twenty hours. The product was a light yellow oil. [b] The reflux period was twenty-six hours, and the product was a yellow oil. [c] The reflux period for this condensation with piperidine was fifty hours, and the product was a dark yellow, viscous oil.

3-Methoxyphenothiazine.—This compound was prepared by the action of sulfur on 4-methoxydiphenylamine.

4-Methoxydiphenylamine was prepared by treating acetyl-*p*-anisidine with excess bromobenzene in the presence of sodium carbonate and copper powder, followed by treatment with dilute hydrochloric acid in order to remove the acetyl group. The yields in two runs were 31 and 48%. The product was separated as steel-gray needles which melted at 106°. Wieland and Wecker[11] gave 105° as the melting point.

An intimate mixture of 37.5 g. (0.189 mole) of 4-methoxydiphenylamine, 12.5 g. (0.378 g. atom) of sulfur, and 1 g. of iodine as a catalyst was placed in a distilling flask immersed in a metal bath. The temperature of the bath was raised to 140–150°. Evolution of hydrogen sulfide began at this temperature and continued for thirty minutes. The reaction mixture was then heated to 175° over a period of fifteen minutes as the evolution of hydrogen sulfide slackened. The black fluid was poured into a mortar and allowed to solidify. The solid cake was then ground up to a yellow powder, which was placed in a Soxhlet extractor and extracted with pet. ether (b. p., 80–110°) for fifty hours. Nineteen and one-half grams of yellow powder melting at 158–159° separated from the pet. ether, which corresponded to a yield of 45%. A second run gave a yield of 51%. Pummerer and Gassner[12] gave 163° as the melting point of 3-methoxyphenothiazine; however, Kehrmann,[13] who later prepared the same compound, reported the melting point as 159°.

3-Methoxy-10-γ-di-*n*-propylaminopropylphenothiazine.—Four grams (0.0131 mole) of crude 3-methoxy-10-γ-chloropropylphenothiazine[14] was refluxed with 15 ml. of di-*n*-propylamine and 0.2 g. of copper bronze for eight hours. The reaction mixture was treated as previously described under the preparation of 10-γ-diethylaminopropylphenothiazine. The product distilled over the range 250–265° (2 mm.). The yield of red oil was 3.2 g. (66%).

Anal. Calcd. for $C_{22}H_{30}ON_2S$: N, 7.56. Found: N, 7.72.

3-Methoxy-10-γ-diethylaminopropylphenothiazine.—Eight grams (0.0262 mole) of the crude 3-methoxy-10-γ-chloropropylphenothiazine was refluxed for ten hours with 30 ml. of diethylamine and 0.2 g. of copper bronze. The product distilled at 220–225° at a pressure of less than 0.5 mm. as a dark yellow oil with a strong green fluorescence. The yield was 4.4 g. (49%).

Anal. Calcd. for $C_{20}H_{26}ON_2S$: N, 8.20. Found: N, 8.46.

3-Methoxy-10-acetylphenothiazine.—Two grams (0.0087 mole) of 3-methoxyphenothiazine was refluxed for four and one-half hours with 50 ml. of acetic anhydride. The solution was poured into excess water, which precipitated a white solid. The solid was removed by filtration and refluxed with enough petroleum ether (b. p. 80–110°) to effect solution. Cooling the petroleum ether solution precipitated two crops of oil from which the clear supernatant solution was decanted. The solution then deposited 0.5 g. (22%) of white rosets which melted at 121–121.5°.

Anal. Calcd. for $C_{15}H_{13}O_2NS$: N, 5.16. Found: N, 5.24.

3-Methylphenothiazine.—3-Methylphenothiazine was prepared by the action of sulfur on 4-methyldiphenylamine.

The preparation of 4-methyldiphenylamine was carried out by the method of Weston and Adkins,[15] in yields of 27 and 28%.

For the conversion of 4-methyldiphenylamine to 3-methylphenothiazine, an intimate mixture of 72 g. (0.394 mole) of 4-methyldiphenylamine, 25.3 g. (0.788 g. atom) of sulfur, and 1 g. of iodine were heated to a temperature of 280° over a period of twenty minutes. The liquid melt was allowed to solidify before being ground up in a mortar to a green powder. This material, which was obtained in a quantitative yield, melted at 160–162°. Two recrystallizations from benzene raised the melting point to 166–168°.

Anal. Calcd. for $C_{13}H_{11}NS$: N, 6.57. Found: N, 6.66.

3,7-Dinitro-10-acetylphenothiazine-5-oxide.—10-Acetylphenothiazine was prepared according to Bernthsen.[16]

(11) Wieland and Wecker, *Ber.*, **43**, 708 (1910).

(12) Pummerer and Gassner, *ibid.*, **46**, 2325 (1913).

(13) Kehrmann, *ibid.*, **48**, 327 (1915).

(14) This was prepared from the 3-methoxy-10-lithiophenothiazine and γ-chloropropyl *p*-toluenesulfonate as a viscous orange oil which was intractable to both distillation and crystallization.

(15) Weston and Adkins, THIS JOURNAL, **50**, 862 (1928).

(16) Bernthsen, *Ann.*, **230**, 77 (1885).

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The nitration of 10-acetylphenothiazine was attempted according to the directions of Bernthsen,[16] and it was found that no reaction occurred under these conditions. The following procedure was found satisfactory for the preparation of 3,7-dinitro-10-acetylphenothiazine-5-oxide.

Fifty grams (0.25 mole) of phenothiazine was suspended in 400 ml. of glacial acetic acid and 125 ml. of concd. nitric acid was added over a period of fifteen minutes. Upon standing the solution precipitated 40 g. (46%) of yellow-tan powder which melted with decomposition at 265–267°. Bernthsen[16] gives no melting point for his nitration product.

Anal. Calcd. for $C_{14}H_9O_6N_3S$: N, 12.03. Found: N, 12.21.

3-Nitro-10-ethylphenothiazine-5-oxide.—Kehrmann and Zybs[17] nitrated 10-methylphenothiazine and obtained 3-nitro-10-methylphenothiazine-5-oxide. 10-Ethylphenothiazine was nitrated using the general procedure developed by these workers. The 10-ethylphenothiazine was prepared by the reaction of ethyl bromide and phenothiazine in a steel bomb.[18]

Ten grams (0.044 mole) of 10-ethylphenothiazine was dissolved in 250 ml. of glacial acetic acid, and to this solution was added 10 ml. of concd. nitric acid dissolved in 40 ml. of glacial acetic acid. The mixture was allowed to stand for two days, and the clear yellow solution was poured into excess water. A bright yellow powder which melted at 202–204° was precipitated in a quantitative yield. One recrystallization of the product from a 1:1 mixture of alcohol and glacial acetic acid gave minute canary-yellow crystals which melted at 204.5–205°. Analysis showed this to be a mononitro-10-ethylphenothiazine-5-oxide, and by analogy to the nitration of 10-methylphenothiazine, it was assumed that nitration had occurred in the reactive 3-position of phenothiazine.

Anal. Calcd. for $C_{14}H_{12}O_3N_2S$: N, 9.72. Found: N, 9.82.

10-Allylphenothiazine.—A mixture of 50 g. (0.25 mole) of phenothiazine, 60 g. (0.50 mole) of allyl bromide, 50 ml. of benzene, 20 g. of sodium carbonate, and 2 g. of copper powder was stirred and refluxed for six hours. The hot mixture was filtered and the filtrate was distilled to remove the benzene and excess allyl bromide. The residual oil was distilled at 187–195° (1 mm.), and 37 g. (62%) of product was collected as a light brown oil.

Anal. Calcd. for $C_{15}H_{13}NS$: N, 5.86. Found: N, 5.91.

10-Decylphenothiazine.—A mixture of 50 g. (0.25 mole) of phenothiazine, 55 g. (0.25 mole) of *n*-decyl bromide, 25 g. of sodium carbonate, and 2 g. of copper powder was stirred and heated in an oil-bath at 170–180° for eleven hours. The cooled reaction mixture was extracted with ether, and the combined ether extracts were dried over anhydrous sodium sulfate and the ether removed by evaporative distillation. The residue was distilled at 1 mm. pressure and 21.5 g. of yellow oil was collected at 225–235°. This was redistilled at less than 0.5 mm. pressure, and 8.0 g. (9.4%) of yellow oil was collected at 183–185°.

Anal. Calcd. for $C_{22}H_{29}NS$: N, 4.13. Found: N, 4.16.

3-Nitro-10-decylphenothiazine-5-oxide.—Ten grams (0.295 mole) of 10-decylphenothiazine was dissolved in 75 ml. of glacial acetic acid and 10 ml. of concd. nitric acid in 75 ml. of acetic acid was added with shaking over a period of ten minutes. The mixture was allowed to stand for two days, and was then poured into excess water. The precipitated yellow solid was recrystallized from pet. ether (b. p. 60–68°) to give 4.0 g. (34%) of bright yellow prisms which melted at 102.5–103°.

Anal. Calcd. for $C_{22}H_{28}O_3N_2S$: N, 7.00. Found: N, 7.34.

(17) Kehrmann and Zybs, *Ber.*, **52**, 130 (1919).

(18) Gilman, Van Ess and Shirley, THIS JOURNAL, **66**, in press (1944).

10-Octadecylphenothiazine.—A mixture of 30 g. (0.09 mole) of *n*-octadecyl bromide, 17.9 g. (0.09 mole) of phenothiazine, 10 g. of anhydrous sodium carbonate, and 1 g. of copper powder was heated at 170–180° for twelve hours. The mixture was extracted with ether. The combined ether extracts were dried over anhydrous sodium sulfate and then evaporatively distilled. The residual oil was distilled at a pressure of less than 0.5 mm., and gave 18 g. of yellow oil boiling at 290–300°. Upon cooling, this oil solidified to a waxy solid which was recrystallized from ethanol to give 8.2 g. (20%) of minute, white needles which melted at 53°.

Anal. Calcd. for $C_{30}H_{45}NS$: N, 3.11. Found: N, 3.06.

10-Octadecylphenothiazine-5-oxide.—Five grams (0.011 mole) of 10-octadecylphenothiazine was dissolved in 600 ml. of hot alcohol and 30 ml. of 30% hydrogen peroxide solution was added to the mixture. The solution was heated to boiling for several minutes, and then allowed to stand at room temperature for two days. Pouring the reaction mixture into water precipitated 4.2 g. of a pink powder which upon recrystallization from pet. ether (b. p. 80–110°) gave 2.7 g. (53%) of light pink to white plates which melted at 98°.

Anal. Calcd. for $C_{30}H_{45}ONS$: N, 3.00. Found: N, 3.07.

10-Phenylphenothiazine-5-oxide.—Two grams (0.0073 mole) of 10-phenylphenothiazine was dissolved in 50 ml. of hot alcohol and treated with 5 ml. of 30% hydrogen peroxide as in the preparation of 10-octadecylphenothiazine-5-oxide. The product melted at 170–171° after recrystallization from a mixture of benzene and pet. ether (b. p. 80–110°) and consisted of white prisms. The yield was 1.5 g. (71%).

Anal. Calcd. for $C_{18}H_{13}ONS$: N, 4.81. Found: N, 4.66.

3-Nitro-10-phenylphenothiazine-5-oxide.—Ten grams (0.036 mole) of 10-phenylphenothiazine was suspended in 75 ml. of glacial acetic acid, and a solution of 10 ml. of concd. nitric acid in 75 ml. of acetic acid was added. The mixture was allowed to stand for two days and then was poured into water. The precipitated yellow solid was recrystallized once from ethanol and once from a mixture of ethanol and acetic acid to yield 8.5 g. (70%) of yellow minute crystals melting at 223.5–224.5°.

Anal. Calcd. for $C_{18}H_{12}O_3N_2S$: N, 8.33. Found: N, 8.51.

Pharmacological Tests.—The authors are grateful to Parke, Davis and Company for arranging for the tests on experimental avian malaria. In addition to the compounds mentioned in the Introduction, the following phenothiazine derivatives were tested, and showed no activity: 10-(4′-carboxy)-phenyl-; 3-methyl-; 1-carboxy-; 3-nitro-10-phenyl-5-oxide; 10-methyl-; 10-β-chloroethyl-; 10-phenyl-; 10-allyl-; 10-decyl-; 10-octadecyl-; and phenothiazine.

In connection with the decrease in toxicity of some derivatives substituted in the 10-position, the following information on the lethal dose for canaries in milligrams (in parentheses) is of interest: phenothiazine (20), 3-methylphenothiazine (50), 10-phenylphenothiazine (>50), and 10-phenyl-3-nitrophenothiazine-5-oxide (100).

The relatively low toxicity of phenothiazine and many of its derivatives suggests an examination of some non-oxidized types containing, in addition to a basic side chain, two nuclear substituents drawn from groups like methyl, methoxyl, chloro, or diethylamino. In particular, a compound patterned somewhat after atabrine and containing a methoxyl and a chlorine might help provide more decisive information on the possibilities of effective non-oxidized phenothiazine types.

Summary

The relatively low toxicity of phenothiazines suggested an examination in avian malaria of a miscellany of non-oxidized phenothiazine derivatives containing a basic side-chain and, parti-

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cularly, substituents on the nitrogen. Of the compounds synthesized and tested, only one had any activity [10-(4′-γ-diethylaminopropylamino)-phenylphenothiazine], and this was of a doubtful nature.

AMES, IOWA RECEIVED FEBRUARY 1, 1944

[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY OF THE ETHYL CORPORATION]

Zinc Alkyls from Secondary Alkyl Halides

BY HAROLD SOROOS AND MORLEY MORGANA

Of zinc alkyls derived from secondary alkyl halides, the literature reports the preparation of only one, diisopropylzinc.[1] In the reported preparations of this compound, isopropyl iodide was added all at once to zinc or zinc–copper couple, and heat was applied. The yields were low, and mainly gaseous products were obtained. Recent attempts to repeat and confirm this work, by methods known to be successful for the preparation of zinc alkyls from primary halides, were unsuccessful.[2]

Recently, in studies conducted in this Laboratory, it was found that both diisopropylzinc[3] and di-*s*-butylzinc could be obtained in essentially as good yields as the zinc alkyls derived from primary alkyl halides, by a modification of Noller's procedure.[2] The method consists simply of adding a mixture of the secondary alkyl bromide and iodide slowly with stirring under controlled temperature conditions to an excess of zinc–copper couple, followed by distillation of the reaction mixture at as low a temperature and pressure as possible.

In contrast to the preparation of zinc alkyls from primary alkyl halides, the reaction with the secondary halides starts easily and proceeds smoothly if properly controlled. Only a trace of gas is formed, and the reaction mixture consists of a clear oily liquid[4] and the excess couple. Distillation of the reaction mixtures under reduced pressure gives the zinc alkyls in good yield.

Both compounds are spontaneously inflammable and somewhat less stable than the primary analogs, decomposing slowly in diffused daylight with the deposition of metallic zinc.

(1) Bohm (*J. Russ. Phys.-Chem. Soc.*, **31**, 46 (1899); *Chem. Zentr.*, **70**, I, 1067 (1899)) reports obtaining diisopropylzinc in 25% yield from isopropyl iodide and zinc; Gladstone and Tribe (*J. Chem. Soc.*, **26**, 961 (1873)) obtained the compound in 13% yield from isopropyl iodide and zinc-copper couple; Ragosin (*J. Russ. Phys.-Chem. Soc.*, **24**, 549 (1892); *Ber.*, **26** (Ref.), 380 (1893)) obtained the compound by interaction of isopropyl iodide in ether with zinc and a small amount of sodium–zinc alloy.

(2) Noller, THIS JOURNAL, **51**, 594 (1929).

(3) The preparation of this compound was investigated in a study sponsored and supported by the National Advisory Committee for Aeronautics.

(4) The oily liquid is apparently the RZnX compound, which on subsequent heating disproportionates to R_2Zn and ZnX_2. It was necessary to heat the reaction mixtures at 1 mm. to considerably higher temperatures than required for distillation of the zinc alkyls alone before the latter distilled from the reaction mixtures. Also, the liquid was observed to be considerably more stable toward oxidation on exposure to air than the zinc alkyls.

Experimental

Zinc–Copper Couple.—A wrought-iron alloy pot, flushed with nitrogen, was charged with 3319 g. (51 g. atoms) of zinc and 369 g. (3.55 g. atoms Cu, 2.11 g. atoms Zn) of Tobin bronze brazing rod, and loosely covered. The mass was heated to 600° with an oxy-acetylene torch and shaken vigorously for five minutes, maintaining the temperature at 600°. The melt was discharged into a one-inch iron pipe mold, cooled in air, and finally quenched in water. The rod was machined into turnings without the use of cutting oil. *Anal.*[5] Zn, 94.5; Cu, 5.86.

Diisopropylzinc.—To a 500-ml., 3-neck flask, equipped with a reflux condenser, an efficient stirrer, and a Hershberg dropping funnel, was added 104.5 g. (98.9 g. Zn, 1.5 g. atom) of zinc–copper couple turnings. The system was evacuated to 1 mm. while stirring and warming gently with a free flame, and then flushed several times with dry nitrogen. A trap cooled in dry-ice was connected to the outlet of the reflux condenser and a mixture of 61.5 g. (0.5 mole) of isopropyl bromide and 85.0 g. (0.5 mole) of isopropyl iodide was added to the dropping funnel. A water-bath at 50° was raised around the flask and the stirrer started. About 2 ml. of the alkyl halide mixture was added rapidly. Within two minutes, reaction had started as shown by a trace of white fumes, a darkening of the couple, and the oily appearance of the liquid on the walls of the flask. The 50° bath was replaced by a water-bath at 20°, and dropwise addition of the halides was started. The drop rate was adjusted so that addition was complete in five and one-half hours. At this rate not more than 0.5 ml. of liquid collected in the trap; a faster rate caused undue gas formation as shown by liquid in the dry-ice trap. After addition, stirring was continued for 30 minutes. The reaction mixture consisted of a clear, colorless, liquid and the almost black excess zinc–copper couple.

For distillation of the diisopropylzinc, one neck of the three-neck flask was stoppered, the other was equipped with a simple distillation head and thermometer, and the rubber sleeve of the stirrer was wired to the shaft. Three traps were placed in series, the first two being equipped with Vaseline-lubricated stopcocks, all being large enough so that freezing of the distillate would not cause plugging. With the first two traps at room temperature and the third in liquid nitrogen, the system was slowly evacuated to 1 mm. Low-boiling material was collected in the cold trap until ebullition ceased in the flask. The first two traps were then cooled in a dry-ice mixture at −65° and an oil-bath, placed around the flask, was heated rapidly to about 100°. The oil-bath was maintained at 90–140° for forty-five minutes until distillation was almost complete, at the end of which time it was raised to 200° to remove the last trace of product. It was necessary to maintain the oil pump on the system throughout, owing to some pyrolytic decomposition. Without the liquid nitrogen trap, an oil pump would not maintain a pressure of 1 mm. and the yield was lowered. The residue was a

(5) Spectrographic analysis of the zinc used in this preparation, kindly obtained for us by Dr. F. L. Howard of the National Bureau of Standards, showed the metal to contain trace amounts (less than 0.01%) of Au, Ba, Cd, Cu, Fe, Mg, Mn, Ni, Pb, and Si.

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hard, gray cake. The yield of crude product was 64.2 g. (0.42 mole), or 85% based on the isopropyl halides.

The boiling points of a middle fraction of redistilled material at various pressures were obtained by distillation of a sample through a short Stedman column. The relation between temperature and pressure (in mm.) is given to within ±1.0 mm., which is within the accuracy of the measurements, by the equation $\log P = 7.987 - 1858/(t + 230)$.

Di-*s*-butylzinc.—By a procedure similar to that described above, di-*s*-butylzinc was prepared from 68.5 g. (0.5 mole) of *s*-butyl bromide, 92.0 g. (0.5 mole) of *s*-butyl iodide, and 140 g. (132 g. Zn, 2.0 g. atom) of zinc–copper couple. The starting temperature was 60°, and the reaction temperature 25°. The yield of crude product was 64.5 g. (0.36 mole), or 72%. On redistillation, the material distilled at 56° at 4 mm. *Anal.* Calcd. for $(C_4H_9)_2Zn$: Zn, 36.4. Found: Zn, 36.1.

Summary

Diisopropylzinc and di-*s*-butylzinc have been prepared from zinc–copper couple and secondary alkyl halides in good yield by a modification of the procedure usually used for preparation of the primary analogs.

DETROIT, MICHIGAN RECEIVED FEBRUARY 19, 1944

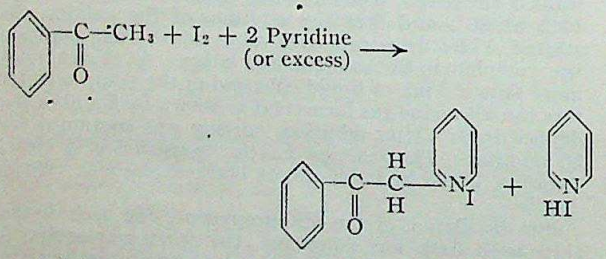
[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

The Reaction of Iodine with Some Ketones in the Presence of Pyridine

BY L. CARROLL KING

In an investigation of the reactions of compounds containing reactive hydrogen atoms with iodine in the presence of a base it was observed that acetophenone, 1-naphthyl methyl ketone, 1-anthryl methyl ketone and propiophenone react directly with one mole of iodine and two moles (or excess) of pyridine to give excellent yields of 1-phenacylpyridinium iodide, 1-(1-naphthoylmethyl)-pyridinium iodide, 1-(1-anthroylmethyl)-pyridinium iodide and 1-(α-methylphenacyl)-pyridinium iodide, respectively, and, in each case, pyridine hydroiodide.

If acetophenone is used as an example the reaction may be formulated as follows



1-Phenacylpyridinium iodide has been reported.[1] It was further characterized by conversion to the known 1-phenacylpyridinium perchlorate.[2,3] 1-(α-Methylphenacyl)-pyridinium iodide was also characterized by conversion to the known 1-(α-methylphenacyl)-pyridinium perchlorate.[4]

It has been demonstrated previously that 1-phenacylpyridinium bromide[2,5] and 1-(α-methylphenacyl)-pyridinium bromide[3] can be cleaved by means of aqueous alkali to give benzoic acid. The 1-phenacylpyridinium iodide and the 1-(α-methylphenacyl)-pyridinium iodide described in this article when treated with aqueous sodium hydroxide also gave excellent yields of this substance.

The characterization of 1-(1-naphthoylmethyl)-pyridinium iodide and of 1-(1-anthroylmethyl)-pyridinium iodide depends on the mode of formation, the analysis, and on the fact that after treatment with aqueous alkali the respective 1-naphthoic and 1-anthroic acids were isolated in good yield from the cleavage products.[6]

In three of the four reactions carried out 74–92% yields (based on the ketones) of the expected substituted β-ketoalkylpyridinium iodides were obtained and in every case 87–95% of the expected yields of pyridine hydroiodide were observed. 1-(α-Methylphenacyl)-pyridinium iodide was obtained in only 41% yield. The low yield in this case was due to the solubility characteristics of this compound. When the 1-(α-methylphenacyl)-pyridinium compound was isolated as the perchlorate a 64% yield was obtained.

When excess pyridine was used as the solvent, the formation of the substituted β-ketoalkylpyridinium iodides, by means of the above reaction, proceeded smoothly with twenty to thirty minutes heating on the steam-bath and the reaction was complete after standing overnight. In most cases a solid began to separate soon after the heating was started. This substance consisted of pyridine hydroiodide and usually contained some of the substituted β-ketoalkylpyridinium iodide. In the four instances discussed in this paper, it was not found advantageous to use solvents other than an excess of the base when effecting this synthesis.

Preliminary experiments indicate that the above reaction is of value for the synthesis of derivatives of various nitrogeneous bases, particularly in those cases where an intermediate halogen compound is difficult to obtain. These experi-

(1) F. Krohnke, *Ber.*, **66B**, 1386 (1933).
(2) E. Schmidt and H. VanArk, *Archiv. Pharm.*, **238**, 331 (1900).
(3) Krohnke, *Ber.*, **66**, 604 (1933).
(4) F. Krohnke, *ibid.*, **69**, 921 (1936).
(5) Babcock, Nakamura and Fuson, THIS JOURNAL, **54**, 4407 (1932); Babcock and Fuson, *ibid.*, **55**, 2949 (1933); E. Bamberger, *Ber.*, **20**, 3344 (1887).

(6) Krohnke[3] prepared 1-(1-naphthoylmethyl)-pyridinium bromide and showed that after treatment with aqueous alkali 1-naphthoic acid could be obtained from the cleavage products.

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TABLE I

Pyridinium iodide	Formula	M. p.,[a] °C.	Yield, %	Analyses, % Found C	Found H	Found I	Calcd. C	Calcd. H	Calcd. I
1-Phenacyl	$C_{13}H_{12}INO$	215–219	88[b]	48.36	3.72	38.9	48.01	3.7	39.03
1-(1-Naphthoylmethyl)-	$C_{17}H_{14}INO$	219–220	92[b]	55.20	3.74	33.9	54.41	3.76	33.82
1-(1-Anthroylmethyl)-	$C_{21}H_{16}INO$	235–237	74[b]	59.87	3.87	29.6	59.31	3.79	29.84
1-(α-Methylphenacyl)-	$C_{14}H_{14}INO$	152–153	41[b]	49.72	4.20	37.3	49.72	4.17	37.42
Pyridinium perchlorate									
1-Phenacyl	$C_{13}H_{12}ClNO_5$	189–190	90[c]	52.69	4.27		52.5	4.06	
1-(1-Naphthoylmethyl)-	$C_{17}H_{14}ClNO_5$	176–177	90[c]	59.32	4.12		58.69	4.05	
1-(1-Anthroylmethyl)-	$C_{21}H_{16}ClNO_5$	227–230	95[c]	63.81	4.25		63.40	4.05	
1-(α-Methylphenacyl)-	$C_{14}H_{14}ClNO_5$	141–142	64[d]–90[c]	54.29	4.49		53.94	4.52	

[a] All melting points were observed on a Fisher–Jones melting point apparatus. [b] Based on the ketone. [c] Based on the corresponding substituted β-ketoalkylpyridinium iodide. [d] This yield, based on the ketone, was obtained when the crude reaction mixture was converted directly into the perchlorate salt without preliminary isolation of the iodide.

ments also indicate that this reaction followed by alkaline cleavage, may be adapted to the preparation of acids from certain sensitive methyl ketones, particularly in those cases where the ordinary haloform reaction gives poor yields.

Extension of this reaction to other bases, to other halogens, and to various types of compounds containing active hydrogen atoms is in progress.

Experimental

Preparation of the Substituted β-Ketoalkylpyridinium Iodides.—The procedure was essentially the same for each of the four compounds prepared and was about as follows. To 0.1 mole of the appropriate ketone[7] dissolved in 30–50 ml. of pyridine 0.1 mole of iodine was added. The solution was heated thirty minutes on the steam-bath and let stand overnight. The excess pyridine was then removed and the mixture of pyridine hydroiodide and substituted β-ketoalkylpyridinium iodide separated by means of their solubility characteristics. 1-Phenacylpyridinium iodide, 1-(1-naphthoylmethyl)-pyridinium iodide and 1-(1-anthroylmethyl)-pyridinium iodide were comparatively insoluble in water and in methyl or ethyl alcohol and were easily separated from the more soluble pyridine hydroiodide. 1-(α-Methylphenacyl)-pyridinium iodide is very soluble in the solvents mentioned above but could be obtained pure from the concentrated methyl alcohol mother liquors after removal of most of the pyridine hydroiodide. In each case the substituted β-ketoalkylpyridinium iodide was crystallized from water or from dilute alcohol before analysis. The critical data for each of these compounds are listed in Table I.

The pyridine hydroiodide isolated in each case was identified by the usual procedures.

Preparation of the Substituted β-Ketoalkylpyridinium Perchlorates.—About 1 g. of each of the above substituted β-ketoalkylpyridinium iodides was dissolved in 50–400 ml. of hot water and 60% perchloric acid added until the solutions contained about 3% of it. The substituted β-ketoalkylpyridinium perchlorates separated at once or as the solution was cooled. The critical data for each of these substances are listed in Table I.

Alkaline Cleavage of the Substituted β-Ketoalkylpyridinium Iodides.—The method of cleavage of each of the four compounds was essentially the same. To suspensions of 1–5 g. of each of the substituted β-ketoalkylpyridinium iodides in 50–100 ml. of water or 50% ethyl alcohol, 1–3 g. of sodium hydroxide was added.

TABLE II

Starting iodide	Acid resulting from alkaline cleavage	Yield, %	M. p., °C.
1-Phenacylpyridinium	Benzoic	90	122
1-(α-Methylphenacyl)-pyridinium	Benzoic	88	122
1-(1-Naphthoylmethyl)-pyridinium	1-Naphthoic[a]	90	160–161
1-(1-Anthroylmethyl)-pyridinium	1-Anthroic[b]	80	251–252

[a] This substance was converted to the amide, m. p. 202–203°. [b] This substance was converted to the methyl ester, m. p. 101–102°.

The suspensions were heated one hour on the steam-bath and the acidic fractions isolated from the resulting homogeneous solutions. A summary of the results of this experiment appears in Table II.

Summary

1. It has been demonstrated that acetophenone, 1-naphthyl methyl ketone, 1-anthryl methyl ketone, and propiophenone react directly with one mole of iodine and two moles (or excess) of pyridine to give 1-phenacylpyridinium iodide, 1-(1-naphthoylmethyl)-pyridinium iodide, 1-(1-anthroylmethyl)-pyridinium iodide and 1-(α-methylphenacyl)-pyridinium iodide, respectively, and, in each case, pyridine hydroiodide.

2. Each of the substituted β-ketoalkylpyridinium iodides produced by the above reaction when treated with aqueous alkali was cleaved, and the corresponding carboxylic acid was isolated from the cleavage products.

EVANSTON, ILLINOIS RECEIVED JANUARY 31, 1944

(7) The 1-anthryl methyl ketone, m. p. 108°, was prepared by Mr. Clair J. Collins. The author is also indebted to Mr. Collins for the procedure for purification of 1-anthroic acid, and for the authentic samples of 1-anthroic acid and its methyl ester.

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[CONTRIBUTION FROM THE UNIVERSITY OF TEXAS, BIOCHEMICAL INSTITUTE, AND THE CLAYTON FOUNDATION FOR RESEARCH]

The Assay of Purified Proteins, Enzymes, Etc., for "B Vitamins"

BY ROGER J. WILLIAMS, FRITZ SCHLENK[1] AND MARGARET A. EPPRIGHT[2]

Microbiological assay methods for "B vitamins" have been used extensively in this Laboratory to assay small samples of tissues and foods.[3,4] In the present study the same methods were applied to various purified proteins, etc., as indicated in Table I.

The purpose of the investigation was to gain insight into the possible importance of "B vitamins" as prosthetic groups in proteins known to possess unusual physiological functions. It is common to assume that those B vitamins whose functions are unknown will ultimately be found to have a catalytic role and to be essential parts of specific enzyme systems. The possibility that some of these B vitamins should be constituent parts of already recognized enzymes and other physiologically active substances seemed worth exploring. Obviously in the case of comparatively low molecular weight proteins, a vitamin in order to be a constituent part of the molecule must be present in relatively large amounts, and relatively crude tests may serve to settle the question. It was of additional interest, however, to know in some cases whether specific proteins contained substantial amounts of B vitamins even though the vitamins were not present in amounts sufficient to be integral parts of the protein molecules, and were presumably held only by adsorption.

The results of the assays are given in Table I.

Of the 33 samples tested, the urease, ferritin and two ribonuclease samples were prepared by one of us (F. S.) using published methods[5,6,7,8,9]; the casein samples were obtained commercially. The others are described and their origin indicated in Table I.

The various preparations were not in general assayed for riboflavin because it is a highly colored substance and could hardly be an integral part of a purified protein (except highly colored ones) without revealing its presence visually.

Quantitative determinations on poor sources of B vitamins such as those investigated in this study are, in the nature of the case, subject to large percentage errors. The method for inositol is not on a par with the other methods because the organism (yeast) is far less sensitive to it, and the enzyme preparation used for digestion is comparatively rich and introduces a high correction. For this reason the low values for inositol content are relatively unreliable.

For determination of biotin and *p*-aminobenzoic acid, acid digestion replaced enzyme digestion; hence there was no "enzyme blank" to be used as a correction. The determinations of *p*-aminobenzoic acid were made with slight modifications according to the method of Lewis.[10]

Discussion

Most of the preparations of enzymes, hormones, proteins and other principles assayed contained measurable amounts of the various B vitamins. In most cases, however, the amounts are so small that the vitamins could not constitute an integral part of the molecules concerned.

Two samples yielded results of unusual interest, namely, pancreatic amylase and the yeast carboxylase. The pancreatic amylase preparation was capable of yielding 11,000 times its weight of maltose under standard test conditions. This is as high a potency as has been reported for any amylase preparation. Its inositol content is sufficiently high (4.1 mg. per gram) so that in order to be an integral part of the enzyme, the molecular weight of the latter would need to be no more than 44,000. That this inositol content is real and not due to error is indicated by the fact that a duplicate set of assays using acid extraction instead of enzymatic extraction gave results which were in substantial agreement (4.4 mg. per gram). This interesting observation regarding the amylase will be investigated further in collaboration with Dr. Caldwell.

Both yeast carboxylase preparations yielded an amount of nicotinic acid which was far above that obtained from other proteins. Preparation 1 was approximately 25% pure. The second preparation was "put through the same purification procedure that leads to the purest material recorded in our paper. However, the purity of this preparation is certainly far below what it ought to be. I have no explanation for this discrepancy except to point out that the activity of our starting material was 10% of that we used in England."[11] The possible existence of nicotinic acid in carboxylase will require further investigation, but the results obtained are suggestive.

The fact that for the most part B vitamins are found not to be constituents of the enzymes, etc., tested indicates, assuming that the less known B vitamins are enzyme constituents, that there exists a multiplicity of enzymes which are not at present available in concentrated form.

(1) Biochemist in the M. D. Anderson Hospital for Cancer Research, Houston, Texas.

(2) Standard Brands Fellow, The University of Texas.

(3) R. J. Williams, *et al.*, *Univ. Texas Pub.*, **4137** (1941).

(4) R. J. Williams, *et al.*, *ibid.*, **4237** (1942).

(5) J. B. Sumner, *J. Biol. Chem.*, **69**, 435 (1926).

(6) A. L. Dounce, *ibid.*, **140**, 307 (1941).

(7) M. Kunitz, *J. Gen. Physiol.*, **24**, 15 (1941).

(8) S. Granick and L. Michaelis, *J. Biol. Chem.*, **146**, 451 (1942).

(9) S. Granick and L. Michaelis, *ibid.*, **147**, 91 (1943).

(10) J. C. Lewis, *ibid.*, **146**, 441 (1942)

(11) Personal communication from Dr. David E. Green.

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TABLE I

B VITAMIN CONTENT OF ENZYMES, ETC.

Preparation tested	Description	Source[a]	Thiamin, γ/g.	Niacin, γ/g.	Pantothen, γ/g.	Pyridoxin, γ/g.	Biotin, γ/g.	Inositol, γ/g.	PAB, γ/g.	Folic acid, γ u./g.
Urease	Crystalline	..	1.8	2.4	0[b]	0.47	0.096	0[c]	...	0.3
Trypsin	Cryst. + $MgSO_4$	MB	1.0	3.1	1.2	0.16	.036	0[b]	0.36	0[b]
Chymotrypsin	Cryst. + $MgSO_4$	MB	3.1	3.5	1	0.1	.041	270	...	0[b]
Ribonuclease	5 × crystallized	MK	1	4.6	0[b]	0[b]	0[b]	0[c]	0.61	0[b]
Ribonuclease	Preparation 1	..	0.7	7.3	5.2	.4	0.037	0[b]	1.3	0[b]
Ribonuclease	Preparation 2	..	0.1	6.9	5.7	.25	0.012	0[b]	*ca.* 1.4	0.4
Carboxylase	Preparation 1[d]	DG	940	145	6.7	.27	[e]	0[c]	...	0[b]
Carboxylase	Preparation 2. See text	DG	530	131	1.3	.45	[e]	0[b]	...	0[b]
Muscle phosphorylase	[f]	GC	0.24	1.2	2.1	..	.019	0[b]	...	0[b]
Pancreatic amylase	[g]	MC	...	19.7	1.3	..	.013	4100	....	13
Myokinase	Impure[h]	HK	2.7	8.3	1.8	..	.026	0[b]	0.31	0[b]
Tyrosinase	Impure[i]	JN	3.7	24	..	0	.2	120	...	low
Cytochrome reductase	6.2% pure	EH	19.3	84	6.6	2.8	1.4	0[c]	...	0.3
Alkaline phosphatase	Preparation 1[j]	GS	0[c]	11	..	..	0.017	0[c]	...	low
Alkaline phosphatase	Preparation 2[j]	GS	1	...	..	0.1	.15	278	...	low
Insulin	Crystalline	VV	0.33	1.6	2.5	.13	.008	60	...	0[b]
Lactogenic hormone	About 90% pure	HE	0.87	0[b]	3	.47	.023	0[c]	*ca.* 1.5	low
Renin	[k]	IP	2.3	20	18	.30	.048	158	1	11
Heparin	Pure	TJ	0.3	1.8	0.6	.06	.005	60[c]	0.26	0[b]
Silk fibroin	[l]	MB	1.4	3.4	2.1	.27	0[b]	0[c]	...	0[b]
Nucleoprotein	[m]	AM	22	2.6	0.8	.41	0.023	330	...	0[b]
Lactoglobulin	3 × recryst.	MB	0.5	1.2	2.1	0[b]	0[b]	0[b]	0.08	0[b]
Horse hemoglobin	1 × recryst.	MB	0[b]	3.2	0.8	0[b]	0[b]	0[b]	0.19	0[b]
Horse hemoglobin	3 × recryst.	MB	.35	1.7	0.9	0[b]	.033	0[b]	0.25	0[b]
Egg albumin	[n]	MB	.7	0[b]	0[b]	0[b]	.008	0[c]	...	0[b]
Ferritin	Preparation 1	..	.33	0[c]	0[b]	0[c]	.012	0[c]	...	0[b]
Ferritin	Preparation 2	..	.06	2.5	0[b]	0[c]	...	0[c]	...	0[b]
Casein	Vit. free 9763	..	.13	0[b]	.7	.4	.006	0[c]	...	0[b]
Casein	Vit. free 9884	..	.18	0[b]	.8	.3	.008	0[c]	...	0[b]
Casein	Vit. free 9885	..	.13	0[b]	.8	.4	.010	0[c]	...	0[b]
Casein	Vit. free 10088	..	.21	0[b]	.7	.4	.007	110	...	..
Casein	Vit. free 10089	..	.28	0[b]	.9	.4	.005	110	...	..
Tobacco mosaic virus[o]	[p]	WS	2.3	1.1	.3	.18	.017	0[b]	...	0[b]
Enzyme mixture "papain" and "taka-diastase" used for digestion (usually at 10% level)		..	1.7	50.5	22.6	1.5	...	8000	...	3.8

[a] Symbols stand for the following sources: MB = Max Bergmann, MK = Moses Kunitz, DG = David E. Green, GC = Gerty T. Cori, MC = Mary L. Caldwell, HK = Herman M. Kalckar, JN = J. M. Nelson, EH = Erwin Haas, GS = Gerhardt Schmidt, VV = Vincent du Vigneaud (Eli Lilly product), HE = Herbert M. Evans, IP = Irvine H. Page, TJ = T. H. Jukes (Lederle Labs.), AM = Alfred E. Mirsky, WS = W. M. Stanley. [b] Values obtained were not necessarily zero, but were so low as to be probably negligible. [c] These tests were not entirely satisfactory. In most cases a slight growth inhibition was observed and this makes the result open to some question. [d] Approximately 25% pure, contained about 15 mg. dry wt. protein and approximately 20 units carboxylase activity per cc. [e] Many times recrystallized, washed with potassium chloride, dried *in vacuo*. [f] Highly purified, will produce approximately 11,000 times its weight of maltose under standard conditions. [g] Three to four times less active than material which catalyzes transfer of 5γ P per 1γ protein per minute. [h] From common mushroom; one cc. contains 10,200 Miller–Dawson catecholase units. [i] One mg. of dry enzyme forms 20 mg. of inorganic P within fifteen minutes from glycerophosphate. [j] About ten times more concentrated than preparation 1. [k] Relatively impure, but very potent. [l] N = 18.9% dry wt., ash = 0.08% (sulfate). [m] Purified from calf thymus. [n] Three times recrystallized, then denatured. [o] Partial assays were made of three other viruses, samples of which were kindly furnished by Dr. W. M. Stanley, *e. g.*, tobacco necrosis virus, bushy stunt virus and a centrifugally purified preparation of PR8 influenza virus. In no case did any vitamin appear to be present in substantial amounts; their contents of B vitamins appeared to be of a similar order to those of the tobacco mosaic virus. The small amounts of the other viruses which were available made the assays less satisfactory and less complete. [p] Crystalline, prepared by three differential centrifugative cycles.

The existence of appreciable amounts of the various B vitamins in all forms of living matter which have been investigated suggests the possibility of utilizing the presence or absence of these vitamins as a criterion with regard to the animate and inanimate nature or origin of a material in question. If we accept this criterion and the probability that viruses maintain their identity in the absence of all B vitamins, we must conclude that they are what we call inanimate.

Acknowledgment.—We wish to acknowledge most gratefully the kindness of the numerous

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individuals and laboratories referred to in Table I for furnishing us with the samples which made this investigation possible.

Summary

A series of protein, enzyme, hormone, and miscellaneous preparations have been assayed for B vitamins. Only traces have been found in most; however, inositol appears to be a constituent of purified amylase and the impure carboxylase preparations available contained a suggestively high content of nicotinic acid in addition to the thiamin already known to be present. The viruses investigated were found to be nearly devoid of B vitamins, and in this respect they appear to resemble "inanimate" rather than "animate" matter.

AUSTIN, TEXAS RECEIVED MARCH 2, 1944

[FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY AND RADCLIFFE COLLEGE]

Some Experiments on the *in vitro* Formation of Thyroxine from Diiodotyrosine

BY ARCHIE E. BARKDOLL[1a] AND WILLIAM F. ROSS[1b]

Following the report of von Mutzenbecher[1c] that thyroxine is readily formed *in vitro* from diiodotyrosine as well as from iodinated proteins,[2] considerable interest has been expressed in the nature of the reaction. As normally carried out, slightly alkaline digestion of diiodotyrosine over a period of two weeks gives a very small quantity of thyroxine. Block[3] repeated von Mutzenbecher's work using completely synthetic diiodotyrosine in order to eliminate the possibility that a trace of impurity, responsible for the thyroxine formation, had accompanied the tyrosine from its natural source. Johnson and Tewkesbury[4] made a further study of the reaction, obtaining a slight increase in the yield of thyroxine on the addition of hypoiodite to the solution and establishing pyruvic acid and ammonia as further products. As a result of their work, they postulated a mechanism evolved from the work of Pummerer[5] on the oxidation of *o*- and *p*-substituted phenols in alkaline solution. Their paper may be consulted for the proposed mechanism. We have made additional observations on the nature of the reaction, which throw further light on several points.

It appeared plausible that thyroxine may have been formed by the oxidizing action of the iodine solution originally used for the preparation of the diiodotyrosine rather than during the incubation of the diiodotyrosine. This possibility was eliminated when a sample of crude diiodotyrosine, as it was obtained from the iodination reaction, was subjected to butyl alcohol extraction for thyroxine. No thyroxine was found.

It was equally possible that a small amount of precursor was formed during the iodination and that this and not diiodotyrosine was converted into thyroxine during the long incubation period. A quantity of diiodotyrosine was therefore very carefully purified, but the yield of thyroxine after digestion was not altered.

To further eliminate the role of a small amount of accompanying impurity, diiodotyrosine which had already yielded thyroxine by incubation, was recovered, purified and re-incubated. Again thyroxine was formed.

In order to prove or disprove that oxidation, presumably by air, is involved in the formation of thyroxine, a solution of diiodotyrosine was incubated in an oxygen-free system under the usual conditions; it yielded no thyroxine. Whereas diiodotyrosine recovered from experiments carried out in the presence of air contain much brown, amorphous material, the diiodotyrosine recovered from this experiment was crystalline and only slightly darker than the starting material.

Conversely, the yield of thyroxine from a given amount of diiodotyrosine was increased by passing a slow stream of carbon dioxide-free air through the solution during the incubation.

In view of the work of Pummerer, *et al.*,[6] it was thought that incubation in the presence of a small amount of potassium ferricyanide might increase the yield of thyroxine. This appeared to be too drastic an oxidizing agent, however, as no thyroxine whatever was formed and the diiodotyrosine was converted to a dark brown amorphous substance.

A possible intermediate in the formation of thyroxine would be 3,5-diiodo-4-hydroxybenzoic acid, formed through the oxidative degradation of diiodotyrosine. An incubation carried out in the presence of this compound, instead of increasing the yield of thyroxine, completely prevented the conversion.

It was also found that 2,4,6-triiodophenol would not act as an intermediate to increase the

(1) (a) Present Address: Experimental Station, du Pont Company, Wilmington, Delaware. (b) Present Address: Shell Oil Company, Inc., Wood River, Illinois.

(1) (c) von Mutzenbecher, *Z. physiol. Chem.*, **261**, 253 (1939).

(2) Ludwig and von Mutzenbecher, *ibid.*, **258**, 195 (1939).

(3) Block, *J. Biol. Chem.*, **135**, 51 (1940).

(4) Johnson and Tewkesbury, *Proc. Natl. Acad. Sci.*, **28**, 73 (1942).

(5) Pummerer and Rieche, *Ber.*, **59**, 2161 (1926).

(6) Pummerer, Puttfarcken and Schopflocher, *ibid.*, **58**, 1808 (1925).

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yield. The normal amount of thyroxine was obtained in the presence of this substance.

Experimental

3,5-Diiodotyrosine Dihydrate—This substance was prepared from *l*-tyrosine by the method of Bauer and Strauss.[7] It crystallizes as the dihydrate, which fact was overlooked by these authors but was pointed out by Savitskii.[8] From 32.6 g. of tyrosine, in a typical experiment, 62 g. (66%) of diiodotyrosine dihydrate of m. p. 198° (dec.) was obtained.

Thyroxine from the Alkaline Digestion of Diiodotyrosine.—The procedure of earlier workers[1,3] was adopted for our experiments. This involved digestion of 14 g. of diiodotyrosine in 325 cc. of 0.1 *N* sodium hydroxide at *p*H 8.8 for two weeks at 37.5°, followed by isolation of the thyroxine through its butyl alcohol-soluble potassium salt. From 25 to 40 mg. of thyroxine was normally obtained.

No Thyroxine from Undigested Diiodotyrosine.—A solution of 14 g. of diiodotyrosine dihydrate in 25 cc. of 2 *N* sodium hydroxide was extracted with twelve 25-cc. portions of wet *n*-butyl alcohol. On working up the combined butyl alcohol extracts by the usual procedure none of the potassium salt of thyroxine was obtained.

Digestion of Analytically Pure Diiodotyrosine.—Crude diiodotyrosine (30.2 g.) was dissolved in 175 cc. of 0.85 *N* hydrochloric acid, treated three times with activated carbon and crystallized by the addition of 20 g. of sodium acetate in 30 cc. of water. The dried product weighed 17.7 g. and melted at 202° (dec.).

Anal. Calcd. for $C_9H_9O_3NI_2$: I, 58.62. Found: I, 58.41.

Fourteen grams of this product digested in the usual way yielded 24 mg. of thyroxine; m. p. 228 (dec.).

Digestion of Recovered Diiodotyrosine.—A solution in 180 cc. of 0.12 *N* hydrochloric acid of 41.3 g. of diiodotyrosine recovered from previous runs was filtered free of brown, amorphous material, saturated with sulfur dioxide and treated twice with activated carbon. The diiodotyrosine was crystallized by the addition of 40 cc. of 50% sodium acetate. It was then recrystallized from 0.1 *N* hydrochloric acid by the addition of sodium acetate to give 17.1 g. of light yellow crystals melting at 200°.

Incubation of 14 g. of this recrystallized diiodotyrosine in the customary manner gave 39 mg. of thyroxine.

Digestion of Diiodotyrosine in the Presence of Potassium Ferricyanide.—Ten grams of diiodotyrosine dihydrate and 3.29 g. of potassium ferricyanide were dissolved in 231 cc. of 0.1 *N* sodium hydroxide, and the *p*H of the solution adjusted to 8.8. After the usual incubation period the solution was black. A dark brown amorphous precipitate was thrown out by acidification. This was examined in the usual way for thyroxine, but none was obtained.

A control experiment run simultaneously with the same diiodotyrosine gave a good yield of thyroxine.

Digestion of Diiodotyrosine in the Presence of 2,4,6-Triiodophenol and of 3,5-Diiodo-4-hydroxybenzoic Acid.—A. A mixture of 10 g. of diiodotyrosine dihydrate and 2.28 g. of triiodophenol, prepared by the method of Datta and Prosad,[9] was added to 280 cc. of 0.1 *N* sodium hydroxide. The solution, of *p*H 9.0, was placed in the incubator at 37.5° for fifteen days, although the triiodophenol was not entirely dissolved. The mixture was shaken daily to maintain saturation. After eleven days the *p*H had fallen to 8.7; it was raised to 8.9 and the solution digested five more days. The undissolved triiodophenol (1.68 g.) was filtered off and the solution worked up in the usual way for thyroxine, of which 29 mg. of m. p. 227° (dec.) was obtained.

B. A mixture of 10 g. of diiodotyrosine dihydrate and 1.56 g. of diiodohydroxybenzoic acid,[9] was added to 250 cc. of 0.1 *N* sodium hydroxide. All the diiodotyrosine dissolved but an appreciable amount of the benzoic acid remained undissolved. The system was incubated at *p*H 8.8, 37.5°, for fifteen days with daily shaking. The acids were precipitated by acidification and extracted in the usual fashion for thyroxine with a negative result.

Identification of Thyroxine.—The sample of our synthetic thyroxine employed for analysis and physiological testing was purified[10] by conversion into the potassium salt, followed by regeneration of thyroxine. This procedure was repeated three times. The material was obtained as microcrystalline sheaves and rosets, m. p. 233° (dec.). The sample was dried before analysis over phosphorus pentoxide for one hour at 100° (1 mm.).

Anal. Calcd. for $C_{15}H_{11}O_4NI_4$: I, 65.34. Found: I, 65.10.

The material gave a deep red color with nitrous acid and ammonia,[11] a specific reagent for ortho-iodophenols.

The method of Gaddum[12] for the qualitative assay of thyroxine and thyroid active substances by the use of tadpoles was employed for physiological testing. Our material proved to be fully as active as crystalline thyroxine, obtained from E. R. Squibb and Sons, in producing metamorphosis in tadpoles (*rana sylvatica*).

Summary

Some experiments on the *in vitro* formation of thyroxine from diiodotyrosine are reported.

RECEIVED FEBRUARY 10, 1944

(7) Bauer and Strauss, *Ber.*, **68**, 1108 (1935).
(8) Savitskii, *J. Gen. Chem.* (U. S. S. R.), **9**, 1342 (1939).
(9) Datta and Prosad, THIS JOURNAL, **39**, 44 (1917).
(10) Harington, *Biochem. J.*, **20**, 293 (1926).
(11) Kendall and Osterberg, *J. Biol. Chem.*, **40**, 265 (1919).
(12) Gaddum, *J. Physiol.*, **64**, 246 (1927–1928).

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, THE UNIVERSITY OF WISCONSIN]

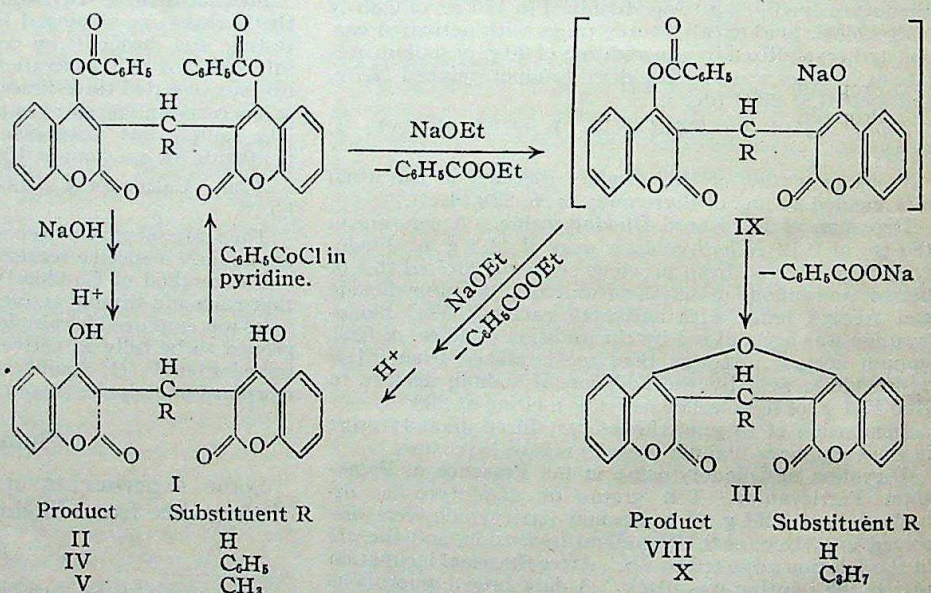
Studies on 4-Hydroxycoumarins. IV. Esters of the 4-Hydroxycoumarins[1]

BY MARK A. STAHMANN, LLOYD H. GRAF, CHARLES F. HUEBNER, SAUL ROSEMAN AND KARL PAUL LINK

The 3,3′-alkylidenebis- and -arylidenebis-(4-hydroxycoumarin)s (I) aldehyde condensation products of 4-hydroxycoumarin, may exist in an enol or keto form. In the enol form they may react with acid halides or acid anhydrides to esterify both enolic hydroxyl groups. This paper discusses the synthesis of some of these diesters, principally those of 3,3′-methylenebis-(4-hydroxycoumarin) (II). Since certain experiments of Link, *et al.*,[2] indicate that the 4-hydroxycoumarins may exert their anticoagulant action after degradation in the body to salicylic acid, salicylic acid esters are included. These compounds were prepared as part of the study dealing with the relation of structure in the 4-hydroxycoumarin group to anticoagulant activity.

II was readily converted to its acetate by treatment with acetic anhydride in pyridine.[3] In this study other diesters of II were prepared by a similar method.

When the methylene carbon atom of I carries a substituent other than hydrogen, treatment with acetic anhydride or acetyl chloride in pyridine does not give the esters. Dehydration occurs between the enolic hydroxyls with the formation 3,3′-alkylidene- or -arylidene-4,4′-epoxydicoumarins (III).[4] IV and V appear to be the most easily dehydrated bis-4-hydroxycoumarins. Both are dehydrated by refluxing with acetic anhydride, the former also being dehydrated by treatment with benzoyl chloride in pyridine. In contrast, VI and VII form stable diacetates when refluxed in acetic anhydride, and stable dibenzoates when treated with benzoyl chloride in pyridine. When a diester of I is treated with one equivalent of sodium ethoxide, a partial conversion to the unesterified parent substance and to the anhydride, III results. Studies with the dibenzoate of II revealed that the acyl residue is removed as sodium benzoate and ethyl benzoate. Since it has been shown that treatment of the monobenzoate and mono-(dimethylphosphate) of II with one mole of sodium ethoxide transforms them to the anhydro compound, 3,3′-methylene-4,4′-epoxydicoumarin (VIII), the conversion of the diesters of II to VIII (and in general the conversion of a diester of I to III) probably proceeds over a mono ester (IX) as an intermediate. This mono ester then loses one mole of acid (as the sodium salt) intramolecularly to form the dehydration product. These reactions can be illustrated by the following transformations of the dibenzoate of I



Product	Substituent R
II	H
IV	C_6H_5
V	CH_3
VI	C_2H_5
VII	C_3H_7

Product	Substituent R
VIII	H
X	C_3H_7

o-Hydroxy substituted salicylates of II were prepared by condensation with the appropriate acid chloride in pyridine. The di-(carbomethoxysalicylate) of II was used in an attempt to prepare the disalicylate, but all efforts to remove the carbomethoxy group (acidic and basic hydrolysis and ammonolysis) resulted in further hydrolysis and loss of the salicylate group. The remarkable lability of the salicylate linkage is illustrated by the conversion of the di-(carbomethoxysalicylate) of II to VIII by as weak a base as sodium acetate. In this reaction some carbomethoxysalicylic acid is formed. This indicates that the salicylate linkage is as labile as the readily hydrolyzed carbomethoxy group. The disalicylate of II was successfully prepared by hydrogenolysis of the di-(*o*-benzyloxybenzoate)

(1) Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. Supported through special grants from the Graduate School Research Committee and the Wisconsin Alumni Research Foundation.

(2) Link, Overman, Sullivan, Huebner and Scheel, *J. Biol. Chem.*, 147, 463 (1943).

(3) Stahmann, Huebner and Link, *ibid.*, 138, 513 (1941).

(4) Huebner, Sullivan, Stahmann and Link, THIS JOURNAL, 65, 2292 (1943).

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TABLE I

ESTERS OF 3,3′-ALKYLIDENEBIS-(4-HYDROXYCOUMARIN)S AND 3-PHENYL-4-HYDROXYCOUMARIN

Derivative	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
(a) Esters of 3,3′-methylenebis-4-hydroxycoumarin							
Dipropionate	77	247–248[d]	$C_{26}H_{20}O_8$	66.96	67.03	4.46	4.57
Di-*n*-butyrate	69	227–228	$C_{27}H_{24}O_8$	68.07	68.52	5.04	5.26
Di*iso*butyrate	82	233–234	$C_{27}H_{24}O_8$	68.07	67.78	5.04	5.15
Di-*n*-valerate	48	224–225	$C_{29}H_{28}O_8$	69.05	68.87	5.55	5.60
Di*iso*valerate	63	220–221	$C_{29}H_{28}O_8$	69.05	69.01	5.55	5.55
Dicaproate	62	225–226	$C_{31}H_{32}O_8$	69.93	69.93	6.02	6.22
Diheptanoate	50	215–216	$C_{33}H_{36}O_8$	70.72	70.86	6.43	6.03
Dibenzoate	81	263–264	$C_{33}H_{20}O_8$	72.97	73.22	3.68	3.80
Di-(trimethylacetate)	27	210–211	$C_{29}H_{28}O_8$	69.06	69.37	5.55	5.76
Di-(benzylcarbonate)[a]	60	188–189	$C_{35}H_{24}O_{10}$	69.55	69.32	3.97	4.03
Di-(acetylsalicylate)[b]	62	253–256	$C_{37}H_{24}O_{12}$	67.27	66.85	3.64	3.38
Di-(carbomethoxysalicylate)[c]	63	213–216	$C_{37}H_{24}O_{14}$	64.16	63.89	3.47	3.77
Di-(*o*-benzyloxybenzoate)[b]	67	212–213	$C_{47}H_{32}O_{10}$	74.60	74.21	4.23	4.39
Di-(*o*-chlorobenzoate)[d]	31	250–252	$C_{33}H_{18}O_8Cl_2$	64.60	64.76	2.94	3.45
Di-(*p*-chlorobenzoate)[d]	71	288–291	$C_{33}H_{18}O_8Cl_2$	64.60	64.27	2.94	3.38
Difuroate[d]	29	298–300[d]	$C_{29}H_{16}O_{10}$	66.41	66.11	3.06	3.52
(b) Further esters, R = 4-hydroxycoumarin							
3,3′-Ethylidenebis-(R) dibenzoate	76	209–210	$C_{34}H_{22}O_8$	73.12	73.09	3.94	4.23
3,3′-Propylidenebis-(R) diacetate	54	202–203	$C_{25}H_{20}O_8$	66.98	66.97	4.46	4.71
3,3′-Propylidenebis-(R) dibenzoate	84	203–204	$C_{35}H_{24}O_9$	73.42	73.47	4.20	4.31
3,3′-Butylidenebis-(R) diacetate	69	210–211	$C_{26}H_{22}O_8$	67.53	67.28	4.76	5.25
3,3′-Butylidenebis-(R) dibenzoate	85	226–227	$C_{36}H_{20}O_8$	73.72	73.91	4.44	4.72
3-Phenyl-R acetylsalicylate[a]	60	183–185	$C_{24}H_{16}O_6$	72.00	71.63	4.00	4.40
3-Phenyl-R *o*-benzyloxybenzoate[e]	65	173–175	$C_{29}H_{20}O_5$	77.67	77.67	4.46	4.53

[a] Recrystallized from acetic acid. [b] Recrystallized from amyl alcohol. [c] Recrystallized from dioxane. [d] Recrystallized from β,β′-dichloroethyl ether. [e] Recrystallized from ethyl acetate.

at high pressure over Raney nickel. The crude product is separated from the small quantity of II which is produced in the reaction by repeated recrystallizations from dioxane. The *o*-benzyloxybenzoate of 3-phenyl-4-hydroxycoumarin is converted to 3-phenyl-4-hydroxycoumarin salicylate by hydrogenolysis at atmospheric pressure over palladium. Under these conditions the di-(*o*-benzyloxybenzoate) of II is unchanged. Table I lists the esters prepared.

The anticoagulant activity of the ester is lower than that of the parent 3,3′-alkylidenebis-(4-hydroxycoumarin). It appears that they act as anticoagulants after hydrolysis *in vivo*. A report on their activity will appear elsewhere.

Experimental

Esterification of 3,3′-Methylenebis-(4-Hydroxycoumarin) (I).[5]—All the diesters of II were prepared by slowly adding with vigorous stirring, 4 equivalents (100% excess) of the corresponding acid chloride to an 8% solution of the parent substance (usually about 2 g.) in dry pyridine (25 ml.) at 0°. After a few minutes the diesters usually crystallized from the reaction mixture. The mixture was allowed to stand for six hours at 25°, filtered, and washed with ethanol. In most cases, the crude product was recrystallized from cyclohexanone. The exceptions are noted in Table I.

(5) The 3,3′-alkylidenebis-(4-hydroxycoumarin)s were prepared by condensing 4-hydroxycoumarin with the corresponding aldehyde by the method of Sullivan, *et al.*, THIS JOURNAL, 65, 2288 (1943). 4-Hydroxycoumarin was prepared by the method of Stahmann, *et al.*, *ibid.*, 65, 2285 (1943).

Acetylation of I was accomplished by refluxing the parent substance (usually about 2 g.) with 12.5 parts of acetic anhydride (25 g.) for six hours. In some cases the diacetate crystallized out when the reaction mixture was cooled. When this did not take place the excess anhydride was decomposed by pouring the reaction mixture into six volumes of ice-water. The acetates then separated as crystalline products. IV and V were converted to the anhydrides by this procedure.

Benzoylation of 3,3′-Alkylidenebis-(4-hydroxycoumarin)s.—Benzoates were prepared by adding benzoyl chloride to a pyridine solution of the 3,3′-alkylidenebis-(4-hydroxycoumarin). 3,3′-Benzylidenebis-(4-hydroxycoumarin) underwent dehydration under these conditions, but all the other compounds which were studied formed stable dibenzoates which were recrystallized from cyclohexanone.

Action of Bases on Esters of I.—A mixture of 5 g. of **3,3′-methylenebis-(4-hydroxycoumarin) dipropionate,** and 0.76 g. of sodium ethoxide was suspended in 100 ml. of absolute ethanol and refluxed for twelve hours. The mixture was then filtered while hot, yielding 1.85 g. (49%) of VIII m. p. 317–321°. After recrystallization from cyclohexanone the melting point was 320–323°. II (1.55 g.) was recovered from the filtrate by acidification. Treatment of **3,3′-methylenebis-(4-hydroxycoumarin) diacetate** with sodium ethoxide under these conditions gave a lower yield of the dehydration product. Saponification of the esters of I with aqueous sodium hydroxide gave the unesterified parent substances.

Treatment of **3,3′-butylidenebis-(4-hydroxycoumarin) diacetate** with one equivalent of sodium ethoxide in boiling ethanol for twelve hours gave a 40% yield of X, m. p. 246°.

3,3′-Methylenebis-(4-hydroxycoumarin) di-(carbomethoxysalicylate) (1.0 g.) was dissolved in 45 ml. of boiling dioxane. A solution of 4.70 g. of hydrated sodium acetate in 25 ml. of water was added and the mixture was refluxed for ten hours. The following products were iso-

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lated: 0.31 g. of VIII (63%); 0.19 g. of II (35%); 0.20 g. of salicylic acid and traces of carbomethoxysalicylic acid. One gram of the ester under the same conditions yielded 0.18 g. of VIII after refluxing for five minutes.

3,3′-Methylenebis-(4-hydroxycoumarin) dibenzoate (1.12 g.) in 12 ml. of absolute ethanol was refluxed with 2 moles of sodium ethoxide for fifteen hours. Two moles of 1 *N* hydrochloric acid was added and the combined precipitate of II and VIII was filtered off and II separated from VIII by means of its solubility in dilute NaOH. VIII (0.13 g.) m. p. 318–320° and II (0.56 g.) m. p. 290° were obtained. One mole of $NaHCO_3$ was added to the filtrate and after concentration to dryness *in vacuo*, the residue was acidified and extracted with ether. The acid fraction yielded 0.12 g. of benzoic acid, m. p. 118–120°, and the neutral solution yielded 0.02 g. of ethyl benzoate, b. p. 206–207°.

3,3′-Methylenebis-(4-hydroxycoumarin) Disalicylate.—The di-(*o*-benzyloxybenzoate) of I (3.9 g.) in 200 ml. of dioxane was hydrogenated at 1900 pounds pressure and 100° for three hours over Raney nickel. The catalyst was filtered off and the filtrate concentrated to dryness *in vacuo*. The residue was taken up in a small volume of hot dioxane and the insoluble residue of II was filtered from the hot solution. This process was repeated three times. After a final recrystallization from acetic acid the disalicylate of II melted at 223–225°, yield 0.7 g.

Anal. Calcd. for $C_{33}H_{20}O_{10}$: C, 68.75; H, 3.47. Found: C, 68.62; H, 3.68.

3-Phenyl-4-hydroxycoumarin Salicylate.—3-Phenyl-4-hydroxycoumarin *o*-benzyloxybenzoate (1.5 g.) was dissolved in 200 ml. of acetic acid–ethyl acetate (1:1) and hydrogenated at 1 atmosphere over palladium on charcoal. In thirty minutes one mole of hydrogen had reacted. The catalyst was filtered off and the filtrate concentrated to dryness *in vacuo*. The residue was recrystallized twice from ethyl acetate and once from benzene, m. p. 185–187°, yield 0.9 g.

Anal. Calcd. for $C_{22}H_{14}O_6$: C, 73.74; H, 3.63. Found: C, 73.72; H, 4.09.

Acknowledgment.—The authors are indebted to Dr. Ivan Wolff for carrying out the high pressure hydrogenation experiments and to Mr. Miyoshi Ikawa for some of the C and H determinations.

Summary

1. A series of diesters of some 3,3′-alkylidenebis-(4-hydroxycoumarin)s and of monoesters of 3-phenyl-4-hydroxycoumarin have been prepared.

2. The *o*-benzyloxybenzoic acid esters have been converted to the corresponding salicylic acid esters by hydrogenolysis.

3. The 3,3′-alkylidenebis-(4-hydroxycoumarin)s yield 3,3′-alkylidene-4,4′-epoxydicoumarins upon treatment with sodium ethoxide.

MADISON, WIS. RECEIVED DECEMBER 14, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, THE UNIVERSITY OF WISCONSIN]

Studies on 4-Hydroxycoumarins. V. The Condensation of α,β-Unsaturated Ketones with 4-Hydroxycoumarin[1]

BY MIYOSHI IKAWA, MARK ARNOLD STAHMANN AND KARL PAUL LINK

It has been observed by Sullivan, *et al.*,[2] that when salicylaldehyde is condensed with 4-hydroxycoumarin (I), an α,β-unsaturated ketone is formed, which reacts with another molecule of I by a Michael type addition. Accordingly a study of the condensation of other α,β-unsaturated ketones with 4-hydroxycoumarin was undertaken. The Michael type condensation is usually carried out in an alcoholic medium in the presence of an acid[3] or base catalyst. According to Conner and McClellan[4] secondary amines (*e. g.*, piperidine) are the most suitable catalysts in that they seldom cause other than the normal condensation, but they are not as effective as the metallic alkoxides.

The condensation of benzalacetone with 4-hydroxycoumarin under the usual conditions in ethanol with either sodium ethylate, hydrochloric acid, or piperidine as catalyst gives a mixture of products. The mixture contains the normal condensation product and the cyclic ketal formed by reaction with ethanol. However, by carrying out the reaction in pyridine alone, satisfactory yields of the Michael condensation products can be obtained. The condensation of benzalacetone with 4-hydroxycoumarin can also be brought about by refluxing the two components with water without the addition of a catalyst.

The α,β-unsaturated ketones II–VIII which were condensed with 4-hydroxycoumarin (I) are indicated below along with the structures of the resulting condensation products (IX–XV). On treatment of the condensation products (IX–XV) with 4% hydrogen chloride in absolute methanol cyclic ketals (XVI–XXII) are formed. This reaction is rationalized on the basis that the Michael type condensation products are δ-hydroxy ketones and can therefore undergo ring closure to the corresponding cyclic hemi-ketals which are then methylated. An analogous example is the reversible ketal formation of 4-salicyl-butan-2-one.[5] Evidence for the cyclic ketal structure of the benzalacetone product XVIII resides in the following transformations. When XI was methylated with diazomethane, the methyl ether XXIII was obtained, which differed from the isomeric cyclic ketal XVIII. By refluxing XVIII with aqueous methanolic HCl the

(1) Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. Supported through special grants from the Graduate School Research Committee, and the Wisconsin Alumni Research Foundation.

(2) Sullivan, Huebner, Stahmann and Link, THIS JOURNAL, 65, 2288 (1943).

(3) Breslow and Hauser, *ibid.*, 62, 2385 (1940).

(4) Conner and McClellan, *J. Org. Chem.*, 3, 570 (1939).

(5) Baker and Walker, *J. Chem. Soc.*, 646 (1935).

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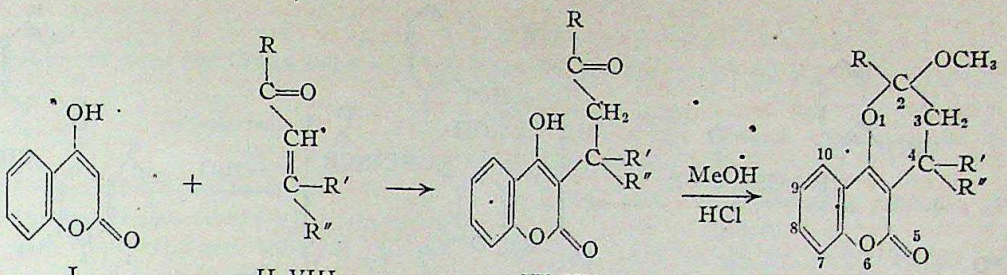
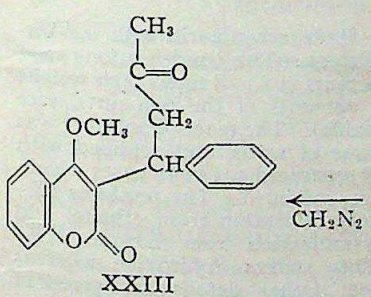
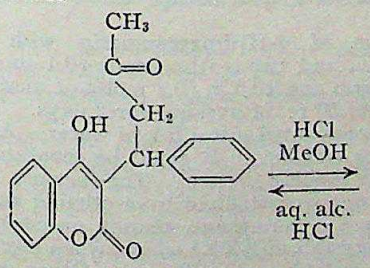


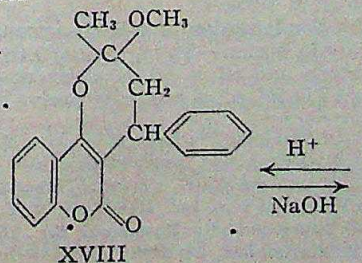
Ketones — Products — Substituent groups

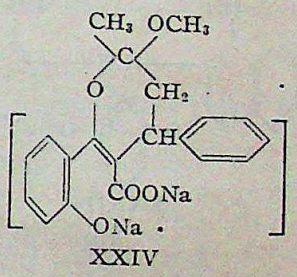
			R	R′	R″
Ethylideneacetone (II)	IX	XVI	$-CH_3$	$-CH_3$	$-H$
Mesityl oxide (III)	X	XVII	$-CH_3$	$-CH_3$	$-CH_3$
Benzalacetone (IV)	XI	XVIII	$-CH_3$	$-C_6H_5$	$-H$
Anisalacetone (V)	XII	XIX	$-CH_3$	$-C_6H_4OCH_3$	$-H$
Vanillylalacetone (VI)	XIII	XX	$-CH_3$	$-C_6H_3(OCH_3)OH$	$-H$
Benzalacetophenone (VII)	XIV	XXI	$-C_6H_5$	$-C_6H_5$	$-H$
Benzal-*o*-hydroxyacetophenone (VIII)	XV	XXII	$-C_6H_4OH$	$-C_6H_5$	$-H$

original material XI was recovered. On treatment of XVIII with aqueous methanolic NaOH an alkali soluble product was obtained, which on acidification gave XVIII with no trace of XI. The sodium hydroxide had evidently opened up









the lactone ring (product XXIV), which closed on acidification, without affecting the ketal system.

When α,β-unsaturated ketones derived from salicylaldehyde (XXV–XXVII) are condensed with 4-hydroxycoumarin, the Michael condensation products undergo spontaneous dehydration to give products with high melting points, which are alkali insoluble and have low solubility in ethanol (XXVIII–XXX).

A similar dehydration has been observed by Sullivan, *et al.*,[2] in the condensation of salicylaldehyde with 4-hydroxycoumarin.

Mesityl oxide (III) when condensed with 4-hydroxycoumarin gives rise to two compounds. In addition to the normal condensation product (X) there is obtained an alkali insoluble product. It can easily be separated from X by its solubility in hexane. The properties and elementary analysis indicate XXXI to be the structure for this compound.

The compound XV resulting from the condensation of benzal-*o*-hydroxyacetophenone (VIII) with 4-hydroxycoumarin has also been prepared by degrading 3,3′-benzylidenebis-(4-hydroxycou-

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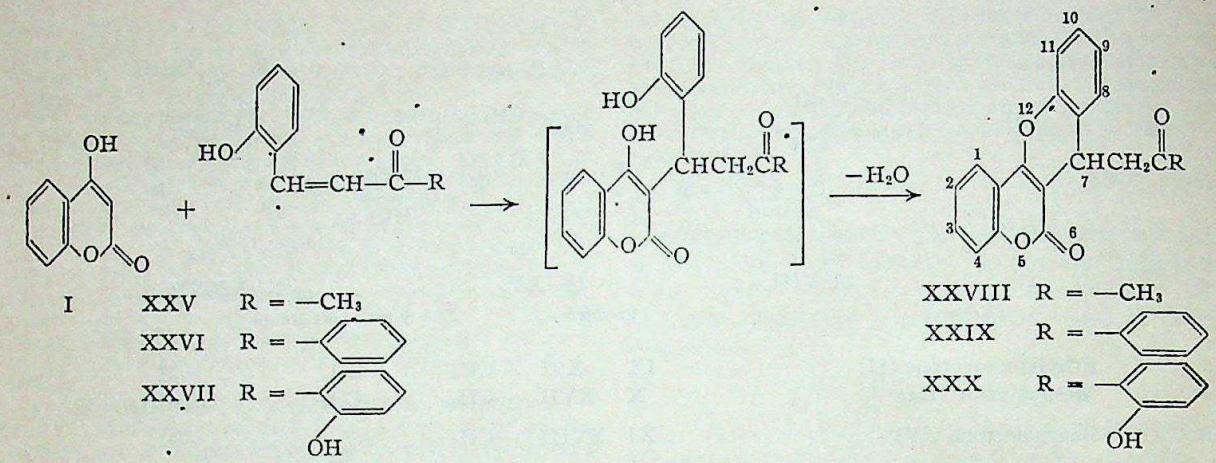
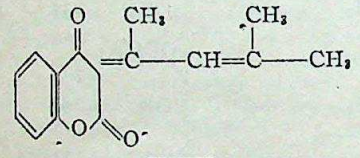


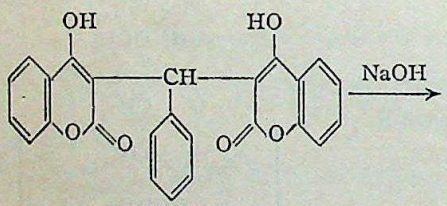
I XXV R = —CH_3
XXVI R = —C$_6$H$_5$
XXVII R = —C$_6$H$_4$OH

XXVIII R = —CH_3
XXIX R = —C$_6$H$_5$
XXX R = —C$_6$H$_4$OH

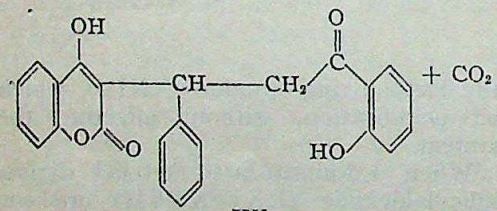


XXXI

marin) (XXXII) with sodium hydroxide.[6] The synthesis of XV by these two different methods establishes its structure.



XXXII



XV

The α,β-unsaturated esters, ethyl cinnamate and ethyl benzalmalonate, as well as phorone, dibenzalacetone, and furfuralacetone, when refluxed in pyridine with 4-hydroxycoumarin failed to yield the Michael products.

The condensation products obtained from 4-hydroxycoumarin and α,β-unsaturated ketones as well as the corresponding cyclic ketals have relatively high anticoagulant properties when compared with 3,3′-methylenebis-(4-hydroxycoumarin). A report on their physiological activity will appear elsewhere.

Experimental

The α,β-Unsaturated Ketones and Esters.—The mesityl oxide (III), benzalacetone (IV), anisalacetone (V), *o*-hydroxybenzalacetophenone (XXVI), furfuralacetone, dibenzalacetone, ethyl cinnamate and phorone were obtained from the Eastman Kodak Company. Ethylideneacetone[7] (II), vanillylalacetone[8] (VI), benzalacetophenone[9] (VII), benzal-*o*-hydroxyacetophenone[10] (VIII), salicylalacetone[11] (XXV), and ethyl benzalmalonate[3] were prepared according to the references cited.

2,2′-Dihydroxybenzalacetophenone (XXVII).—Ten grams of salicylaldehyde and 10 g. of *o*-hydroxyacetophenone were dissolved in 300 cc. of water containing 10 g. of sodium hydroxide and kept at 85° for ten to fifteen hours. Upon acidification of the reaction mixture an oil was obtained which crystallized partially on standing. The product was filtered off and recrystallized from ethanol, m. p. 160° dec., yield 2.4 g. (14%).

Anal. Calcd. for $C_{15}H_{12}O_3$: C, 75.0; H, 5.0. Found: C, 75.0; H, 5.2.

The **dibenzoate** was prepared by heating XXVII with benzoyl chloride in pyridine and was recrystallized from ethanol, m. p. 114°.

Anal. Calcd. for $C_{29}H_{20}O_5$: C, 77.7; H, 4.5. Found: C, 77.5; H, 4.8.

The Condensation of 4-Hydroxycoumarin with α,β-Unsaturated Ketones and Esters.—The condensations were made by refluxing the reactants in 2 to 3 times their weight of pyridine. Equimolar amounts of the reactants were used (except for mesityl oxide). The reaction mixture was poured into a large volume of water and acidified with hydrochloric acid. An oil separated out in all cases which, if condensation took place, solidified. The products IX–XV were purified by recrystallization from ethanol and XXVIII–XXX by recrystallization from dioxane. IX–XV were soluble in dilute sodium hydroxide whereas XXVIII–XXX were not. Other details are given in Table I.

Condensation of 4-Hydroxycoumarin with Mesityl Oxide.—Sixteen and two-tenths grams (0.1 mole) of 4-hydroxycoumarin and 19.6 g. (0.2 mole) of mesityl oxide were refluxed in 50 cc. of pyridine for 2 days. The reaction mixture was poured into 1.5 l. of water. An oil was obtained which solidified. It could be separated into 2 fractions with boiling hexane. The hexane insoluble material (X) was recrystallized from ethanol and melted at 212° (3.3 g.). The hexane solution on concentration yielded large crystals of XXXI which, when recrystallized from hexane, melted at 93° (8.3 g.). Other details are included in Table I.

The Condensation of 4-Hydroxycoumarin with Benzalacetone in Water.—Thirty grams (0.18 mole) of 4-hydroxycoumarin and 27 g. (0.18 mole) of benzalacetone were refluxed in 500 cc. of water for twelve hours. The mixture

(6) Unpublished work of this Laboratory.

(7) Grignard and Fluchaire, *Ann. chim.*, **9**, 10 (1928).

(8) Francesconi and Cusmano, *Gazz. chim. ital.*, **38**, II, 75 (1908).

(9) Gilman and Blatt, "Organic Synthesis," Coll. Vol. I, 2nd ed., John Wiley and Sons, Inc., New York, N. Y., 1941, p. 78.

(10) Feurstein and v. Kostanecki, *Ber.*, **31**, 715 (1898).

(11) Harries, *ibid.*, **24**, 3180 (1891).

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TABLE I

PRODUCTS FROM THE CONDENSATION OF α,β-UNSATURATED KETONES WITH 4-HYDROXYCOUMARIN

No.	Compound	Reflux time, hours	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
	(a) R = 4-hydroxycoumarin								
IX	3-(α-Methyl-β-acetylethyl)-R	24	44	141	$C_{14}H_{14}O_4$	68.3	68.0	5.7	5.5
	3-(α-Methyl-β-acetylethyl)-R methyl ether[a]			liq.	$C_{15}H_{16}O_4$				
X	3-(α,α-Dimethyl-β-acetylethyl)-R	48	13	212	$C_{15}H_{16}O_4$	69.2	69.2	6.2	6.3
XI	3-(α-Phenyl-β-acetylethyl)-R	4–8	40	161	$C_{19}H_{16}O_4$	74.0	74.2	5.2	5.4
	3-(α-Phenyl-β-acetylethyl)-R methyl ether[b]			127	$C_{20}H_{18}O_4$	74.5	74.3	5.6	5.7
XII	3-(α-Anisyl-β-acetylethyl)-R	4–12	45	160	$C_{20}H_{18}O_5$	71.0	70.9	5.3	5.2
	3-(α-Anisyl-β-acetylethyl)-R methyl ether[c]			Sirup	$C_{21}H_{20}O_5$				
XIII	3-[α-(p-Hydroxy-m-methoxyphenyl)-β-acetylethyl]-R	6–24	18	181	$C_{20}H_{18}O_6$	67.8	68.0	5.1	5.2
XIV	3-(α-Phenyl-β-benzoylethyl)-R	4	37	160	$C_{24}H_{18}O_4$	77.8	77.7	4.9	5.0
	3-(α-Phenyl-β-benzoylethyl)-R methyl ether[d]			91	$C_{25}H_{20}O_4$	78.1	78.0	5.2	5.3
XV	3-(α-Phenyl-β-salicylylethyl)-R	12	34	194	$C_{24}H_{18}O_5$	74.6	74.8	4.7	4.6
	(b) R = (1)benzopyrano-(4,3-b)(1)benzopyran								
XXVIII	6-Oxo-7-acetonyl-R	1	69	263d	$C_{19}H_{14}O_4$	74.5	74.4	4.6	4.6
XXIX	6-Oxo-7-benzoylmethyl-R	12	76	240d	$C_{24}H_{16}O_4$	78.25	78.25	4.4	4.4
XXX	6-Oxo-7-salicylylmethyl-R	12	75	241d	$C_{24}H_{16}O_6$	75.0	74.7	4.2	4.3
XXXI	3-(2-Methyl-Δ²-penten-4-ylidene)-2,4-diketochroman	48	34	93	$C_{15}H_{14}O_3$	74.4	74.1	5.8	6.0

[a] Distilled at 0.5 mm. at a bath temperature of 170°. *Anal.* Calcd. OCH_3, 11.9; found, 11.4. [b] *Anal.* Calcd. OCH_3, 9.6; found, 9.4. [c] Distilled at 0.5 mm. at a bath temperature of 240°. *Anal.* Calcd. OCH_3, 17.6; found 16.1. [d] *Anal.* Calcd. OCH_3, 8.1; found, 8.3.

TABLE II

PRODUCTS FROM THE METHANOLIC HYDROGEN CHLORIDE TREATMENT OF THE MICHAEL CONDENSATION PRODUCTS

No.	Derivatives of -5-oxo-dihydropyrano(3,2-c)(1)benzopyran	Reflux time, hours	Yield, %	M. p., °C.	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Methoxyl Calcd.	Methoxyl Found
XVI	2,4-Dimethyl-2-methoxy-	1	29	124	$C_{15}H_{16}O_4$	69.2	69.4	6.2	6.0	11.9	11.6
XVII	2,4,4-Trimethyl-2-methoxy-	24	80	102	$C_{16}H_{18}O_4$	70.1	70.1	6.6	6.4	11.3	10.1
XVIII	2-Methyl-2-methoxy-4-phenyl-	1/4	83	166	$C_{20}H_{18}O_4$	74.5	74.5	5.6	5.9	9.6	9.5
XIX	2-Methyl-2-methoxy-4-anisyl-	4	75	163	$C_{21}H_{20}O_5$	71.6	71.5	5.7	5.8	17.6	16.7
XX	2-Methyl-2-methoxy-4-(p-hydroxy-m-methoxyphenyl)-	1	82	187	$C_{21}H_{20}O_6$	68.5	68.6	5.5	5.6	16.8	16.5
XXI	2,4-Diphenyl-2-methoxy-	20	13	205	$C_{25}H_{20}O_4$	78.1	77.9	5.2	5.4	8.1	8.4
XXII	2-Salicyl-2-methoxy-4-phenyl-[a]	1	50	194d	$C_{25}H_{20}O_5$	75.0	74.9	5.0	5.1	7.7	7.6

[a] Recrystallized from 4% hydrochloric acid in methanol. Should be thoroughly dried before taking a melting point. Gave a melting point depression when mixed with XV.

was cooled to 0° for twelve hours, whereupon a heavy gum separated out. The aqueous phase was decanted off and the gum recrystallized from an acetone–water mixture. The yield of XI was 27.5 g. (48%).

Treatment of the Michael Condensation Products with Methanolic Hydrogen Chloride.—One gram of the condensation products was refluxed with 10 g. of 4% hydrochloric acid in absolute methanol for the times indicated in Table II. The products were obtained either directly from the reaction mixture on cooling or by the addition of water, and were recrystallized from ethanol. Further details are given in Table II.

2-Methyl-2-ethoxy-4-phenyl-5-oxo-dihydropyrano(3,2-C)(1)benzopyran.—Two grams of XI was refluxed with 25 cc. of 3% hydrochloric acid in ethanol for twenty-two hours. Crystals were obtained on cooling (m. p. 135–152°). After two recrystallizations from ethanol 70 mg. of the desired product was obtained melting at 177°. It was also obtained in poor yield when 4-hydroxycoumarin and benzalacetone were refluxed in ethanol + sodium ethylate for two days.

Anal. Calcd. for $C_{21}H_{20}O_4$: C, 75.0; H, 6.0. Found: C, 75.0; H, 6.2.

Methylation of the Michael Condensation Products with Diazomethane.—The methyl ethers of IX, XI, XII, XIV were prepared by distilling an excess of ethereal diazomethane into an ether suspension of the compounds and allowing to stand for several hours. On methylation the solids went into solution. The excess diazomethane was decomposed by adding glacial acetic acid. The ether solutions were concentrated and the products, when solid, recrystallized from ethanol. The ethers of XII and IX could not be crystallized and were therefore distilled under low pressure. Further details are included in Table I.

Treatment of XVIII with Aqueous Methanolic Hydrochloric Acid.—One-half gram of XVIII was refluxed with 50 cc. of 10% hydrochloric acid (in 50% methyl alcohol) for six hours. The methanol was distilled off. The reaction mixture was made alkaline with sodium hydroxide, thoroughly triturated and filtered. The filtrate was acidified with hydrochloric acid and the precipitate obtained recrystallized from ethanol: 170 mg. of a product was obtained which melted at 159–161° and showed no m. p. depression when mixed with XI.

Treatment of XVIII with Aqueous Methanolic Sodium Hydroxide.—One-half gram of XVIII was refluxed with 50

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cc. of 10% sodium hydroxide (in 50% methyl alcohol) for six hours. The methyl alcohol was distilled off. An oil was obtained which on the addition of water dissolved completely. Upon acidification of the aqueous solution with hydrochloric acid an oil separated which solidified. This acidic solution including the solid was again made alkaline with sodium hydroxide, thoroughly triturated and filtered. This time some insoluble material remained. The filtrate was acidified with hydrochloric acid and 97 mg. of an oily precipitate was obtained from which no XI could be isolated. From the sodium hydroxide insoluble solid the starting material XVIII was isolated.

Acknowledgment.—We are indebted to Mr. Lloyd Graf for some of the C and H determinations and to Dr. Charles F. Huebner for the many valuable suggestions that he contributed to this work.

Summary

1. 4-Hydroxycoumarin has been condensed with the following α,β-unsaturated ketones by the Michael type addition: ethylideneacetone, mesityl oxide, benzalacetone, anisalacetone, vanillylalacetone, benzalacetophenone, benzal-*o*-hydroxyacetophenone, salicylalacetone, salicylalacetophenone, and 2,2′-dihydroxybenzalacetophenone. The condensations were carried out by refluxing in pyridine.

2. The condensation products from salicylalacetone, salicylalacetophenone, and 2,2′-dihydroxybenzalacetophenone undergo spontaneous dehydration to 7-substituted 6-oxo-(1)benzopyrano(4,3-b)(1)-benzopyrans.

3. The other condensation products (not included above) were converted to the corresponding cyclic methyl ketals by refluxing in methanolic hydrogen chloride.

MADISON, WIS. RECEIVED DECEMBER 14, 1943

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF WISCONSIN]

Studies on 4-Hydroxycoumarins. VI. Glucosides of 4-Hydroxycoumarins[1]

BY CHARLES F. HUEBNER, SULO A. KARJALA, WILLIAM R. SULLIVAN AND KARL PAUL LINK

Glucosides of the anticoagulant, 3,3′-methylenebis-(4-hydroxycoumarin)[2] and of related 4-hydroxycoumarins were desired for use in the study of the relationship between chemical structure and hypoprothrombinemia inducing capacity. Glucosides of the keto-enol 4-hydroxycoumarins have heretofore not been prepared. Certain chemical properties of these glucosides are worthy of note. They are readily hydrolyzed by alkali and some of them undergo cleavage to the aglucone when their acetates are subjected to catalytic deacetylation in methanol by metal alkoxides. Because of the uniqueness of this behavior, the deacetylation reaction was studied in detail.

When stable silver salts of the enol aglucones were realizable they were treated with acetobromoglucose to form the acetylated glucosides. A modification of Robertson's method for phenol β-glycosides[3] was applied to the cases in which the silver salts of the enol aglucones were unstable. No reaction occurs between these enols and acetobromoglucose in the presence of silver oxide unless a catalytic quantity of quinoline is included. In all probability quinoline hydrobromide is the first product of the coupling and the excess of silver oxide regenerates the catalyst. If more than a trace of quinoline is used, the reaction proceeds with decomposition and the production of uncrystallizable sirups.

4-Hydroxycoumarin glucoside tetraacetate (I), 4-hydroxy-6-methylcoumarin glucoside tetraacetate (II), 3-phenyl-4-hydroxycoumarin glucoside tetraacetate (III), and 3,3′-methylenebis-(4-hydroxycoumarin) monoglucoside tetraacetate (IV) were prepared by the silver salt method. The modified Robertson method was used in the preparation of 3,3′-methylenebis-(4-hydroxycoumarin) diglucoside octaacetate (V) and 3-[6-oxo(1)benzopyrano(4,3-b)(1)benzopyran-7-yl]-4-hydroxycoumarin glucoside tetraacetate (VI).

Because of the method of preparation and the substantial negative rotation of all except two of these glucosides (IV and V), the β-configuration can be assigned with some confidence.

All the glucosides and glucoside acetates involving the 4-hydroxycoumarins reduce boiling Fehling solution within two minutes. The acidic nature of 4-hydroxycoumarin ($K_a = 2.3 \times 10^{-6}$) probably accounts for this alkaline hydrolysis. Hibbert[4] and co-workers have shown that the rate of alkaline hydrolysis of phenol glycosides increases with the order of acidity of the parent phenol.

The deacetylation of I and II was accomplished by the catalytic barium methoxide procedure. No method was found for effecting simple deacetylation of the glucoside acetates in which there are substituents on position 3 of the coumarin residue. When III was catalytically deacetylated, the rate of mutarotation gradually fell and the rotation became constant after two weeks. At least 80% of the starting compound had been

(1) Published with the approval of the Director of the Wisconsin Agricultural Experiment Station. Supported through special grants from the Graduate School Research Committee and the Wisconsin Alumni Research Foundation. Part of this work is from the thesis submitted by Charles F. Huebner to the faculty of the Graduate School of the University of Wisconsin in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1943.

(2) Stahmann, Huebner and Link, *J. Biol. Chem.*, **138**, 513 (1941).

(3) Robertson and Waters, *J. Chem. Soc.*, 2729 (1930).

(4) Fisher, Hawkins and Hibbert, THIS JOURNAL, **63**, 3031 (1941).

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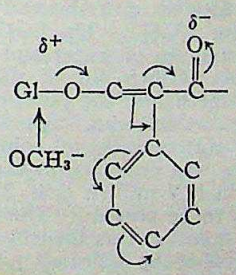
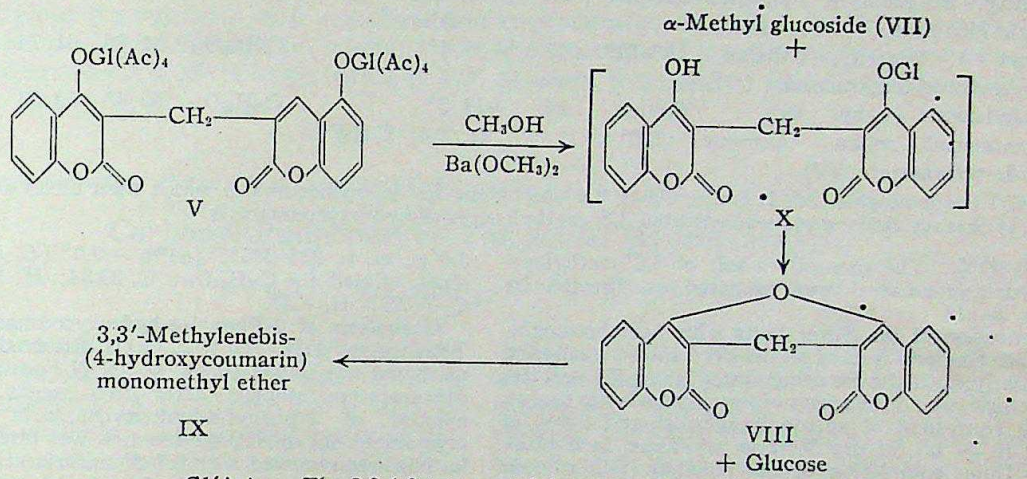
converted to 3-phenyl-4-hydroxycoumarin and α-methyl glucoside (VII).

Isbell[5] has recently pointed out that the cleavage of the sugar-oxygen bond in enol glycosides is favored over fission at the aglucone-oxygen bond. The methanolysis of III furnishes experimental proof for this suggestion. The formation of 3-phenyl-4-hydroxycoumarin rather than 3-phenyl-4-methoxycoumarin and the Walden inversion accompanying the production of VII indicate the point of fission. Conversely, methanolysis of sugar esters usually occurs at the aglycone–oxygen bond with no inversion and formation of the methyl ester of the acid involved in the sugar ester. The presence of the phenyl and carbonyl groups in III favors the indicated electronic shift. The glucosidic carbon is the positive center of this polarized molecule and it is attacked by the methoxyl anion with cleavage of the sugar–oxygen bond.



III

When the catalytic deacetylation of V was attempted, 3,3′-methylene-4,4′-epoxydicoumarin (VIII) and some 3,3′-methylenebis-(4-hydroxycoumarin) monomethyl ether (IX) were obtained instead of the glucoside.[6] Recognizing that III yields 3-phenyl-4-hydroxycoumarin and VII under these conditions, the formation of VIII and IX can be attributed to the following reactions. One glucose residue is liberated initially by alcoholysis yielding VII and 3,3′-methylenebis-(4-hydroxycoumarin) monoglucoside (X). A ring closure of the type noted in mono esters of 3,3′-methylenebis-(4-hydroxycoumarin)[6] then produces VIII and glucose. Part of VIII is then converted to IX by the alkoxide as indicated previously.[6] The production of IX in this manner is preferred over formation by methanolysis of X because the latter reaction would be expected to yield as the methylated component, VII rather than IX.



Gl(Ac)$_4$ = The 2,3,4,6-tetraacetylglucopyranose residue

Additional support for the above mechanism was obtained from a study of the glucose content of the resulting reaction mixture. One half of the theoretical amount was present as free glucose based on the exhibited reducing power. The second half of the reducing power could be liberated by acid hydrolysis, indicating the presence of a methyl glucoside in the reaction mixture. The tetraacetate (IV) of the intermediate (X) was synthesized and it showed the predicted properties. It gave VIII and IX on catalytic deacetylation, and the amount of IX increased as larger amounts of catalyst were used. This further substantiates the mechanism of formation of IX, since in the conversion of VIII to IX the amount of IX produced parallels mole for mole the amount of metal alkoxide used. IV can also be converted to VIII by simply dissolving it in pyridine.

Experimental

Preparation of the Silver Salts of the 3-Substituted-4-Hydroxycoumarins.—The following method was used for the silver salts, with a slight modification in the case of 4-hydroxycoumarin. The 3-substituted-4-hydroxycoumarin was dissolved in one equivalent of 1.5 *N* aqueous sodium hydroxide and one equivalent of silver nitrate plus 2% excess, dissolved in a small amount of water, was added with vigorous stirring. The gelatinous, white silver salt precipitated immediately. It was filtered and resuspended in water, washed thoroughly with water, pressed dry on the funnel and washed once with ethanol. Precautions were taken to work in a feeble light. Since the silver salt of 4-hydroxycoumarin is appreciably soluble in water it was not washed but recrystallized from the minimum volume of water. The salts were dried over calcium chloride *in vacuo*, finely pulverized and dried again at 45° under 0.05 mm. pressure over phosphorus pentoxide.

(5) Isbell, *Ann. Rev. Biochem.*, XII, 215 (1943).
(6) Huebner, Sullivan, Stahmann and Link, THIS JOURNAL, 65, 2292 (1943).

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TABLE I

MONOGLUCOSIDES OF 4-HYDROXYCOUMARINS

Compound	Recrystallized from	M. p., °C.	Yield, %	$[\alpha]^{25}D$	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
4-Hydroxycoumarin glucoside tetraacetate (I)	Methanol	178–179	40	−63.2° (*C*, 2; $CHCl_3$)	$C_{23}H_{24}O_{12}$	56.09	56.17	4.88	4.97
4-Hydroxycoumarin glucoside	Methanol	201–202	90	−106° (*C*, 16; CH_3OH)	$C_{15}H_{16}O_8$	55.55	55.72	4.94	4.94
4-Hydroxy-6-methylcoumarin glucoside tetraacetate (II)	Ethanol	168–170	36	−24.9° (*C*, 2; C_6H_6)	$C_{24}H_{26}O_{12}$	56.91	57.11	5.14	5.35
4-Hydroxy-6-methylcoumarin glucoside	Pyridine water	223–224	90	−86° (*C*, 0.75) pyridine	$C_{16}H_{18}O_8$	56.80	56.98	5.32	5.32
3-Phenyl-4-hydroxycoumarin glucoside tetraacetate (III)	Ethanol	156–158	47	−58.4° (*C*, 3.2; C_6H_6)	$C_{29}H_{28}O_{12}$	61.35	61.74	4.94	5.12
3,3′-Methylenebis-(4-hydroxycoumarin) monoglucoside tetraacetate (IV)	Dry benzene	Sinters 185[a]	25	+14.0° (*C*, 2.5; C_6H_6)	$C_{33}H_{30}O_{15}$	59.45	59.53	4.50	4.67

[a] At 185° the monoglucoside is converted to 3,3′-methylene-4,4′-epoxydicoumarin which then melts at 290°. This behavior is characteristic of monosubstituted 3,3′-methylenebis-(4-hydroxycoumarin)s.[6]

yields 80–90%. The monosilver salt of 3,3′-methylenebis-(4-hydroxycoumarin) was prepared as directed by Huebner, *et al.*[6]

Condensation of the Silver Salts with Acetobromoglucose.—The condensations of all the silver salts were carried out similarly until the resulting sirupy glucoside acetates were crystallized. Five grams of the silver salt was shaken with 0.9 equivalent of acetobromoglucose and 1.0 g. of Drierite in 50 ml. of dry benzene contained in a black bottle. Upon completion of the reaction (two to four days), the silver salts were centrifuged off and washed with hot benzene. The benzene solution was concentrated *in vacuo* yielding a sirup. These sirups were crystallized from a suitable solvent as indicated in Table I. Deacetylation of I and II was accomplished by the method of Brauns[7] (Table I).

Preparation of 3,3′-Methylenebis-(4-hydroxycoumarin) Diglucoside Octaacetate (V).—A solution of 25 g. of acetobromoglucose in 150 ml. of dry benzene was shaken with 10 g. of 3,3′-methylenebis-(4-hydroxycoumarin), 8 g. of silver oxide, 10 g. of Drierite and 4 drops of quinoline for four days. The silver salts and unreacted 3,3′-methylenebis-(4-hydroxycoumarin) were centrifuged off and washed with cold benzene. The combined benzene fraction was concentrated to half its volume, and cooled. The small amount of 3,3′-methylenebis-(4-hydroxycoumarin) that crystallized was filtered off. The benzene solution was extracted with cold 1% sodium hydroxide, then with cold 1% hydrochloric acid solution, and finally with ice water. It was dried over sodium sulfate and concentrated to a sirup. The sirup was dissolved in a minimum of ethanol, filtered from some 3,3′-methylenebis-(4-hydroxycoumarin) which had crystallized out, and stored at 0°. After seven months, partial crystallization had taken place. These crystals were dissolved in the minimum of hot ethanol, the solution filtered while hot and, on cooling, 1 g. of hair-like crystals, m. p. 160–165°, was deposited. After eight crystallizations from ethanol the rotation and m. p. remained constant, m. p. 167–168°; $(\alpha)^{30}D$ + 58.0° (*C*, 2.5; benzene). *Anal.* Calcd. for $C_{47}H_{48}O_{24}$: C, 56.62; H, 4.84. Found: C, 56.97; H, 4.50.

Preparation of 3-[6-Oxo(1)benzopyrano(4,3-b)(1)benzopyran-7-yl]-4-hydroxycoumarin Glucoside Tetraacetate (VI).—A mixture of 4 g. of 3-[6-oxo(1)benzopyran(4,3-b)(1)benzopyran-7-yl]-4-hydroxycoumarin, 12 g. of acetobromoglucose, 5 g. of silver oxide, 5 g. of Drierite, and 5 drops of quinoline was shaken for twenty-four hours. The procedure for working up the reaction mixture was the same as that given for V. The sirup obtained after concentration was rubbed with a small amount of hot ethanol and crystallization occurred. This crop was recrystallized from pyridine diluted with water; yield 3.0 g., m. p. 234–235°: $(\alpha)^{25}D$ −9.0° (*C*, 8; pyridine). *Anal.* Calcd. for $C_{39}H_{32}O_{15}$: C, 63.24; H, 4.32. Found: C, 63.27; H, 4.38.

Alcoholysis of 3-Phenyl-4-hydroxycoumarin Glucoside Tetraacetate (III).—To 10 g. of III dissolved in 300 ml. of methanol was added 10 ml. of 0.2 *N* barium methoxide. Mutarotation stopped after two weeks. The small amount of 3-phenyl-4-hydroxycoumarin which had crystallized out during the reaction was filtered off. The barium was removed with 0.1 *N* sulfuric acid. An equal volume of water was added, the solution concentrated to 50 ml. and the aglucone that crystallized during the concentration was filtered off; 3.4 g. of 3-phenyl-4-hydroxycoumarin was obtained, (81%), m. p. 233–236°. The filtrate was concentrated to a sirup and dissolved in a minimum of hot ethanol. On cooling 1.2 g. of α-methylglucoside (VII) crystallized, m. p. 165–167°; $(\alpha)^{30}D$ +159° (*C*, 1.2; water).

Alcoholysis of 3,3′-Methylenebis-(4-hydroxycoumarin) Monoglucoside Tetraacetate (IV).—In 10 ml. of dry methanol to which had been added 0.2 ml. of 0.5 *N* sodium methoxide solution, 87.8 mg. of IV was refluxed for one half hour; needles of the anhydride VIII crystallized out in the first minute. VIII, which is practically insoluble in methanol, was filtered on a sintered glass funnel, the yield being 23.2 mg. (55%). The methanol filtrate was poured into two volumes of water and a flocculent precipitate of IX was thrown out of solution. After recrystallizing from methanol, the product melted at 171–172°, yield 24 mg. A reducing sugar determination[8] on an aliquot of the water–methanol solution showed that 20.2 mg. of glucose was produced in the reaction. After hydrolysis at 95° in 1 *N* sulfuric acid, 22.0 mg. of glucose (93%) was shown to be present. The reducing sugar in an aliquot of the solution was identified by the osazone method.[9] If one half of the indicated quantity of $NaOCH_3$ was used the yield of VIII was increased to 86%.

Alcoholysis of 3,3′-Methylenebis-(4-hydroxycoumarin) Diglucoside Octaacetate (V).—In 4 ml. of dry methanol to which had been added 0.1 ml. of 0.2 *N* barium methoxide, 67.8 mg. of V was refluxed for one half hour. The technique of separation was the same as above; 12.7 mg. (59%) of VIII was formed. Before the acid hydrolysis, 13.0 mg. of reducing sugar (as glucose) was present (theoretical for one mole of glucose from V is 12.2 mg.). After acid hydrolysis 24.0 mg. of glucose was present (theoretical for two moles of glucose is 24.4 mg.).

Summary

1. A series of glucosides of the 4-hydroxy-

(7) Brauns, THIS JOURNAL, 48, 2776 (1926).

(8) Shaffer and Somogyi, *J. Biol. Chem.*, 100, 695 (1933).

(9) Hassid and McCready, *Ind. Eng. Chem., Anal. Ed.*, 14, 683 (1942).

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coumarins has been prepared. The glucoside acetates of 4-hydroxycoumarin, 4-hydroxy-6-methylcoumarin, 3-phenyl-4-hydroxycoumarin and the monoglucoside acetate of 3,3′-methylenebis-(4-hydroxycoumarin) were prepared by treating the enol silver salts with acetobromoglucose.

2. The diglucoside octaacetate of 3,3′-methylenebis-(4-hydroxycoumarin) and of 3-[6-oxo(1)-benzopyrano(4,3-b)(1)benzopyran-7-yl]-4-hydroxycoumarin glucoside tetraacetate were prepared by coupling the aglucone with acetobromoglucose in the presence of catalytic amounts of quinoline and an excess of silver oxide.

3. The two 4-hydroxycoumarin glucoside tetraacetates unsubstituted on position 3 were successfully deacetylated by the catalytic barium methoxide procedure.

4. The 3-substituted-4-hydroxycoumarin glucoside acetates underwent alcoholysis with the removal of the glucose residue involving a Walden inversion. A course of reaction in which both glucoside residues were removed from 3,3′-methylenebis-(4-hydroxycoumarin) diglucoside octaacetate with the formation of 3,3′-methylene-4,4′-epoxydicoumarin, and 3,3′-methylenebis-(4-hydroxycoumarin) monomethyl ether is proposed

MADISON, WISCONSIN RECEIVED DECEMBER 14, 1943

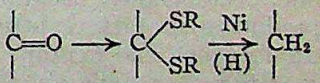
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

Carbonyl Reduction by Thioacetal Hydrogenolysis

BY M. L. WOLFROM AND J. V. KARABINOS

In connection with another problem being pursued in this Laboratory, we were interested in convenient methods of synthesis for 1- and 2-desoxy sugar alcohols. The present methods are laborious and are not always of general applicability. The reduction of the 2-desoxyaldoses, synthesized through the glycals, constitutes the only present synthesis for the 2-desoxy sugar alcohols.[1] More numerous are the procedures for the preparation of the 1-desoxy sugar alcohols. These may be prepared through the reduction of a terminal halide in a sugar alcohol and special methods exist for obtaining these halides by utilizing the preferential reactivity of the primary alcohol function.[2] The 1-desoxy sugar alcohols are also preparable by reduction of the ω-desoxy-aldoses, either naturally occurring or synthesized[3] from the aldoses by reduction therein of a terminal halide group. In the acyclic sugar derivatives, a diisopropylidene-*aldehydo*-pentose has reacted with methyl Grignard reagent to produce, after hydrolysis of the isopropylidene groups, a 1-desoxy-hexitol.[4] Reduction of the first carbon of the diazomethyl ketones[5] of the acyclic sugar acetates or the reaction of diazomethane with *aldehydo*-sugar esters,[6] led to the synthesis of 1-desoxy-*keto*-sugar acetates which on reduction with subsequent deacetylation, led to the synthesis of a mixture of two 1-desoxy sugar alcohols.[7]

The remarkable discovery of the simultaneous desulfurizing and reducing action of Raney nickel[8] by Bougault, Cattelain and Chabrier[9] and its subsequent extension by Mozingo and co-workers,[10] offered the promise of establishing a simple and direct route to the 1- and 2-desoxy sugar alcohols. The French workers had demonstrated this reaction with the thiocarbonyl compounds, thiols, disulfides and heterocyclic sulfur (thiophene); the latter group had extended the reaction to sulfides, sulfoxides and sulfones; and Richtmyer, Carr and Hudson[11] had ememployed reductive hydrolysis with Raney nickel in their synthesis of polygalitol (1,5-anhydro-(*levo*)-sorbitol) tetraacetate from the acetates of glucothiopyranose and its disulfide. We have now found that this reaction is applicable to thioacetals, leading to easy reduction to the hydrocarbon stage.



The other products of the reaction are presumably sulfide sulfur (verified in the present work) and the hydrocarbon RH. Following the directions of Mozingo and co-workers, we employed dilute ethanol as the solvent. Under these conditions we have noted that acetaldehyde is formed. This is to be expected from the dehydrogenating action of Raney nickel in the liquid phase,[12] but it may play some part in the reaction by furnishing a source of active hydrogen.

(1) M. Bergmann, H. Schotte and W. Leschinsky, *Ber.*, **56**, 1052 (1923); E. Fischer, *ibid.*, **47**, 196 (1914).

(2) *Cf.* R. M. Hann, A. T. Ness and C. S. Hudson, THIS JOURNAL, **66**, 73 (1944).

(3) *Cf.* E. Fischer and K. Zach, *Ber.*, **45**, 3761 (1912).

(4) K. Gätzi and T. Reichstein, *Helv. Chim. Acta*, **21**, 914 (1938).

(5) M. L. Wolfrom and R. L. Brown, THIS JOURNAL, **65**, 1516 (1943).

(6) P. Brigl, H. Mühlschlegel and R. Schinle, *Ber.*, **64**, 2921 (1931); M. L. Wolfrom, D. I. Weisblat, W. H. Zophy and S. W. Waisbrot, THIS JOURNAL, **63**, 201 (1941).

(7) Unpublished work of Dr. B. W. Lew of this Laboratory.

(8) M. Raney, U. S. Patent 1,628,190 (1927).

(9) J. Bougault, E. Cattelain and P. Chabrier, *Bull. soc. chim.*, [5] **5**, 1699 (1938); *ibid.*, [5] **7**, 780, 781 (1940).

(10) R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers, THIS JOURNAL, **65**, 1013 (1943); V. du Vigneaud, D. B. Melville, K. Folkers, D. E. Wolf, R. Mozingo, J. C. Keresztesy and S. A. Harris, *J. Biol. Chem.*, **146**, 475 (1942).

(11) N. K. Richtmyer, C. J. Carr and C. S. Hudson, THIS JOURNAL, **65**, 1477 (1943).

(12) W. Reeves and H. Adkins, *ibid.*, **62**, 2874 (1940).

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D-Galactose diethyl thioacetal (mercaptal) was reduced to L-fucitol but a higher yield (66%) was obtained when the pentaacetate was employed. In view of the ready availability of the aldose thioacetals and their acetates, this procedure gives easy access to the 1-desoxy sugar alcohols. Extension to D-glucose diethyl thioacetal pentaacetate yielded L-gulomethylitol pentaacetate.

The high acidity required for aldose thioacetal formation destroys the acid-sensitive ketoses[13] and thus the thioacetals of the ketoses cannot be obtained directly from the sugars. They are obtainable from the *keto*-acetates[14] and recently a general method for the synthesis of *keto*-acetates has been devised.[15] D-Fructose diethyl thioacetal (mercaptole) pentaacetate was subjected to hydrogenolysis and yielded 2-desoxy-(*levo*)-sorbitol pentaacetate, albeit in rather low yield. Even with this low yield, the present method is preferable to the former procedure[1] and it is possible that future work may lead to better reaction conditions and higher yields. Deacetylation to the parent alcohol, while not carried out in the present work, is a well-known and relatively simple process.

The above-described reduction of a carbonyl to a methylene group by means of neutral Raney nickel in dilute alcohol, offers promise in general organic preparative work. A previous reduction of a mercaptal with zinc dust and alkali is recorded[16] and recently the desulfurizing action of Raney nickel alloy and alkali in the hydrogenolysis of aromatic sulfonic acids has been described.[17] The present general methods for the reduction of a carbonyl group to the methylene stage are the Clemmensen reduction, the Wolff–Kishner method, high-pressure catalytic methods and electrolytic reduction. The thioacetal hydrogenolysis procedure adds an alternative method and descriptions are made of applications to benzaldehyde, benzophenone, acetophenone, heptanal and heptanone-2, producing in turn, toluene, diphenylmethane, ethylbenzene and heptane. The intermediate thioacetals are readily obtained and were used without purification.

Experimental

Preparation of Raney Nickel Catalyst.—The nickel catalyst was prepared from nickel–aluminum alloy (Raney) according to the procedure of Mozingo and co-workers,[18] employing their later-described[10] modifications. The nickel should be washed well to remove all traces of alkali

A. Preparation of Desoxyhexitols

1-Desoxy-D-galactitol (L-Fucitol) Pentaacetate (Procedure A).—To 1.00 g. of D-galactose diethyl thioacetal (mercaptal) pentaacetate[19] was added 100 cc. of 70% ethanol and 15 g. of Raney nickel catalyst and the mixture was refluxed for five hours. At the end of this period a filtered test portion of the solution no longer evolved ethyl mercaptan on acidification with hydrochloric acid and heating. The nickel was removed by centrifugation and was washed several times with hot ethanol by centrifugation followed by decantation, and the centrifugates were combined. (It was noted that the nickel residue evolved hydrogen sulfide (tested with lead acetate paper) on treatment with dilute hydrochloric acid.) These were concentrated under reduced pressure at 40° to a volume of 10–20 cc., whereupon the product crystallized and was collected by filtration after cooling in an ice-bath; yield 0.55 g. (66%), m. p. 118–121°. Pure material was obtained on one recrystallization from ethanol; m. p. 126–127° unchanged on admixture with authentic L-fucitol pentaacetate of m. p. 126–127°, spec. rot. +20.9° (17°, *c* 2.8, $CHCl_3$, D line). The constants recorded[20] for L-fucitol pentaacetate are: m. p. 127°, spec. rot. +20.5° (25°, *c* 3.0, $CHCl_3$, D line).

1-Desoxy-D-glucitol (1-Desoxy-(*levo*)-sorbitol, L-Gulomethylitol) Pentaacetate.—D-Glucose diethyl thioacetal pentaacetate[21] (0.50 g.) was subjected to hydrogenolysis as in the preceding experiment (procedure A) and the reaction product was isolated in the same manner; yield 0.25 g. (60%), m. p. 98–101°. Pure material was obtained on further crystallization from ethanol; m. p. 102–103°, m. p. 102–104° on admixture with authentic L-gulomethylitol pentaacetate of m. p. 103–104°, spec. rot. +22° (17°, *c* 0.7, $CHCl_3$, D line), +20° (20°, *c* 0.5, MeOH, D line). The recorded[4] constants for L-gulomethylitol pentaacetate are: m. p. 105–106°, spec. rot. +21° (21°, *c* 2, MeOH, D line).

2-Desoxy-D-mannitol (2-Desoxy-(*levo*)-sorbitol, 2-Desoxy-D-glucitol) Pentaacetate.—D-Fructose diethyl thioacetal pentaacetate[14] (500 mg.) was subjected to hydrogenolysis as in procedure A except that the time of reaction was decreased to three hours. On concentration of the centrifugate under reduced pressure there was obtained a sirup (300 mg.) which crystallized with some difficulty; yield 82 mg. (20%), m. p. 68–70°, spec. rot. +31° (24°, *c* 2.8, $CHCl_3$, D line). Pure material was obtained on further crystallization from ether–petroleum ether; m. p. 85–87° unchanged on admixture with an authentic specimen of 2-desoxy-(*levo*)-sorbitol of m. p. 86–87°. The constants for this substance are: m. p. 86–87°, spec. rot. +35° (25°, *c* 3, $CHCl_3$, D line).[22]

1-Desoxy-D-galactitol (L-Fucitol) from D-Galactose Diethyl Mercaptal.—D-Galactose diethyl thioacetal[19] (1.00 g.) was subjected to hydrogenolysis as described in procedure A except that the reaction time was decreased to one hour and the nickel residues were washed thoroughly with water. The centrifugate was concentrated under reduced pressure to a thin sirup which was brought to crystallization by the addition of absolute ethanol; yield 140 mg. (24%) in 2 crops, m. p. 149–151°. Pure material was obtained on recrystallization from absolute ethanol; m. p. 152–153° unchanged on admixture with authentic L-fucitol of like m. p., spec. rot. +4.4° (25°, *c* 3, saturated aqueous borax solution, D line). The recorded[23] constants for L-fucitol are: m. p. 153–154°, spec. rot. +4.7° (20°, *c* 3, aqueous borax (1 part borax: 10 parts water) solution).

B. Thioacetal Formation and Hydrogenolysis of Several Simple Aldehydes and Ketones

Thioacetal Formation.—The aldehyde or ketone (0.1 mole) was added slowly with cooling (ice-bath), to a mixture of 20 cc. (*ca.* 2.7 moles) of ethyl mercaptan, 2.5 g. of freshly fused zinc chloride and 2 g. of anhydrous sodium

(13) E. Fischer, *Ber.*, **27**, 673 (1894).

(14) M. L. Wolfrom and A. Thompson, THIS JOURNAL, **56**, 880 (1934); *cf.* P. Brigl and R. Schinle, *Ber.*, **66**, 325 (1933).

(15) M. L. Wolfrom, S. W. Waisbrot and R. L. Brown, THIS JOURNAL, **64**, 2329 (1942).

(16) C. Kelber and A. Schwarz, *Ber.*, **44**, 1693 (1911); **45**, 2484 (1912).

(17) E. Schwenk, D. Papa, B. Whitman and Helen Ginsberg, *J. Org. Chem.*, **9**, 1 (1944).

(18) R. Mozingo, K. Adkins and L. Richards, "Organic Syntheses," **21**, 15 (1941).

(19) M. L. Wolfrom, THIS JOURNAL, **52**, 2467 (1930).

(20) M. L. Wolfrom, W. J. Burke and S. W. Waisbrot, *ibid.*, **61**, 1828 (1939).

(21) (a) W. Schneider and Johanna Sepp, *Ber.*, **51**, 226 (1918); (b) M. L. Wolfrom, THIS JOURNAL, **51**, 2190 (1929).

(22) Unpublished work of Dr. M. Konigsberg of this Laboratory.

(23) E. Votoček and B. Potměšil, *Ber.*, **46**, 3053 (1913).

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sulfate, contained in a glass-stoppered bottle. The aldehydes reacted more vigorously than the ketones. The mixture was maintained at 5° for twenty hours and then at room temperature for four hours, whereupon it was poured into 50 cc. of ice and water in a separatory funnel. The water-insoluble layer was washed consecutively with 10% aqueous sodium hydroxide and water, and dried with sodium sulfate. This crude product was used directly for the hydrogenolysis. The yields were nearly quantitative.

Hydrogenolysis of Benzaldehyde Diethyl Thioacetal.—The hydrogenolysis was carried out on 0.01 mole of the thioacetal as described in procedure A. After a reaction period of two hours, the mixture was diluted with 300 cc. of water and distilled until the cessation of ethanol distillation. The process was repeated on the distillate and to the azeotrope distilling over was added sufficient water to separate the toluene which was collected, dried and distilled; yield 0.60 g. (65%), b. p. 110° at 750 mm., $n^{25}D$ 1.498. The generally accepted constants for toluene are: b. p. 111° at 760 mm., $n^{16}D$ 1.4978.

Hydrogenolysis of Acetophenone Diethyl Thioacetal.—The thioacetal (0.01 mole) was treated in the manner described above for the hydrogenolysis of benzaldehyde diethyl thioacetal; yield of ethylbenzene 0.70 g. (66%), b. p. 134° at 750 mm., $n^{25}D$ 1.498. The accepted constants for ethylbenzene are: b. p. 136° at 760 mm., $n^{14.5}D$ 1.4983.

Hydrogenolysis of Heptanone-2 Diethyl Thioacetal.—The hydrogenolysis was carried out on 0.01 mole of the thioacetal as described in procedure A. The reaction product was distilled out of the reaction mixture, the distillate was diluted with a large volume of water and extracted twice with ether. The ether extract was washed with 50% calcium chloride aqueous solution, then with water, dried over sodium sulfate and distilled; yield 0.50 g. (50%), b. p. 96–100° at 750 mm., $n^{25}D$ 1.390. The accepted constants for heptane are: b. p. 98.4° at 760 mm., $n^{23}D$ 1.3867.

Hydrogenolysis of Heptanal Diethyl Thioacetal.—The thioacetal (0.01 mole) was treated in the manner described above for the hydrogenolysis of heptanone-2 diethyl thioacetal; yield of heptane 0.40 g. (40%), b. p. 98–100° at 750 mm., $n^{25}D$ 1.395.

Hydrogenolysis of Benzophenone Diethyl Thioacetal.—The thioacetal (0.01 mole) was subjected to hydrogenolysis as described in procedure A. The sirup obtained on solvent removal from the centrifugate was dissolved in ether, dried with sodium sulfate, and the solvent removed; yield 1.3 g. (77%), b. p. 255° at 740 mm. A boiling point of 261–262° at 760 mm. is recorded for diphenylmethane. Further identification was afforded by the preparation[24] of the 2,4,2′,4′-tetranitro derivative which after two recrystallizations from glacial acetic acid melted at 170–173° (accepted value 172°).

Identification of Acetaldehyde Formed During the Hydrogenolysis.—In one of the experiments (the hydrogenolysis of heptanal diethyl thioacetal) the gases escaping from the top of the condenser during the refluxing were bubbled through 5 cc. of a solution of 2,4-dinitrophenylhydrazine (1 g. of the hydrazine dissolved in 7 cc. of concentrated sulfuric acid, then diluted with 100 cc. of methanol followed by 25 cc. of water). After one hour, crystalline needles separated which after two recrystallizations from ethyl acetate–ethanol were identified as acetaldehyde 2,4-dinitrophenylhydrazone by melting point (161–163°) and mixed melting point (unchanged) with an authentic sample (m. p. 162–164°).

Summary

1. It is shown that the carbonyl group of aldehydes and ketones may be reduced to the hydrocarbon stage by the hydrogenolysis of their thioacetals with Raney nickel in dilute ethanol solution.

2. Examples are cited for the diethyl thioacetals of *aldehydo*-D-galactose (and its pentaacetate), *aldehydo*-D-glucose pentaacetate, *keto*-D-fructose pentaacetate, benzaldehyde, heptanal, heptanone-2, acetophenone and benzophenone.

(24) Shriner and Fuson, "The Systematic Identification of Organic Compounds," John Wiley and Sons, Inc., New York, N. Y., 2nd ed., 1940, p. 163.

COLUMBUS, OHIO RECEIVED MARCH 8, 1944

[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1a]]

Pyrolysis of Nicotine to Myosmine

BY C. F. WOODWARD, ABNER EISNER AND PAUL G. HAINES

Two new processes have been developed in this Laboratory for the preparation of nicotinic acid from nicotine. One involves the catalytic, vapor-phase, air oxidation of nicotine to nicotinonitrile,[1b] which is hydrolyzable to either nicotinic acid[2] or nicotinamide,[3] whereas the second employs the catalytic, liquid-phase, sulfuric acid oxidation of nicotine directly to nicotinic acid.[4]

It appeared that an alternative method could be employed for a stepwise conversion of nicotine to nicotinic acid which would utilize a preliminary pyrolysis of the alkaloid to β-alkyl and β-alkenyl pyridines prior to oxidation of these products.

This paper discloses the results obtained in a study of the pyrolytic reaction. Preliminary experiments indicated that the yields of such products as β-picoline, β-ethylpyridine, and β-vinylpyridine were too low to justify the utilization of this reaction in the preparation of nicotinic acid from nicotine. This investigation revealed, however, that myosmine (III) can be produced in fair yields, and most of the data herein reported were obtained in an attempt to determine the optimum pyrolytic conditions for the production of this rare alkaloid.

Brief references to the pyrolysis of nicotine have been made previously by Cahours and Étard,[5] but the two experiments reported were

(1) (a) This is one of four Regional Research Laboratories operated by the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

(1) (b) Woodward, Badgett and Willaman, accepted for publication in *Ind. Eng. Chem.*

(2) McElvain and Goese, THIS JOURNAL, **63**, 2283 (1941).

(3) Krewson and Couch, *ibid.*, **65**, 2256 (1943).

(4) Woodward, Badgett and Kaufman, accepted for publication in *Ind. Eng. Chem.*

(5) Cahours and Étard, *Compt. rend.*, **90**, 275 (1880); **92**, 1079 (1881).

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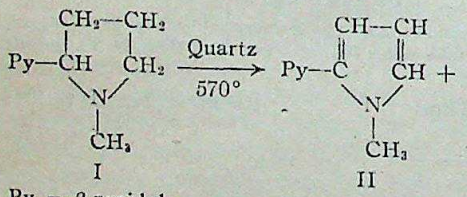
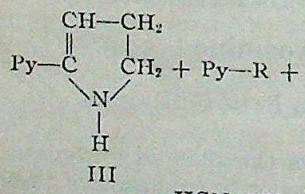
apparently only incidental to the investigation of the reaction of nicotine with sulfur and selenium. In these procedures, nicotine was passed through an iron pipe filled with porcelain chips while the reactor was "heated to dark red" on one occasion and to "cerise red" in the other experiment. In addition to appreciable quantities of unchanged nicotine, these investigators obtained pyridine, "picoline," and a "collidine," which was later postulated to be "a propyl pyridine," since it was oxidized to the same acid obtained by the oxidation of nicotine. It was further reported that the "propyl pyridine fraction tended to form resinous polymerides." In view of this observation, it appears that the product under consideration contained at least small amounts of a β-alkenyl pyridine.

The present investigation has shown that β-vinylpyridine is produced in the pyrolysis of nicotine (I), but in general the pyrolytic fission of nicotine results in the formation of a variety of products rather than a high yield of any one material. The N-methylpyrrolidine nucleus of the nicotine molecule appears to be the more susceptible to pyrogenic disintegration, since the following pyrolysis products were obtained: ammonia, methylamine, hydrogen cyanide, pyridine, β-picoline, β-ethylpyridine, β-vinylpyridine, 3,2′-nicotyrine (II), myosmine (III), and a high-boiling fraction not yet identified.



I II

Py, = β-pyridyl



III

HCN, NH_3 and CH_3NH_2

R = CH_3, C_2H_5 and C_2H_3 (vinyl)

The pyrolysis of nicotine over quartz at 570° produced a fair yield of myosmine but only small quantities of other identifiable reaction products. Pyridine was not isolated under these experimental conditions, but it was produced in low yields when the pyrolysis temperature was increased to 700° or when the quartz contact material was replaced by activated alumina at 500°. These latter conditions were too drastic for the obtention of myosmine.

In addition to being the principal pyrolysis product obtained with a quartz contact material at 570°, myosmine was of particular interest from an historical as well as a theoretical viewpoint. This base was first isolated from cigar smoke by Wenusch and Schoeller,[6] and since the alkaloid had never been found in the *Nicotiana* genus it was postulated by these investigators that myosmine was probably formed from nicotine during the smoking process. Although our experiments were conducted in the absence of air, the pyrolysis of nicotine to myosmine lends some credence to this theory.

The myosmine obtained from cigar smoke was assigned formula III by Späth, Wenusch, and Zajic.[7] This structural configuration was later confirmed synthetically by Späth and Mamoli.[8] N-Benzoylpyrrolidone was condensed with ethyl nicotinate, and the resulting 3-nicotinyl-N-benzoylpyrrolidone-2 was heated with concentrated hydrochloric acid. The latter reaction involved hydrolysis, decarboxylation, and ring closure to the desired product (III). Myosmine was prepared by a similar procedure in the present investigation, and the picrate derivative was found to be identical with the picrate of the pyrolysis material.

A study of the pyrolytic reactions of nicotine and resulting products, such as nicotyrine, directs attention to the pyrogenic behavior of N-substituted pyrroles and pyrrolidines. The pyrolysis of N-substituted pyrroles yields two types of reaction products. One reaction course, exemplified by the isomerization of N-acetylpyrrole to 2-acetylpyrrole, involves a migration of the substituting group from the 1 to 2 position.[9] The pyrogenic conversion of N-methylpyrrole to pyridine illustrates a second reaction type resulting in ring enlargement.[10] In this reaction the formation of a six-membered ring is apparently preceded by isomerization to 2-methylpyrrole. Similar reactions have not been reported in the pyrrolidine series.

Insofar as the authors are aware, the pyrolytic conversion of nicotine to myosmine is a new type of reaction. Since the formation of methane was not established, it is not known whether myosmine is produced by the direct elimination of methane from nicotine or by a more involved reaction. The fact that Meisenheimer and Schütze[11] obtained fair yields of methane and 2-propylquinoline by continued refluxing of N-methyl-2-propyldihydroquinoline at 270° may be indicative of the simpler reaction mechanism.

Experimental

Apparatus.—The iron reactor employed in most of the pyrolysis experiments consisted of a 4-foot length of 1-inch iron pipe maintained in a vertical, tubular, electrically heated furnace. An iron "Y" tube was connected to the upper opening of the reactor. The top of the vertical side of this fitting was provided with a cap, which served as a support for a sealed-in iron thermocouple well. The

(6) Wenusch and Schoeller, "Fachliche Mitteilungen der Österreichischen Tabakregie," **2**, 15 (1933).
(7) Späth, Wenusch and Zajic, *Ber.*, **69**, 393 (1936).
(8) Späth and Mamoli, *ibid.*, **69**, 757 (1936).
(9) Ciamician and Magnaghi, *ibid.*, **18**, 416, 1828 (1885).
(10) Pictet, *ibid.*, **37**, 2792 (1904); **38**, 1947 (1905).
(11) Meisenheimer and Schütze, *ibid.*, **56**, 1353 (1923).

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other opening of the "Y" tube was employed for addition of the nicotine. The thermocouple well was centered in the iron reactor and extended down through a bed of quartz chips. This well was supplied with a movable thermocouple in order that the temperature could be determined at any point within the heated zone. About 350 cc. of 4- to 6-mesh quartz chips was maintained in a 34-inch length of the heated reactor. At a maximum temperature of 570° within the quartz bed, a 15° temperature differential (555–570°) was observed over a 12-inch length of the reactor. The volume of quartz within this temperature range was 124 cc., and this value was employed in the corresponding space-velocity calculations below. The bottom of the reactor was connected to a receiving train, which consisted in turn of a 1-liter 2-neck flask immersed in an ice-bath, a water-cooled condenser, a dry-ice trap, and an exhaust tube leading to a well-ventilated hood. In experiments at 550° or lower, the iron reactor was replaced by a Pyrex-glass tube of equal size.

Procedure.—The following data, unless otherwise indicated, were taken from Experiment 6 (Table I) to illustrate the experimental procedure. Nitrogen was passed through the apparatus for a period of fifteen minutes before the pyrolysis. Two hundred and fourteen grams of nicotine was then added, at a uniform rate over a period of one hundred and ninety minutes, to the iron reactor, which was maintained at a temperature of 570°. Although a total of 350 cc. of 4- to 6-mesh quartz was employed as a contact material in the heated reactor, only 124 cc. of this volume was within the temperature range of 555–570°. After all the nicotine had been added, the apparatus was again flushed with nitrogen to remove volatile products from the reactor.

The 201 g. of liquid condensate collected in the ice-cooled receiver was fractionally distilled through a helix-packed column (2.2 × 50 cm.) equipped with a reflux head. Several of the fractions were obtained in too small a quantity to be reliably identified by redistillation. In view of these small amounts and the possibility of an azeotropic distillation, each fraction was characterized by means of its picric acid derivative.

Identification of Pyrolysis Products

The identity of the derivatives of all pyrolysis products reported below was confirmed by the fact that the melting points remained unchanged when the derivatives were mixed with authentic specimens.

Myosmine and Nicotyrine.—Since this investigation resolved itself into a determination of the optimum pyrolytic conditions for the production of myosmine, the data relating particularly to myosmine are summarized in Table I. In view of the fact that other identified pyrolysis products were obtained in low yields in all experiments, these values have not been included in the table. Thirty grams of myosmine distilled at 119.0 to 130.0° (4.3 mm.). After recrystallization from water, the picric acid derivative of this fraction melted at 183.0 to 184.0°. An additional 5 g. of myosmine was obtained from higher boiling fractions. On cooling to 5°, all these fractions crystallized. The 35 g. represents an 18.1% conversion on the basis of the weight of the original nicotine and 33.3% of the theoretical yield on the basis of nicotine consumed in the pyrolysis experiment. A 90% recovery of pure product could be obtained by twice recrystallizing the combined myosmine fractions from petroleum ether cooled in an acetone–dry-ice mixture.

TABLE I

EFFECT OF PYROLYLIC CONDITIONS ON YIELDS OF MYOSMINE

Expt.	Max. temp., °C.	Nicotine, g.	Time, min.	Space velocity[a]	Myosmine produced, % of theoretical: On basis of nicotine added	On basis of nicotine destroyed
1[b]	500	201.8	170	166	2.33	13.0
2[b]	600	200.6	220	144	17.5	24.6
3[c]	700	200.3	240	199	0	0
4[c]	600	213.5	200	228	16.4	21.0
5[c]	650	218.4	190	259	3.3	..
6[c]	570	214	190	233	18.1	33.3
7[c]	550	220	325	136	16.5	31.5
8[c]	570	611	380	332	14.1	28.9

[a] Cc. of nicotine at reaction temperature per hour divided by cc. of contact material. [b] Glass reactor used. [c] Iron reactor used.

To remove steam-volatile bases, the crude myosmine was subjected to steam distillation through a six-ball Snyder column. Although Wenusch and Schoeller[6] reported myosmine to be steam volatile, it was observed that the alkaloid did not distill azeotropically with water. With an efficient fractionating column, the base was still retained in the distillation flask when test portions of the aqueous distillate were no longer alkaline. This is in agreement with Smith's observations[12] that nicotine distilled azeotropically with water while nornicotine and anabasine did not. The latter two alkaloids contain a cyclic secondary amino group, as does myosmine.

Portions of the steam distillate were taken at varying intervals and treated with picric acid. The melting points of the picrates showed that nicotine was the principal contaminant in the early stages of the distillation, while traces of 3,2′-nicotyrine were obtained in subsequent portions. The suspected nicotyrine picrate melted at 169.0 to 170.0°.

The steam-distillation residue was made strongly alkaline and extracted many times with ether. The ether extract was dried over anhydrous sodium carbonate and filtered, and the filtrate was then saturated with dry hydrogen chloride until precipitation was complete. The filtered myosmine dihydrochloride was dissolved in sodium hydroxide. Pure myosmine was obtained by extracting the alkaline solution with ether, drying the extract over anhydrous sodium carbonate, removing the drying agent by filtration, and then evaporating the solvent. After being pressed on a porous plate, the residual myosmine melted at 44.0 to 45.0°, which is in agreement with the melting point reported by Späth and Mamoli.[8] *Anal.* Calcd. for $C_9H_{10}N_2$: C, 73.97; H, 6.85; N, 19.18. Found: C, 73.74; H, 6.87; N, 19.38. The picric acid derivative melted at 183.0 to 184°, which agrees with the melting point observed by Späth, Wenusch and Zajic.[7]

The identity of this material was conclusively established by comparison with the picrate of synthetic myosmine. Three and four-tenths grams of N-benzoylpyrrolidone-2 was condensed with 2.7 g. ethyl nicotinate, according to the method of Späth and Mamoli.[8] The reaction mixture was then refluxed for forty-two hours with 60 cc. of 48% hydrobromic acid. After the acid reaction mixture was made strongly alkaline, the solution was thrice extracted with ether, and the ether extract was then dried over anhydrous calcium sulfate. The drying agent was then removed by filtration, and the filtrate was concentrated on a steam-bath. The 0.7 g. of residual oil was treated with an aqueous solution of picric acid. After two recrystallizations from water, the precipitated picrate melted at 183.0 to 184.5° and was identical with the picrate from the purified pyrolysis product because the mixture had the same melting point.

Hydrogen Cyanide, Ammonia and Methylamine.—The presence of hydrogen cyanide in the pyrolysis products was detected in the exit gases. Distillation of the liquid condensate in the receiver resulted in the sublimation of ammonium cyanide, which crystallized on the cold finger of the reflux head. The formation of ammonia in pyrolysis Experiment 4 was confirmed by allowing the products collected in the dry-ice trap to distill into water. Phenyl thiourea melting at 156 to 157.5° was produced when the solution was treated with phenyl isothiocyanate. A similar procedure in Experiment 7 resulted in the formation of methyl phenyl thiourea, which melted at 112 to

(12) Smith, *Ind. Eng. Chem.*, **34**, 251 (1942).

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113°, and thereby established the presence of methylamine.

Pyridine.—Pyridine was not isolated from the pyrolysis products of nicotine over quartz at temperatures of 600° or lower. Pyridine was obtained, however, when nicotine was pyrolyzed at 700° in the presence of quartz or at 500° over activated alumina. The picric acid derivative melted at 168.5 to 170°.

β-Picoline.—Only 1.4 g. of the product distilled at 100 to 135°. Although this fraction appeared to have no definite boiling point, it was shown to be principally β-picoline by its picric acid derivative, which melted at 148.0 to 149.0°. The 4.1 g. distilling at 135.0 to 155.0° was shown to be β-picoline by the same procedure.

β-Ethylpyridine.—The 7.0-g. fraction distilling at 155 to 180° was probably a mixture of β-ethylpyridine and β-vinylpyridine. Repeated recrystallization of the picric acid derivative of this fraction did not yield a pure picrate. Redistillation of the fraction gave a distillate which again yielded an inseparable mixture of picrates, while the residue in the distillation flask yielded a picrate melting at 141 to 143°. The latter compound was identical with β-vinylpyridine picrate.

In Experiment 8, however, the fraction distilling at 155 to 180° yielded a picrate which melted at 128.0 to 129.5°. Since this is the reported melting point of β-ethylpyridine picrate, a synthetic sample of β-ethylpyridine was prepared by the following procedure:

A solution of 7.6 g. of β-acetylpyridine hydrochloride[13] dissolved in 30 ml. of water was added to a solution of 5.6 g. of semicarbazide hydrochloride and 8.0 g. of sodium acetate in 30 ml. of water. After being warmed on the steam-bath for twenty minutes and then cooled in an ice-bath, the semicarbazone acetate salt precipitated. The yield of product after drying *in vacuo* was 13.1 g.

The semicarbazone acetate salt was reduced to β-ethylpyridine by the general method of Wolff and Kishner. Thirteen grams of the semicarbazone acetate salt was mixed with 15.6 g. of sodium ethylate in a distillation flask, which was then heated in an oil-bath. As the oil-bath temperature was gradually increased to 180°, a few grams of liquid distilled which had the smell of alcohol and formed no picrate. The 2.8 g. of liquid distillate obtained at a bath temperature of 180 to 220° formed a picrate melting at 128.5 to 130.0° (cor.) after two crystallizations from water. Stoehr[14] reported 128.0 to 130.0° as the melting point of β-ethylpyridine picrate. The melting point was not depressed when this picrate was mixed with the suspected β-ethylpyridine picrate from the nicotine pyrolysis.

β-Vinylpyridine.—About 0.7 g. of the pyrolysis product distilled at 57.0 to 66.0° (2.7 mm.). The picric acid derivative melted at 142.0 to 144.0°, which is in agreement with the reported melting point of β-vinylpyridine picrate. An authentic sample of β-vinylpyridine was prepared by the dehydration of 3-(α-hydroxyethyl)-pyridine with phosphorus pentoxide.[15] The picrate of the synthetic material melted at 142.0 to 144.0°, and was identical with the picric acid derivative of the pyrolysis product.

Nicotine.—A total of 97.4 g. of unchanged nicotine was recovered from the reaction mixture. The major portion distilled at 104 to 109° (4.9 mm.). The limited number of experiments herein reported indicated that the highest yields of myosmine were obtained under experimental conditions which did not completely destroy the nicotine.

Unidentified Fraction and Residue.—The 4.1-g. fraction distilling at 152.0 to 165.0° (2.8 mm.) was not soluble in water or distillable with steam. No crystalline derivatives were obtained with methyl iodide or picric acid.

The 46.0 g. of distillation residue solidified to an amorphous mass on cooling. No nicotinic acid was isolated from the oxidation products when this residual, resinous material was oxidized with alkaline permanganate. This negative result may indicate that the pyridine nucleus of the nicotine molecule was partially destroyed in the pyrolysis but no conclusive evidence was obtained to confirm this assumption.

Summary

1. Ammonia, methylamine, hydrogen cyanide, pyridine, β-picoline, β-ethylpyridine, β-vinylpyridine, and 3,2′-nicotyrine have been obtained in small quantities from the pyrolysis products of nicotine.

2. Myosmine, a comparatively rare alkaloid, has been obtained in fair yields by the pyrolysis of nicotine over quartz at 570°.

3. A new synthesis of β-ethylpyridine is described.

(13) Strong and McElvain, THIS JOURNAL, **55**, 816 (1933).

(14) Stoehr, *J. prakt. Chem.*, [2] **45**, 38 (1892).

(15) Iddles, Lang and Gregg, THIS JOURNAL, **59**, 1945 (1937).

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Dissociation of Hexaarylethanes. XVI.[1] Alkyl and Halogen Derivatives

BY C. S. MARVEL, H. W. JOHNSTON, J. W. MEIER, T. W. MASTIN, JOHN WHITSON AND CHESTER M. HIMEL

Earlier papers in this series[2] have shown that in general unsymmetrically substituted hexaarylethanes are less dissociated than are closely related symmetrically substituted ethanes. Thus, di-*p*-*t*-butylphenyltetraphenylethane is dissociated to the extent of 7.5 ± 1% and tetra-*p*-*t*-butylphenyldiphenylethane to the extent of 8.5 ± 1% under the same conditions where hexa-*p*-*t*-butylphenylethane is dissociated to the extent of 20–25%.[2] Likewise di-*p*-tolyl-tetra-*p*-*t*-butylphenylethane and di-*p*-*t*-butylphenyl-tetra-*p*-tolylethane show equal degrees of dissociation of 5 ± 1%. We were accordingly very much surprised to find in the present work that a variety of alkyl substituted hexaarylethanes with mixed *m*- and *p*-substitution showed in general a higher degree of dissociation than many related hexa-*p*-alkylphenylethanes. We have no theory to account for the unexpected values which are reported here, for the work was stopped before a sufficiently large variety of compounds could be studied to make generalization significant.

The *p*-*t*-butyl group seems to have a very marked effect in promoting dissociation in the

(1) For the fifteenth communication in this series, see THIS JOURNAL, **66**, 415 (1944).

(2) Marvel, Kaplan and Himel, THIS JOURNAL, **63**, 1892 (1941); Marvel and Himel, *ibid.*, **64**, 2227 (1942).

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TABLE I

DISSOCIATION OF SUBSTITUTED HEXAARYLETHANES

Ethane	% in Benzene	Molarity	$-\chi_{sol.} \times 10^6$	α, % (observed)	α, % 0.1 M (calcd.)
Tetra-*m*-cyclohexylphenyl-di-*p*-cyclohexylphenyl	11	0.1	0.6000	39	39
Tetra-*p*-cyclohexylphenyl-di-*m*-cyclohexylphenyl	5.6	.05	.6757	21	16
Di-*p*-*t*-butylphenyltetra-*m*-cyclohexylphenyl	5.3	.05	.6616	27	20
Di-*m*-tolyltetra-*p*-*t*-butylphenyl	8.4	.1	.5908	42	42
	8.4	.1	.6160	33	33
	8.4	.1	.5891	42	42
Di-*o*-tolyltetra-*p*-*t*-butylphenyl	4.25	.05	.6003	76	65
	3.85	.046	.6045	80.4	68
Di-*m*-bromophenyltetra-*p*-*t*-butylphenyl	11.6	.1	.5869	40	40
	11.4	.1	.5841	38	38
Di-*o*-bromophenyltetra-*p*-*t*-butylphenyl	5.8	.05	.5618	97	94
	5.8	.05	.5566	100	
Diphenyltetra-*p*-fluorophenyl	3.2	.05	.6948	7.2	5.3
	3.2	.05	.6903	10.2	7.6
Hexa-*p*-fluorophenyl	3.4	.05	.7111	5.2	3.8
Tetraphenyldi-*m*-fluorophenyl	5.9	.1	.6885	5.8	5.8
	4.4	.073	.6952	5	4
Diphenyltetra-*m*-fluorophenyl	6.4	.1	.6856	5.5	5.5
	6.3	.1	.6902	3.9	3.9
Tetra-*p*-tolyldi-*m*-tolyl	6.5	.1	.7011	2.1	2.1

hexaarylethanes of this type. For example, di-*o*-tolyl-tetraphenylethane shows a dissociation of 25 ± 1%[2] whereas introduction of four *p*-*t*-butyl groups in its four unsubstituted benzene rings raises the dissociation of the ethane to 65–68%. Likewise di-*o*-bromophenyltetraphenylethane shows a dissociation of 17 ± 1%[3] whereas di-*o*-bromophenyltetra-*p*-*t*-butylphenylethane shows a value of 94%.

The hexaarylethanes substituted with cyclohexyl groups in the *m*- and *p*-position were prepared in the hope that one would be identical with the hexacyclohexylphenylethane described earlier[4] as the pure *para* isomer but later shown[5] to be a mixture of mixed *m*- and *p*-derivatives. This hope was not realized. It should be noted, however, that the magnetic susceptibility measurements reported on tetra-*p*-cyclohexylphenyl-di-*m*-cyclohexylphenylethane may be low, as this ethane has a tendency to crystallize from a 0.05 *M* solution. However, a more dilute solution gave unsatisfactory readings. All of the ethanes having *p*-cyclohexylphenyl groups were very unstable and in a few hours decomposed in solution as shown by magnetic susceptibility measurements. The *p*-*t*-butylphenyl substituted ethanes were stable in benzene solution over a period of twenty-four hours.

Since it is doubtful when work on this general problem can again be taken up in this Laboratory, we are recording in this paper some fluorine substituted hexaphenylethanes whose dissociations have been checked by the magnetic susceptibility methods. We are also recording a variety of intermediates which have been prepared in anticipation of further study of related ethanes.

(3) Marvel, Dietz and Himel, *J. Org. Chem.*, **7**, 392 (1942).
(4) Brown and Marvel, THIS JOURNAL, **59**, 1175 (1937).
(5) Marvel and Himel, *ibid.*, **62**, 1550 (1940).

The fluoro substituted ethanes showed marked decomposition when their solutions stood for twenty-four hours.

The values for the dissociation of the ethanes (α) recorded in Table I were obtained by the magnetic susceptibility method.[6]

Experimental

***p*-*t*-Butylbenzoic Acid.**—This compound was prepared by the general method illustrated in "Organic Syntheses"[7] for the conversion of *t*-butyl chloride to *t*-butylacetic acid. Thirty-four and seven-tenths grams of magnesium turnings, covered with 100 cc. of dry ether, and 304 g. of *p*-*t*-butylbromobenzene in 300 cc. of dry ether were used for making the Grignard reagent. The crude *p*-*t*-butylbenzoic acid was twice recrystallized from ethanol and water to yield 198 g. (78%) of a product which melted at 164°. Kelbe and Pfeiffer[8] have reported a melting point of 164°.

Ethyl *p*-*t*-Butylbenzoate.—A procedure similar to that used in the preparation of ethyl *m*-methoxybenzoate[9] was followed with the exception that calcium carbide was used to fill the extraction shell. One hundred and twenty-four grams of *p*-*t*-butylbenzoic acid, 1000 cc. of absolute ethanol, 200 cc. of dry benzene and 4 cc. of concentrated sulfuric acid were used as reactants. The reaction mixture was refluxed for seventy-two hours and was then worked up as described in the previous preparation. The yield was 108 g. (75%) of product; b. p. 120–120.5° (4 mm.).

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.72; H, 8.74. Found: C, 75.62; H, 8.63.

Cyclohexylbenzene.—Cyclohexylbenzene was prepared according to the procedure given in "Organic Syntheses."[10] The product boiled at 237–238° (740 mm.).

***p*-Bromocyclohexylbenzene.**—The bromination of cyclohexylbenzene was carried out according to directions given

(6) Mueller, Mueller-Rodloff and Bunge, *Ann.*, **520**, 235 (1935); Roy and Marvel, THIS JOURNAL, **59**, 2622 (1937).
(7) Gilman and Kirby, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., second edition, 1941, p. 361.
(8) Kelbe and Pfeiffer, *Ber.*, **19**, 1723 (1886).
(9) Marvel, Whitson and Johnston, THIS JOURNAL, **66**, 415 (1944).
(10) Corson and Ipatieff, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 151.

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by Marvel and Himel.[5] The yield of bromo compound was 85% of the theoretical amount; b. p. 135–137° (6 mm.).

p-Aminocyclohexylbenzene.—This compound was prepared by reduction of *p*-nitrocyclohexylbenzene over Raney nickel in 85% yield; m. p. 53–54°.

p-Cyclohexylacetanilide.—Four hundred and seventy-eight grams of *p*-aminocyclohexylbenzene was dissolved in 400 cc. of glacial acetic acid. One gram of zinc dust was added and the solution refluxed for seven hours. Connected to the reaction flask was an air condenser made of an 18-mm. Pyrex tube 120 cm. long. The flame was adjusted so that the condensing vapors of acetic acid remained about 15 cm. from the top of the condenser. By this means, most of the water formed in the acylation was lost through the air condenser thus forcing the reaction forward. This technique is described by Fieser[11] for the preparation of acetanilide.

The hot acetic acid solution was poured into 7 liters of cold water. The precipitated product was filtered off, washed with water and recrystallized from 50% ethyl alcohol. The yield of *p*-cyclohexylacetanilide was 507 g. (86%); m. p. 129–130°. Ipatieff and Schmerling reported a melting point of 130–131°.[12]

2-Bromo-4-cyclohexylacetanilide.—Six hundred and thirty-two grams of *p*-cyclohexylacetanilide was dissolved in 1800 cc. of glacial acetic acid and 3 g. of powdered iron was added to the solution. The reaction vessel was a 3-liter, three-necked flask equipped with a gas trap, dropping funnel and stirrer. The stirrer was started and 480 g. of bromine was added dropwise to the reaction mixture. The temperature was kept between 30 and 40° by means of a cold bath. When about one-third of the bromine had been added, a solid began to precipitate. Stirring was continued for five hours after all the bromine had been added; then the reaction mixture was poured into 12 l. of vigorously stirred cold water. The precipitate was filtered off, washed with water and partially dried. The crude material was recrystallized twice from 70% ethanol. The yield was 580 g. (71.5%) of a product melting at 122–123°.

Hydrolysis of 2-Bromo-4-cyclohexylacetanilide.—Five hundred and eighty grams of 2-bromo-4-cyclohexylacetanilide was dissolved in a mixture of 1600 cc. of 95% ethanol and 1000 cc. of concentrated hydrochloric acid. The solution was boiled for two or three minutes before the hydrochloride started crystallizing out. At this point a cold water-bath was used to prevent the alcohol from going out the top of the condenser. After this initial vigorous reaction had subsided, the solution was refluxed for two hours. The mixture was cooled and the product separated on a Büchner funnel, washed once with cold 95% ethanol and allowed to dry. The yield of 2-bromo-4-cyclohexylaniline hydrochloride was 564 g. (98%); m. p. 207° with decomposition.

m-Bromocyclohexylbenzene.—In a 5-liter flask equipped with a dropping funnel, stirrer and thermometer were placed 363 g. of 2-bromo-4-cyclohexylaniline hydrochloride, 1800 cc. of glacial acetic acid, 1200 cc. of water, and 400 cc. of concentrated hydrochloric acid. The stirrer was started and the mixture cooled to 0–5° in an ice-bath. From the dropping funnel was added slowly 92 g. of sodium nitrite dissolved in 500 cc. water. The temperature was kept between 0 and 5° throughout the addition of sodium nitrite solution. The clear diazonium solution (0°) was poured into 2200 cc. of cold (0°) 30% hypophosphorous acid and the total solution allowed to stand in an icebox at 5° for three days. The flask was removed and allowed to stand at room temperature for an additional day. The red-colored oil which separated was removed by use of a separatory funnel, dissolved in ether, washed with water, 5% sodium hydroxide solution and again with water. The ether solution was dried over calcium chloride, the ether removed and the product distilled. The yield of *m*-bromocyclohexylbenzene was 236 g. (79%); b. p. 122–123° (4 mm.); $n^{20}D$ 1.5602.

Anal. Calcd. for $C_{12}H_{15}Br$: C, 60.25; H, 6.29. Found: C, 60.58; H, 6.43.

p-Bromo-*t*-butylbenzenes.—In a 3-liter, three-necked flask equipped with a mechanical stirrer, dropping funnel and reflux condenser leading to a trap for absorption of hydrogen bromide, were placed 375 g. of *t*-butylbenzene[13] and 5 g. of iron powder. The mixture was stirred and cooled by an ice-bath to 0–5°. From the dropping funnel was added, over a period of one to two hours, 500 g. of bromine. Stirring was continued for two hours after all the bromine had been added. The reaction mixture was allowed to stand overnight and then washed with 5% sodium sulfite solution, twice with 5% sodium carbonate solution, twice with water and dried over calcium chloride. The product was distilled from a modified Claisen flask and collected at 80–81° (2 mm.). The yield of *p*-bromo-*t*-butylbenzene was 444 g. (75%). This method of preparation is faster than that described in a previous paper of this series.[14]

p-Amino-*t*-butylbenzene.—This compound was prepared by reduction of *p*-nitro-*t*-butylbenzene over Raney nickel catalyst in a manner similar to that used for the preparation of *p*-aminocyclohexylbenzene. The yield was 298 g. (73%) of product from 488 g. of *p*-nitro-*t*-butylbenzene. The boiling point was 90–93° (3 mm.).

m-Bromo-*t*-butylbenzene.—This compound was synthesized in a manner similar to that used for *m*-bromocyclohexylbenzene. The product boiled at 222–223° (740 mm.); $n^{20}D$ 1.5279.

Anal. Calcd. for $C_{10}H_{13}Br$: Br, 37.56. Found: Br, 38.51.

Ethyl *p*-Cyclohexylbenzoate.—A procedure similar to that used in the preparation of ethyl *m*-methoxybenzoate[9] was followed. From 204 g. of *p*-cyclohexylbenzoic acid, 800 cc. of absolute ethanol, and 5 cc. of concentrated sulfuric acid there was obtained 214 g. (92%) of product; m. p. 58–60°.

m-Cyclohexylbenzoic Acid.—This compound was prepared in a manner similar to that for the preparation of *p*-*t*-butylbenzoic acid. From 24.3 g. of magnesium, and 240 g. of *m*-bromocyclohexylbenzene there was obtained 159 g. (68%) of product; m. p. 120–121°.

Anal. Calcd. for $C_{13}H_{16}O_2$: C, 76.50; H, 7.85. Found: C, 77.05; H, 8.18.

Esterification of *m*-Cyclohexylbenzoic Acid.—The esterification was carried out exactly as the esterification of the *para* isomer.[9] The yield of ester from a one mole run was 204 g. (88%); b. p. 137–139° (3 mm.); $n^{20}D$ 1.5239.

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.59; H, 8.62. Found: C, 77.65; H, 8.77.

Ethyl *m*-Toluate.—Seventy-five grams of *m*-toluic acid (m. p. 107–109°) was esterified with 600 cc. of absolute ethanol, 150 cc. of dry benzene and 3 cc. of concentrated sulfuric acid.[9] Five grams of *m*-toluic acid was recovered, and on this basis the yield was 55 g. (64%) of product which boiled at 117° (15 mm.).

Another preparation was made using 200 g. of *m*-toluic acid. The extractor was in this case filled with calcium carbide. The yield was 218 g. (90%) of a product which boiled at 95–97° (15 mm.).

Ethyl *o*-Toluate.—A procedure similar to that for the preparation of ethyl *m*-toluate was used. From 175 g. of *o*-toluic acid, 1200 cc. of absolute ethanol and 4 cc. of concentrated sulfuric acid there was obtained 155 g. (75.5%) of ester; b. p. 88–92° (5 mm.).

Ethyl *o*-Bromobenzoate.—From 165 g. of *o*-bromobenzoic acid, 110 cc. of absolute ethanol, and 6 cc. of concentrated sulfuric acid there was obtained 150 g. (82%) of ester which distilled at 117° (17 mm.).

Ethyl *m*-Bromobenzoate.—In a manner similar to that used for the above esters, 100 g. of *m*-bromobenzoic acid was esterified, using 1000 cc. of absolute ethanol and 3 cc.

(11) Fieser, "Experiments in Organic Chemistry," D. C. Heath Co., New York, N. Y., 1935, p. 163.

(12) Ipatieff and Schmerling, THIS JOURNAL, 59, 1056 (1937).

(13) Huston, Fox and Binder, *J. Org. Chem.*, 3, 251 (1938).

(14) Marvel, Mueller, Himel and Kaplan, THIS JOURNAL, 61, 2771 (1939).

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TABLE II

TRIARYLCHLOROMETHANES

Chloromethane	Solvent	M. p., °C.	Active chlorine analyses, % Calcd.	Found
Phenyldi-*p*-chlorophenyl-	Low-boiling petroleum ether	50–51	10.22	10.11
Di-*m*-cyclohexylphenyl-*p*-cyclohexylphenyl	Ethyl acetate and low boiling petroleum ether	151–152	6.77	7.07
Di-*p*-cyclohexylphenyl-*m*-cyclohexylphenyl		172–173	6.77	6.65
Di-*m*-cyclohexylphenyl-*p*-*t*-butylphenyl	Ethyl acetate and low boiling petroleum ether	133–134	7.11	6.78
Di-*m*-*t*-butylphenyl-*p*-cyclohexylphenyl		127–129	7.53	7.26
o-Tolyldi-*p*-*t*-butylphenyl	Mixed petroleum ether	171–172	8.77	8.79
m-Tolyldi-*p*-*t*-butylphenyl	Ethyl acetate	132–133	8.77	8.52
o-Bromophenyldi-*p*-*t*-butylphenyl	Petroleum ether	135–136	7.56	7.77
m-Bromophenyldi-*p*-*t*-butylphenyl	Mixed petroleum ether	144–145	7.56	7.27
Diphenyl-*m*-fluorophenyl	Low boiling petroleum ether	84–84.5	11.94	12.12
Phenyldi-*m*-fluorophenyl	Low boiling petroleum ether	72.5–73	11.28	11.57
Tri-*m*-fluorophenyl	Ethyl acetate[a]	92–93	10.66	10.92
Phenyldi-*m*-chlorophenyl	Mixed petroleum ether	57–59	10.21	10.10
Tri-*m*-chlorophenyl	High boiling petroleum ether	90–92	9.32	9.57
m-Tolyldi-*p*-tolyl	Ethyl acetate[b]	67–69	11.05	10.92

[a] The chloromethane was best prepared by refluxing the carbinol in dry ethyl acetate for two hours with a large excess acetyl chloride. [b] It was found that the usual refluxing with acetyl chloride and benzene resulted in low yields of chloromethane. A less vigorous treatment consisted of treating the carbinol with a large excess of acetyl chloride for forty-five minutes at room temperature. The excess acetyl chloride was removed under vacuum and the resultant oil recrystallized from dry ethyl acetate containing a trace of acetyl chloride.

of sulfuric acid. The yield was 98 g. (88%); b. p. 115° (7 mm.).

Ethyl *m*-Chlorobenzoate.—From 20 g. of *m*-chlorobenzoic acid, 140 cc. of absolute ethanol and 1 cc. of concentrated sulfuric acid there was obtained in the usual manner 19 g. (81%) of product; b. p. 85–86° (5 mm.).

Phenyl-di-*p*-chlorophenylcarbinol.—The carbinol was prepared in good yield from 17 g. of magnesium, 128 g. of *p*-bromochlorobenzene and 50 g. of ethyl benzoate. The carbinol melted at 87–88° after recrystallization from high petroleum ether. Gomberg and Cone[15] reported a melting point of 87°.

***p*-*t*-Butylphenyl-di-*m*-tolylcarbinol.**—The crude carbinol was prepared from 35 g. of magnesium, 246.3 g. of *m*-bromotoluene and 108 g. of ethyl *p*-*t*-butylbenzoate. It could not be caused to crystallize even though distilled (b. p. 175° (1 mm.)). It was converted into the ethyl ether by treatment of the oily residue with an excess of hot absolute ethanol and a few cc. of concentrated sulfuric acid for two hours. When the solution was cooled, crystallization occurred. After recrystallization from absolute ethanol the yield was 180 g. (67%); m. p. 79–80°.

Anal. Calcd. for $C_{27}H_{32}O$: C, 87.05; H, 8.66. Found: C, 87.06; H, 8.76.

Di-*m*-cyclohexylphenyl-*p*-cyclohexylphenylcarbinol.—From 135 g. of ethyl-*p*-cyclohexylbenzoate, 239 g. of *m*-bromocyclohexylbenzene and 24 g. of magnesium turnings 128 g. (49%) of product was recovered; m. p. 139°, recrystallized from a mixture of dry ethyl acetate and low boiling petroleum ether.

Anal. Calcd. for $C_{37}H_{48}O$: C, 87.87; H, 8.97. Found: C, 87.64; H, 9.01.

Di-*p*-cyclohexylphenyl-*m*-cyclohexylphenylcarbinol.—The same procedure that was used in the preparation of di-*m*-cyclohexylphenyl-*p*-cyclohexylphenylcarbinol was followed. From 24 g. of magnesium, 135 g. of ethyl *m*-cyclohexylbenzoate and 239 g. of *p*-bromocyclohexylbenzene there was obtained an oil which could not be caused to crystallize. A crystalline chloromethane was obtained from this product as described later.

Di-*m*-cyclohexylphenyl-*p*-*t*-butylphenylcarbinol.—From 239 g. of *m*-bromocyclohexylbenzene, 24 g. of magnesium and 103 g. of ethyl *p*-*t*-butylbenzoate an oil was obtained which was converted into a crystalline chloromethane as described later.

Di-*m*-*t*-butylphenyl-*p*-cyclohexylphenylcarbinol.—From 213 g. of *m*-bromo-*t*-butylbenzene, 24 g. of magnesium and 135 g. of ethyl *p*-cyclohexylbenzoate there was obtained an oil which was converted into a crystalline chloromethane as described later.

***o*-Tolyl-di-*p*-*t*-butylphenylcarbinol.**—From 82 g. of ethyl-*o*-toluate, 213 g. of *p*-bromo-*t*-butylbenzene, and 24 g. of magnesium there was recovered 70 g. (32%) of crude crystals. Recrystallization from petroleum ether yielded a product which melted at 129.5–130°.

Anal. Calcd. for $C_{28}H_{34}O$: C, 87.07; H, 8.80. Found: C, 87.23; H, 8.99.

***m*-Tolyl-di-*p*-*t*-butylphenylcarbinol.**—From 213 g. of *p*-bromo-*t*-butylbenzene, 24 g. of magnesium and 74 g. of ethyl *m*-toluate an oil was obtained which was converted into a crystalline chloromethane as described later.

***o*-Bromophenyl-di-*p*-*t*-butylphenylcarbinol.**—From 70 g. of ethyl-*o*-bromobenzoate, 130 g. of *p*-bromo-*t*-butylbenzene, and 14.6 g. of magnesium there was recovered 60 g. (43%) of crude carbinol; m. p. 136.5–137° after recrystallization from high boiling petroleum ether.

Anal. Calcd. for $C_{27}H_{31}OBr$: C, 71.84; H, 6.87. Found: C, 72.01; H, 6.95.

***m*-Bromophenyl-di-*p*-*t*-butylphenylcarbinol.**—From 90 g. of *p*-bromo-*t*-butylbenzene, 9.9 g. of magnesium and 47 g. of ethyl *m*-bromobenzoate there was obtained an oil which could not be caused to crystallize. A crystalline chloromethane was obtained from this product as described later.

Phenyl-di-*p*-fluorophenylcarbinol.—The crude carbinol has been prepared by Bacon and Gardner.[16] A white crystalline product melting at 100° was obtained after several recrystallizations from petroleum ether.

Anal. Calcd. for $C_{19}H_{14}OF_2$: C, 77.03; H, 4.73. Found: C, 77.03; H, 4.76.

Tri-*p*-fluorophenylcarbinol.—Bacon and Gardner[16] obtained the crystalline carbinol but did not report the melting point or analysis. We have recrystallized the carbinol from low petroleum ether; m. p. 94°.

Anal. Calcd. for $C_{19}H_{13}OF_3$: C, 72.61; H, 4.14. Found: C, 72.63; H, 4.25.

Diphenyl-*m*-fluorophenylcarbinol.—From 82 g. of benzophenone, 80 g. of *m*-fluorobromobenzene, and 10.9 g. of magnesium there was obtained 100 g. (80%) of the crude

(15) Gomberg and Cone, *Ber.*, **39**, 1461 (1906).

(16) Bacon and Gardner, *J. Org. Chem.*, **3**, 283 (1938).

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TABLE III

PEROXIDES

Radical	Formula	M. p., °C.	Analyses, % Calcd. C	Calcd. H	Found C	Found H
Di-*m*-cyclohexylphenyl-*p*-cyclohexylphenylmethyl	$C_{74}H_{99}O_2$	169–170	87.8	8.97	87.47	9.16
Di-*p*-cyclohexylphenyl-*m*-cyclohexylphenylmethyl	No peroxide isolated					
p-*t*-Butylphenyl-di-*m*-cyclohexylphenylmethyl	$C_{70}H_{82}O_2$	163–164.5	87.99	8.66	88.11	9.27
o-Tolyldi-*p*-*t*-butylphenylmethyl	$C_{56}H_{66}O_2$	159–161	87.23	8.62	87.41	8.46
m-Tolyldi-*p*-*t*-butylphenylmethyl	$C_{56}H_{66}O_2$	185–186	87.23	8.62	87.24	8.54
o-Bromophenyldi-*p*-*t*-butylphenylmethyl	No peroxide isolated					
m-Bromophenyldi-*p*-*t*-butylphenylmethyl	No peroxide isolated					
Phenyldi-*p*-fluorophenylmethyl	No peroxide isolated					
Tri-*p*-fluorophenylmethyl	No peroxide isolated					
Diphenyl-*m*-fluorophenylmethyl	$C_{38}H_{28}O_2F_2$	173–174	82.29	5.10	82.44	5.32
Phenyldi-*m*-fluorophenylmethyl	$C_{38}H_{26}O_2F_4$	169–170	77.27	4.43	77.24	4.54
Di-*p*-tolyl-*m*-tolylmethyl	No peroxide isolated					

carbinol, which, after recrystallization from high boiling petroleum ether, melted at 117°.

Anal. Calcd. for $C_{19}H_{15}OF$: C, 82.01; H, 5.40. Found: C, 81.96; H, 5.48.

Phenyl-di-*m*-fluorophenylcarbinol.—From 25.7 g. of ethyl benzoate, 60 g. of *m*-fluorobromobenzene, and 8.25 g. of magnesium, 35 g. (70%) of crude carbinol was obtained; m. p. 114–114.5°, recrystallized from high boiling petroleum ether.

Anal. Calcd. for $C_{19}H_{14}OF_2$: C, 77.03; H, 4.73. Found: C, 77.19; H, 4.85.

Tri-*m*-fluorophenylcarbinol.—From 20.8 g. of ethyl carbonate, 100 g. of *m*-fluorobromobenzene, and 13.7 g. of magnesium 40 g. (80%) of crude carbinol was isolated; m. p. 118.5–119° after recrystallization from high boiling petroleum ether.

Anal. Calcd. for $C_{19}H_{13}OF_3$: C, 72.61; H, 4.14. Found: C, 72.76; H, 4.13.

Phenyl-di-*m*-chlorophenylcarbinol.—From 125 g. of *m*-chlorobromobenzene, 15.6 g. of magnesium and 47 g. of ethyl benzoate a concentrated oil was obtained which failed to crystallize. A crystalline chloromethane was obtained from this product as described later.

Tri-*m*-chlorophenylcarbinol.—From 39.5 g. of *m*-bromochlorobenzene, 5 g. of magnesium, and 19 g. of ethyl *m*-chlorobenzoate a concentrated oil was obtained which was converted into a crystalline chloromethane as described later.

***m*-Tolyldi-*p*-tolylcarbinol.**—From 67 g. of ethyl *m*-toluate, 150 g. of *p*-bromotoluene, and 21 g. of magnesium, 78 g. (62%) of crude carbinol was obtained; m. p. 95–96° after recrystallization from petroleum ether.

Anal. Calcd. for $C_{22}H_{22}O$: C, 87.44; H, 7.28. Found: C, 87.44; H, 7.42.

Triarylchloromethanes.—The chloromethanes were prepared by treating the carbinols in dry benzene with excess acetyl chloride.[17] They are described in Table II.

Preparation of Peroxides.—After the magnetic susceptibility measurements had been completed the benzene solutions of the ethanes were exposed to air and then worked up for peroxides. The yields of pure crystalline peroxide usually ran about 40–60% of the theoretical. The peroxides were crystallized from benzene by the addition of five to six volumes of absolute alcohol and slow evaporation of the resultant solution at room temperature. Recrystallization was accomplished by redissolving the crystals in hot dry benzene and addition of absolute alcohol in large excess to the hot solution after which the solvent was permitted to evaporate at room temperature.

The new peroxides are listed in Table III.

Summary

Twelve new substituted hexaarylethanes containing different alkyl groups and various halogen atoms have been prepared and their dissociations measured by the magnetic susceptibility method. Some related derivatives have been characterized and the methods of preparation are reported.

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(17) Gomberg, *Chem. Rev.*, 1, 91 (1924).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CHICAGO AND THE UNIVERSAL OIL PRODUCTS COMPANY]

Surface of Solids. X. Extension of the Attractive Energy of a Solid into an Adjacent Liquid or Film, the Decrease of Energy with Distance, and the Thickness of Films

BY WILLIAM D. HARKINS AND GEORGE JURA

1. Introduction: Heats of Adsorption.—A fundamentally important, entirely unsolved problem of physics and chemistry, is that of the distance to which the attractive field from a solid has an effect upon the energy of molecular interaction with an adjacent liquid or film. The solution of this problem involves a determination of the variation of the intermolecular energy with the distance. This paper presents an experimental, though difficult, method by means of which the problem may be solved, together with experimental data for a single case, that of water on titanium dioxide in the form of pure anatase. From earlier results obtained in this Laboratory, many other solids should exhibit the same general relationship between energy and distance.

Although calculations have been made of the heats of adsorption of gases on ionic crystals,[1] on metals,[2] and on graphite,[3] no calculation, which is even approximately correct, has been made of the variation of the attractive energy with the distance.

2. Theories of Adsorption.—For many years there have been two contradictory theories of the ultimate thickness of adsorbed films on a solid subphase: (1) the *monomolecular* theory, the principal exponent of which is Langmuir, and (2) the *polymolecular* theory.[3a] The latter theory does not assume that all adsorbed films are polymolecular, since it is evident that films of water on paraffin, graphite, talc and other hydrophobic solids may be monomolecular even at values of p/p_0 nearly as high as unity. Indeed it seems possible in such cases that even at saturation, the film is either monomolecular, or, if a second layer is formed, it is far from completely filled. However, *evidence* which indicates the existence of adsorbed monolayers on *non-porous solids at high values of* p/p_0 *is almost non-existent*, since there seems to be not *more than a single known isotherm for a non-porous solid*, that of propyl alcohol on barium sulfate, which indicates a film that remains almost monomolecular up to pressures as high as $p/p_0 = 0.95$. Presumably this is due to some extent to the neglect by investigators of systems of this type. This isotherm is discussed later (Section 6). Langmuir's recent statement[4] of the monomolecular nature of films is, that for films of argon, nitrogen, hydrogen, and methane, at liquid air temperatures "the amount adsorbed increases about in proportion to the pressure, but at higher pressures reaches a limiting value which in every case studied corresponds to less than a monolayer. Evidently, therefore, even with these cases of adsorption which involve merely van der Waals forces, the effective range of action of the forces responsible for the adsorption is less than the molecular diameter, so that we are still clearly dealing with forces which act between atoms or molecules in contact."

Many other investigators have adopted this general point of view, as expressed by Langmuir's adsorption isotherm.[5]

A theory which gives an isotherm which indicates polymolecular adsorption, has been developed by Brunauer, Emmett and Teller[6] (BET) on the basis of the earlier work of Emmett and Brunauer.[7] This isotherm has proved to be remarkably successful and will be discussed in a later paper of this series.

3. Variation of the Attractive Energy with Distance: Thermodynamic Theory and Experimental Method.—We will first consider a sample of a crystalline powder which exhibits an area of 1 sq. cm. The surface of the solid (quartz, TiO_2, $BaSO_4$, $ZrSiO_4$, etc.) is made clean by outgassing at as elevated a temperature as can be employed without affecting the nature of the surface. During this operation the powder is in the tube H of Fig. 1. The apparatus is now placed in a thermostat and after thermal equilibrium is attained, the tip of the small glass tube T is broken. This tube contains a small amount of water whose weight is determined on a microbalance. In different experiments the amounts of liquid are so chosen that the final vapor pressures of the adsorbed films at equilibrium cover well the range from $p = 0$ (no liquid) to $p/p_0 = 1$.

A calorimeter (Fig. 2) which contains n' moles of liquid is used for the measurements of energy. A 36-junction copper–constantan thermel with a sensitivity of 2×10^{-5}° was employed. For the sake of simplicity the equations are developed for an amount of powder which has an area of 1 sq. cm. The processes (Fig. 3) are as follows:

(1) F. V. Lenel, *Z. physik. Chem.*, **B23**, 379 (1933); W. J. C. Orr, *Trans. Faraday Soc.*, **35**, 1247 (1939); *Proc. Roy. Soc.* (London), **A173**, 349 (1939).

(2) J. E. Lennard-Jones, *Trans. Faraday Soc.*, **28**, 333 (1932); Bardeen, *J. Phys. Rev.*, **58**, 727 (1940); H. Margenau and W. G. Pollard, *Phys. Rev.*, **60**, 128 (1941).

(3) R. M. Barrer, *Proc. Roy. Soc.* (London), **A161**, 476 (1937).

(3a) The prefixes mono- and poly- are adopted on account of prevalent usage, and not from their etymological suitability.

(4) I. Langmuir, *J. Chem. Soc.*, 511 (1940).

(5) I. Langmuir, THIS JOURNAL, **40**, 1361 (1918).

(6) S. Brunauer, R. H. Emmett, and E. Teller, *ibid.*, **60**, 309 (1938).

(7) For references to these and other papers on adsorption, see S. Brunauer, "The Adsorption of Gases and Vapors," Princeton University Press, Princeton, N. J., 1943.

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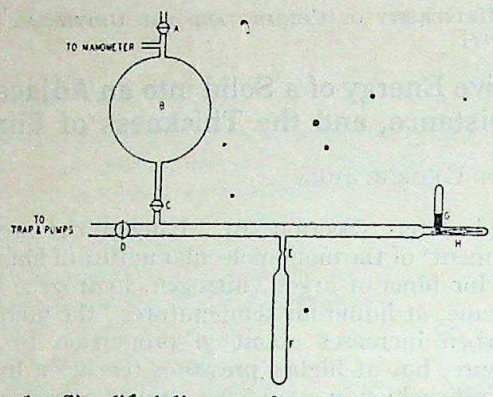
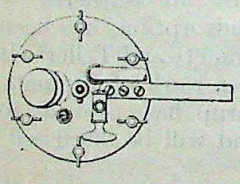


Fig. 1.—Simplified diagram of apparatus for the adsorption of water vapor on a finely divided crystalline solid in *six* bulbs (F). The water is weighed in the tube H before adsorption and adsorbed on the solid in the bulbs. G is a piece of soft iron used for breaking off the point of the tube H, and B is a gas filled bulb used for the determination of the free volume of the remainder of the apparatus up to the stopcocks C and D.

first step, the powder, with an area of 1 sq. cm., on which area n moles of liquid has been adsorbed at a value of $p/p_0 \leqq 1$, is immersed in the liquid. The change (ΔH) in the value of the Gibbs heat function (enthalpy) which accompanies this proccess is:



$$\Delta H_1 = -h_{E(S_fL)} \quad (1)$$

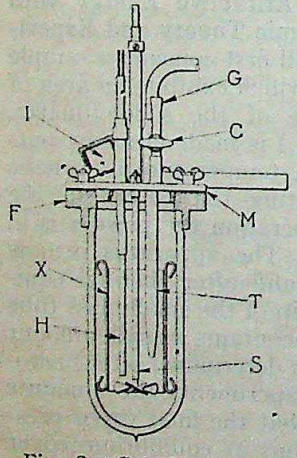


Fig. 2.—Calorimeter. T, 36-junction thermel; H, heating element; G, inlet for liquid; C, stopcock; X, chimney to give better circulation of powder; I, opening for introduction of powder. For non-aqueous liquids the calorimeter used is shown by Boyd and Harkins, THIS JOURNAL, 64, 1791 (1942).

where E indicates the process of emersion, which is the opposite of immersion, h indicates the increase in the value of enthalpy per unit area, and $E_{(S_fL)}$ indicates the emersion of the solid, covered by its film, from the liquid. Second step: since by the actual process (immersion) n moles of liquid have been added to the n' moles initially present, this amount of n moles is now evaporated from the liquid. Now for this step

$$\Delta H_2 = n\lambda \quad (2)$$

where λ is the molar latent heat of vaporization of the liquid. Third step: the sample of powder is now emersed from the liquid into a vacuum, carrying no film with it, so

$$\Delta H_3 = h_{E(SL)} \quad (3)$$

It is obvious that this process must be carried out in the reverse direction, *i. e.*, by immersion instead of emersion, so $q_{I(SL)} = h_{E(SL)}$, where $q_{I(SL)}$ is the heat evolved in the process of immersion.

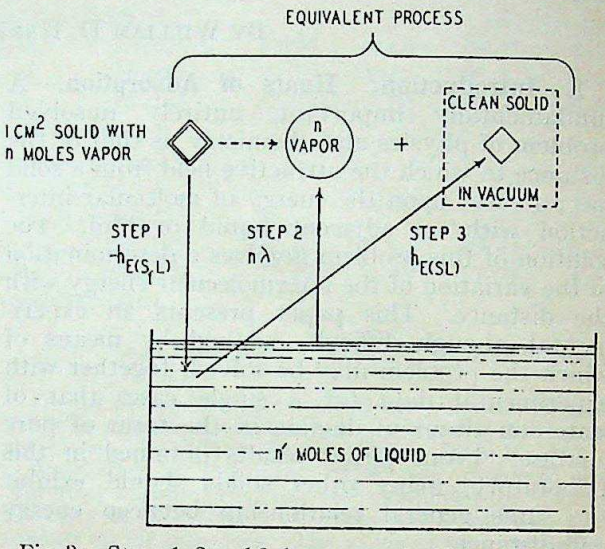


Fig. 3.—Steps 1, 2 and 3, by means of which a solid with an area of 1 sq. cm., with n moles adsorbed on the surface, is transformed into n moles of vapor and the solid in a vacuum. The equivalent process involves merely the desorption of the n moles from the surface.

As the effect of the summation of these three processes the solid of area 1 sq. cm., covered by a film of n moles in equilibrium with vapor at a pressure p, is converted into the solid with a clean surface and n moles of vapor. Thus the complete process corresponds to the desorption of n moles of vapor from 1 sq. cm. of surface of the solid, so the increase of enthalpy on desorption [$h_{D(VS_f)}$] is given by the summation of the three terms or

$$h_{D(VS_f)} = h_{E(SL)} - h_{E(S_fL)} + n\lambda \quad (4)$$

Now

$$h_{E(SL)} = h_S - h_{SL} \quad (5)$$

and

$$h_{E(S_fL)} = h_{S_f} - h_{SL} \quad (6)$$

Substitute (5) and (6) in (4), which gives

$$h_{D(VS_f)} = h_S - h_{S_f} + n\lambda \quad (7)$$

Now, since in general if γ represents the free surface energy

$$h = \gamma - T(\partial\gamma/\partial T)_{p,\Sigma} \quad (8)$$

$$h_{D(VS_f)} = \gamma_S - \gamma_{S_f} - T\left(\frac{\partial\gamma_S}{\partial T} - \frac{\partial\gamma_{S_f}}{\partial T}\right)_{p,\Sigma} + n\lambda \quad (9)$$

In cal. g.$^{-1}$ Eq. 7 may be written

$$H_{D(VS_f)} = H_{E(SL)} - H_{E(S_fL)} + n'\lambda \quad (10)$$

where n' is now the number of moles adsorbed per gram. $H_{E(SL)}$ is the heat of emersion of the clean powder from the liquid in cal. g.$^{-1}$, and $H_{E(S_fL)}$ is that for 1 g. of solid on whose surface n' moles of vapor has been adsorbed. In cal. mole^{-1}

$$H_{D(VS_f)} = \frac{1}{n'}\left[H_{E(SL)} - H_{E(S_fL)}\right] + \lambda \quad (11)$$

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These equations are applicable to porous as well as non-porous solids.

The relationship used *universally* in the literature *is incorrect*, even though it is believed to be applicable only at saturation

$$H_{D(vs_f)} = H_{E(sL)} + n'\lambda \qquad (A)$$

For example, the correct equation applied to the data of Razouk[8] gives a heat of adsorption (q_a) of 9.9 cal. g.$^{-1}$ for methyl alcohol on charcoal at 13.5% of saturation, while the *incorrect* equation (A) gives $q_a = 22.4$ cal. g.$^{-1}$.

γ free surface energy
γ_s the free surface energy of the clean solid (ergs cm.$^{-2}$)
γ_{s_f} the free surface energy of the solid with adsorbed film
λ heat of vaporization (cal. mole^{-1})
Σ area

4. Variation of Energy of Interaction with Distance from the Surface of the Solid.—For the experimental work a sample of pure non-porous titanium dioxide in the form of anatase was used. This is oil free, not surface treated, and its cell constants have been determined as $a = 3.77$ Å. and $c = 9.49$ Å. while Wyckoff gives $a = 3.78$ Å. and $c = 9.50$ Å. A part of this same sample was photographed by the use of an electron microscope (Fig. 4).

The area of this sample is 13.8 m.^{2}g.$^{-1}$ as determined by our absolute method. This consists in adsorbing a duplex film of water on the surface in saturated water vapor, and then immersing in water in the calorimeter. The heat developed, expressed in ergs, when divided by 118.5 erg cm.$^{-2}$, the surface energy of water at the temperature employed, gives the area of the powder. A very small correction is made for the known thickness of the duplex film. The area of this same sample when calculated by the use of the isotherm of Brunauer, Emmett and Teller,[8] and of Emmett's value of 16.2 sq. Å. for the mean area of the nitrogen molecule, is 13.9 m.^{2}g.$^{-1}$, or a difference of less than 1% between the results of the two methods.

The isotherms of water on this anatase at 25° and of nitrogen at −195.6° are exhibited in Fig. 5, while Fig. 6 and Table I give the relationship between the energy of emersion of the solid from water at 25°, and the amount of water left on the surface of the solid. For the emersion of the dry solid the energy is 512 erg cm.$^{-2}$.

The relationship between the energy of desorption of water to give a dry surface, with the number of moles per sq. cm., is exhibited in Fig. 7, as calculated by Equation 4, while Figure 8 gives values for the molal heat of desorption of the vapor as a function of the weight of water adsorbed.

These figures give in addition the thickness (T) of the films in Å. These are calculated on the basis of the assumption that the *mean density* of the film is the same as that of the three dimen-

(8) R. I. Razouk, *J. Phys. Chem.*, **45**, 100 (1941).

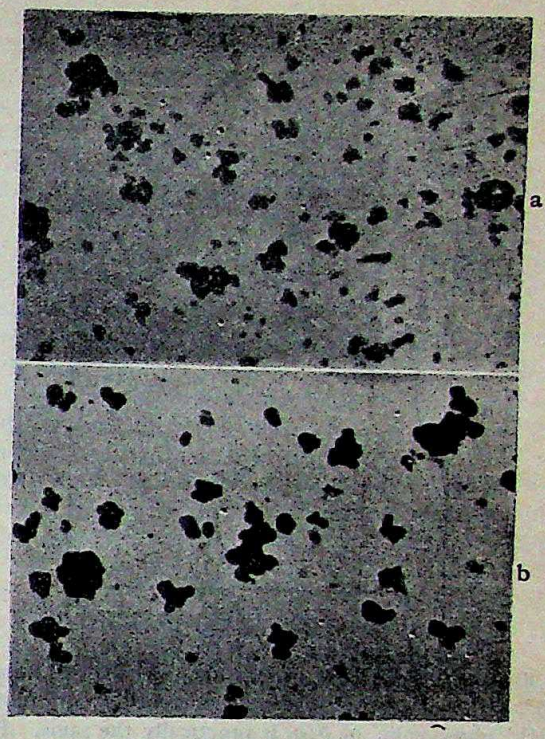

Fig. 4.—(a) Electron microscope photograph (×14,600) of a TiO_2 (anatase) powder of area 13.8 sq. m.g.$^{-1}$ by our absolute method, and 13.9 sq. m.g.$^{-1}$ by the method of Brunauer, Emmett and Teller on the basis of the assumption that the mean area per N_2 molecule is 16.2 Å.^{2} (Emmett). (b) The same (×14,600) for TiO_2 of area 8.7 sq. m.g.$^{-1}$. (Photographs by E. F. Fullam, Interchemical Corporation.)

TABLE I

ENERGY OF EMERSION OF TITANIUM DIOXIDE (ANATASE) FROM WATER AT 25° AS A FUNCTION OF THE THICKNESS OF THE WATER FILM WITH WHICH IT EMERGES

1 mg. H_2O g.$^{-1}$ in film	2 Mean thickness[a] of film in Å., T	3 Energy of erg cm.$^{-2}$ $h_{E(s_fL)}$
0	0	512[a]
0.548	0.4	399
0.953	0.7	366
1.68	1.2	289
1.99	1.4	279
2.60	1.9	210
3.15	2.3	190
3.68	2.7	172
4.95	3.6	142
5.86	4.2	139
8.66	6.3	127
11.86	8.6	125
14.20	10.0	122
Saturated	>15.0	119

[a] $h_{E(sL)}$.

(1) This was determined by weighing the solid before and after adsorption.

(2) The mass obtained in (1) is divided by the density of the liquid, which gives the volume the film would have in the uncompressed state. The volume (V) divided by the area (Σ) of the solid gives T the thickness.

(3) This is the quantity of heat developed by immersion of the solid in water in the calorimeter, divided by the area (Σ).

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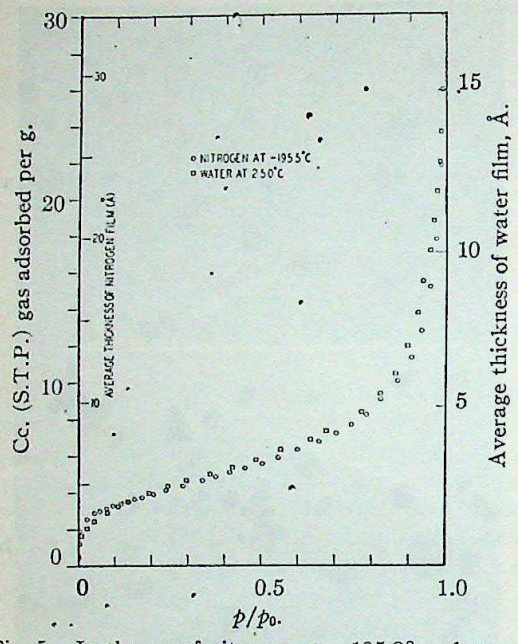

Fig. 5.—Isotherms of nitrogen at −195.8° and water at 25°. The number of molecules adsorbed at any (not too high) given value of p/p_0 is practically the same. However the nitrogen molecules are larger than those of water, so the nitrogen films are thicker (see graph) than those of water. At saturation the nitrogen film is much thicker.

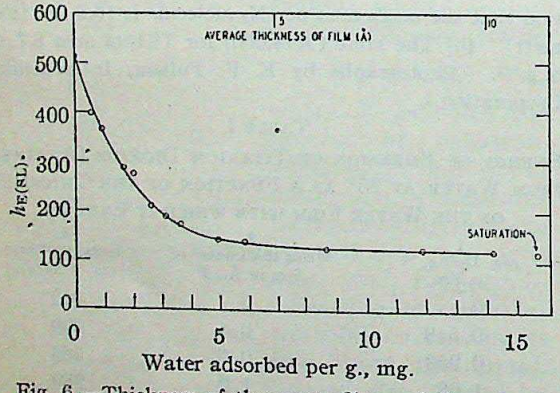

Fig. 6.—Thickness of the water film and the energy of emersion per sq. cm. of the surface of TiO_2 (anatase). The weight of water adsorbed per gram of anatase is also given.

sional liquid at the same temperature. Obviously this cannot be quite correct, but it should become more nearly correct as the film thickens. There is also involved the assumption that the thickness is uniform over the whole surface. The mass of the film was determined by *weighing* in all cases in which the energy was determined. The total amount of water adsorbed is sufficient to allow this to be done.

Figure 5 indicates that at saturation at 25°, the thickness of the adsorbed water film is somewhat greater than 15 Å., (or 5 molecules of water) since it has this thickness at the last point which represents a pressure below saturation. The amounts of water adsorbed for this isotherm were calculated from the volume of vapor.

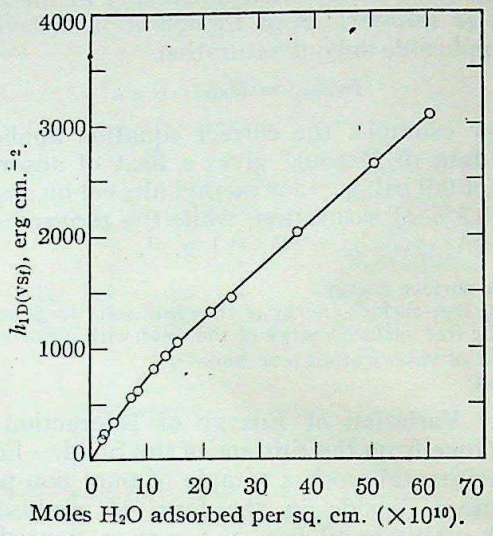

Fig. 7.—Variation of the energy of emersion per sq. cm. of area of TiO_2 (anatase) with the weight of water vapor adsorbed.

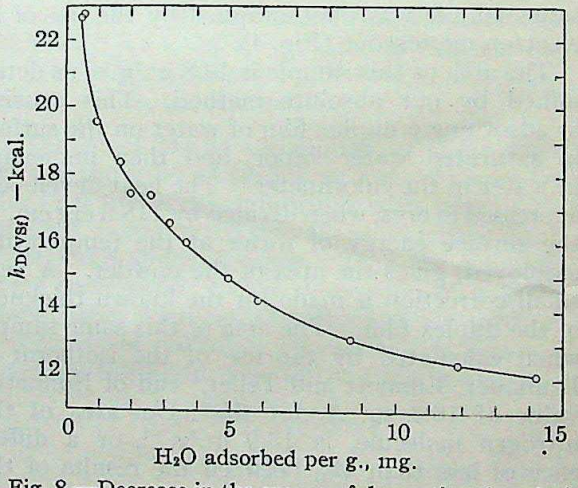

Fig. 8.—Decrease in the energy of desorption, in calories per mole of water, from the surface of TiO_2 (anatase) as a function of the weight of water adsorbed.

5. Variation of the Energy of Desorption with the Number of Molecular Layers.—It is of interest to estimate the variation of the molar energy of desorption with increase in the number of molecular layers (Table II).

The increase in the energy of vaporization of water by the presence of the adjacent solid is given in column 4. Thus the vaporization of the first molecular layer requires 6550, the second 1380, and the third 450 cal. mole^{-1} more energy to vaporize than if water alone were present. Thus these values give the increase in molecular interaction due to the presence of the solid.

The theory of Brunauer, Emmett and Teller was used to calculate the number (N) of molecules in the monolayer (1) next to the surface of the solid. It was assumed as the basis of the cal-

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TABLE II

MOLAR ENERGY OF DESORPTION OF MOLECULAR LAYERS OF WATER FROM THE SURFACE OF TITANIUM DIOXIDE (ANATASE)

1	2	3	4	5
Number of layer	Internal energy of desorption, cal. mole^{-1}, $H_{D(V_n S)}$	Internal energy of vaporization of water, λ_i	$H_{D(V_n S)} - \lambda_i$ or $E_n - E_L$ determined	Theory of exponential decay
1	16450	9900	6550[a]	6550
2	11280	9900	1380	1637
3	10350	9900	450	409
4	9980	9900	80	102
5	9940	9900	40 (?)	26
Sum of all above 5			30 (?)	

Column 2 gives the energy of desorption for a whole layer, when all of the lower layers are complete.

Column 3 gives the internal energy of vaporization which does not include the work done.

[a] The BET theory gives a value for E_1-E_L of 2100 cal. mole^{-1}.

culation that the number of molecules in each higher layer is also equal to N. The values obtained by the application of this theory indicate that the water molecules in the first layer (1) are somewhat loosely packed, at 25°, while at −195.8° nitrogen molecules (which are larger) are more nearly in contact.

The values of column 4 suggest an exponential decay in the energy of desorption. In column 5 it is assumed that the value of 6550 cal. mole^{-1}, as given in column 4 is correct, and that the energy for any other layer is one-fourth of that of the layer just beneath it. In *general* this gives the same rate of decay as that exhibited by the experimental values but it may be noted that these latter are lower for even layers and higher for odd layers, than corresponds to the exponential decay. This is just what would be expected if the more polar part of the water molecules is turned toward the solid in the first layer, away from it in the second, toward it in the third, etc. This is exactly the type of orientation exhibited in built-up multilayers of polar–non-polar molecules. Unfortunately, the values of column 4 do not have sufficient accuracy to prove that this alternation in orientation actually occurs.

6. Discussion: Polymolecular Films.—The important relation brought out in Section 4 is that for water on a non-porous crystalline "polar" solid (anatase) the attractive energy exhibits an essentially exponential decay. The term "polar" solid is used because a better term has not, as yet, been introduced. The term is used to designate solids, such as quartz, etc., whose molecular interactions may be considered to exhibit not too small *relative* intensities of both dispersion forces and those due to segregated electrical charges, in addition to repulsive forces. On such solids the curve which represents the decrement ($-\Delta\gamma = \Delta\pi$) of free surface energy due to a film of nitrogen at −195.8° has the same form (with smaller magnitudes) as that for water at 0°. The film of nitrogen attains, very slightly *below* saturation, a thickness of 36 Å., while for water, as cited earlier, the value is 15 Å. On the whole it does not seem improbable that nitrogen, a non-polar adsorbate, also may exhibit an essentially exponential decay of the attractive energy.

The saturated film of butane at 0° on this same solid, is 64 Å. thick, so it is not essential to use a polar adsorbate in order to have a highly polymolecular film. However, it is true that the butane molecule has a high polarizability. While the water film attains a thickness of about 5, and that of nitrogen about 10 molecular layers, the number for butane cannot be specified, since in its first monolayer *the molecules lie flat*, while near the outer surface of the film they must have much more nearly the type of orientation exhibited by the surface of liquid butane. If the thickness of this film is to be specified in molecules as units all that can be said is that its thickness is of the same general order as that of nitrogen (10 molecules).

It is of interest to note in connection with the discussion of the two preceding paragraphs, that with the particular sample of titanium dioxide used for this work the adsorption isotherms for nitrogen at −195.6° and water at 25° are practically identical except possibly very close to saturation, both in form and the volume of gas adsorbed (Fig. 5).

Thus the writers have obtained entirely definite evidence that adsorbed films of water, nitrogen, and butane on titanium dioxide in the form of anatase are highly polymolecular, with *thicknesses* of 15, 36 and 64 Å., respectively, at pressures just below saturation. We believe that these are correct thicknesses for pressures *very* slightly below saturation, except that the thickness of the water film may be greater than 15 Å. As has been specified these values express the volume of the liquid at the given temperature divided by the area, as determined by the area of the surface of the solid. If the film has a density higher than the three dimensional liquid, then these values in actual ångström units are that much too high, but in terms of molecular diameters the values are not affected.

No uncertainty is introduced by the value of the area which is employed for the calculation, since the determination of area was made by our absolute method. This method is based upon the premise that water on anatase forms a film sufficiently thick to be *duplex*, *i. e.*, the surface of the film is sufficiently thick to give inappreciable (experimentally) interaction between the outermost layer of the film and the solid. Thus the surface energy of the outer part of the film is supposed to be the same as that of water at the same temperature. That this is true within the limits of experimental error is shown by the fact that as the thicker films thicken there is no de-

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tectable decrease in the energy of immersion. Thus, for the first time, certain evidence has been obtained for the highly polymolecular character of certain adsorbed films. As mentioned earlier, no attempt is made here to prove the *non-existence* of monomolecular adsorbed films at high values of p/p_0 that are less than unity.

Monomolecular films of stearic acid are formed by adsorption of the acid at the interface between *dry* benzene and TiO_2 (anatase) such as that used in this investigation. In fact, even the monolayer is loosely packed, since only about 70% as much stearic acid is adsorbed as the amount required for close packing.

The writers have considered it important to obtain *definite* evidence, already presented in this paper, which shows that by the adsorption process alone films taken up from vapors on the surfaces of solids become highly polymolecular at the higher values of p/p_0, provided the contact angle between the solid and the liquid is zero. That this point of view is not universal among specialists in the field of adsorption, is shown by a recent statement by Brunauer,[9] who is, himself, an enthusiastic supporter of the theory of polymolecular (multimolecular) adsorption:

"Many advocates of the capillary condensation theory maintain that adsorption in porous bodies is largely due to capillary condensation, although they do not deny the existence of unimolecular adsorption. The two schools (unimolecular and capillary condensation) of thought meet on a common ground, namely, that adsorption on a plane surface where capillaries do not exist must be unimolecular."

Since Langmuir is the principal advocate of the uni- or mono-molecular theory, it is important to consider his point of view, as presented in the following quotations[10]:

"The theory requires that in typical cases of true adsorption the adsorbed film should not exceed one molecule in thickness. This is contrary to the usual viewpoint. The discrepancy is accounted for by the fact that nearly all investigators have worked with porous bodies in which the adsorbing surface is indeterminate, or have used nearly saturated vapors so that condensation of liquid occurred in capillary spaces. Others have mistaken solution or *ab*sorption for adsorption.

"With gases or vapors at pressures much below saturation the surface of a solid tends to become covered with a single layer of molecules. The reason for this is that the forces holding gas molecules (or atoms) on to the surface of solids are generally much stronger than those acting between one layer of gas molecules and the next. When the vapor becomes nearly saturated, however, the rate of evaporation from the second layer of molecules is comparable with the rate of condensation so that the thickness of the film may exceed that of one molecule."

Since the experiments of the authors and of others show that most of the known films on *non-porous* solids are polymolecular at values of p/p_0 greater than 0.3 or less, the above conception of Langmuir cannot be used as the basis of *any* general theory of adsorption.

Capillary Condensation Theory.—The monomolecular theory of adsorption on solids receives support at the present time only because the apparent discrepancies which it introduces are explained away by the theory of capillary *condensation*. Undoubtedly this phenomenon is prominent in highly porous solids, but it does not contribute as much to the "sorption" as is assumed by the adherents of this theory.

Indeed, at high relative pressures, the total amount adsorbed is commonly *greater per unit area on a plane surface*, where the high value cannot be explained by the assumption of capillary condensation, *than the total amount of "sorption" for the same area exhibited by a porous solid*. The explanation of this fact is simple: the adsorption in pores is limited by the growth of the film from all sides of the pore. In the simple case of a pore with parallel plane walls the "film" cannot be thicker than half the distance between the walls. When the values for the thicknesses of films of water, nitrogen, and butane given in this paper are considered, it is evident that many of the smaller pores in a silica gel or a catalyst of high area, would become completely filled by adsorption even if capillary condensation were absent.

That capillary condensation, as suggested by Zsigmondy,[11] plays an important part in the sorption, is undoubtedly true. However, the assumption by others than Zsigmondy that this phenomenon is responsible for all of the material taken up from a vapor by a porous body, with the exception of a single monolayer, is certainly false. If this assumption had not been made, the monomolecular theory of adsorption could not have survived up to the present time.

7. Monomolecular and Slightly Thicker Films on Solids.—It is shown earlier in this paper that almost all of the films on non-porous solids thus far investigated begin to lose their monomolecular character at a relatively small value of p/p_0 which is of the order of 0.08 to 0.12 for nitrogen at $-195.6°$ and of 0.15 to 0.25 for *n*-butane at 0° and for water at 25°.

If it is desired to find a film which remains in the monomolecular state up to high values of p/p_0 when adsorbed on a polar solid, it would seem that the choice of a substance whose molecules are polar–non-polar, would be a good one. Thus molecules of an alcohol should, in the first

(9) S. Brunauer, "The Adsorption of Gases and Vapors," Vol. I, Physical Adsorption, Princeton University Press, Princeton, N. J., 1942.

(10) I. Langmuir, THIS JOURNAL, 40, 1401 (1918), also *J. Chem. Soc.*, 511 (1940).

(11) R. Zsigmondy, *Z. anorg. Chem.*, 71, 356 (1911).

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monolayer, be oriented with their long axis perpendicular to the surface of a polar solid and with the polar group toward the solid. This leaves the hydrocarbon chains, which resemble paraffin, and which exhibit little attractive energy, on the outside. It would seem that this would give a good chance of obtaining a film which remains monomolecular up to high values of p/p_0. However, the presence of the polar group makes the position of the molecule highly dependent on the surface lattice of the crystal used for adsorption, which should on this account give variations in the thickness of the adsorbed film.

As mentioned earlier (Section 2) the only system which the writers know, that exhibits monomolecular adsorption on a non-porous solid, is propyl alcohol on barium sulfate. The area available per molecule of the alcohol, and the mean thickness of the films are given in Table III as a function of the relative vapor pressure (p/p_0).

TABLE III

PROPYL ALCOHOL FILMS; MONOMOLECULAR ON BARIUM SULFATE UP TO $p/p_0 = 0.9$; DO NOT COMPLETE THEIR SECOND LAYER ON TiO_2 AT $p/p_0 = 0.8$, AND COMPLETE THEIR SECOND LAYER ON QUARTZ AT $p/p_0 = 0.7$.

	$BaSO_4$		TiO_2 (Anatase)		SiO_2 (Quartz)	
p/p_0	Area per molecule, Å.²	Film thickness, Å.	Area per molecule, Å.²	Film thickness, Å.	Area per molecule, Å.²	Film thickness, Å.
0.15	..	..	..	..	End of monolayer	
.2	22.5	4.3	18.7	5.2	16.8	5.8
.4	21.6	4.5	17.3	5.7	14.3	7.0
.6	20.6	4.7	15.9	6.1	11.8	8.2
.8	19.6	5.0	14.5	6.7	7.6	12.8
.88	..	..	12.9	7.6	..	..
.90	19.1	5.1	Values calculated from the data of			
.95	16.6	5.9	H. K. Livingston, Ph.D., thesis,			
.99	11.2	8.7	University of Chicago, Dec., 1941.			

The lattice constants of these three types of crystalline solids indicate that the first monolayer of propyl alcohol should exhibit at a given vapor pressure, the most loose packing on barium sulfate, the tightest on quartz, with that for anatase intermediate.

The end of the monolayer on the surface of the solid occurs at a relative pressure (p/p_0) of about 0.9 (which is very high) with barium sulfate, at about 0.2 with anatase, and about 0.15 with quartz. With quartz the second layer is completed at a relative pressure of about 0.7. Since there is no known method of determining at just what pressure the second layer is actually completed, it is assumed that when the first monolayer is completed the propyl alcohol molecules are closely packed, and the same assumption is made for the second layer. Thus where the area per molecule adsorbed is equal to that which a propyl alcohol molecule should exhibit in perpendicular orientation, it is considered that the film is a monolayer, and if the mean molecular area is half as large, the film is assumed to be two molecules thick.

While the literature contains a very great number of isotherms which represent the adsorption of vapors upon the surfaces of solids, it is unfortunate that most of these isotherms were obtained with porous solids, where adsorption and capillary condensation are inextricably mixed. It is also unfortunate that a large percentage of the work on non-porous solids has not been carried to saturation of the vapor. Thus the literature gives almost no data which help in the development of a theory of adsorption uncontaminated by the effects of capillary condensation.

8. Theory of Adsorption.—This paper has considered the decrease in the surface enthalpy which occurs when a film of any thickness is adsorbed upon the surface of a solid. This decrease of enthalpy is equal, within the limits of experimental accuracy, to the decrease ($-\Delta E$) in surface energy. In the case investigated the angle of contact between the solid and liquid is zero. In such a case the amount of vapor adsorbed increases very rapidly with pressure at the lower values of p/p_0.

The relations are very different with a system such as that of water on graphite or on paraffin, which exhibit contact angles of 85.5° and 105 to 111°, respectively. There seem to be no carefully determined adsorption isotherms for a case of this type. A sample of graphite used with water in this Laboratory was found later to contain about 10% of ash, which may have greatly distorted the adsorption isotherm. With pure graphite the adsorption isotherm should be of Type III (convex to the pressure axis).

With films of this type the amount adsorbed increases with extreme slowness with pressure at low relative vapor pressures. The simplest explanation of non-spreading of the liquid in such a case would be to assume that even close to saturation the surface of the graphite (or paraffin) is sparsely populated by water molecules, and that there are many holes of molecular dimensions in the water layer. This gives so few points of attachment for the liquid water that the latter does not spread.

The theory of adsorption may be stated very simply as follows: Adsorption in any closed system which contains a solid and a vapor continues as long as the process can occur with a decrease of the Helmholtz free energy (A), while at constant pressure the condition is the same with respect to the Gibbs free energy (F). Since for unit area of the solid the decreases of free energy on adsorption is represented by

$$-\Delta F = -\Delta\gamma = \pi$$

the value of the film pressure (π) gives the decrease in free energy per unit area. It is not at all difficult to calculate π at any vapor pressure (p) if data are available for the adsorption isotherm at all pressures below p down to sufficiently low

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pressures. This is done by the method of Bangham.[12]

By a consideration of this free energy decrease on adsorption, and a simple assumption, a method has been developed for the determination of the area of a solid from an adsorption isotherm.

The free energy changes involved in adsorption will be treated in a later paper of this series. The free surface energy of *decrease* (π) of the surface of a solid increases with increase of thickness of a film upon it. Since $\pi = -\Delta\gamma$, the free surface energy decreases with thickness of the film.

From our calorimetric measurements the decrease of internal or "total" surface energy $(E_S - E_{S_f}) = (h_S - h_{S_f})$ may be calculated. The values of this quantity, together with the related values of the *decrease* of free surface energy, and of the latent heat $[T(s_S - s_{S_f})]$, where s is the entropy, are represented in Fig. 9.

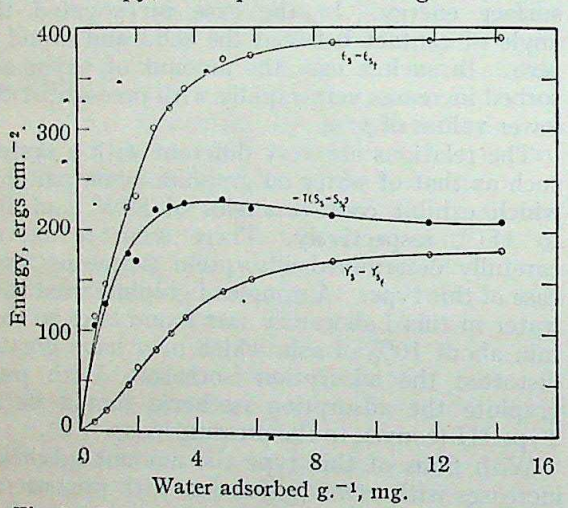

Fig. 9.—Lowering of the surface energy of TiO_2 (anatase) by an adsorbed water film. The *lowering* of the total surface energy is $\epsilon_S - \epsilon_{S_f}$, of the free energy $\pi = \gamma_S - \gamma_{S_f}$, and of the latent heat $l = T(s_S - s_{S_f})$, where s is the entropy per unit area.

All of these quantities increase very rapidly at first with the amount adsorbed, but the free energy changes much less rapidly than either the total surface energy (E) or the latent heat ($l = TS$). It should be kept in mind that increases in the values of these quantities, which give the effects of the film on the surface of the solid, represent *decreases* in the surface energy of the solid. Thus the maximum in the curve for latent heat in Fig. 9 represents a *minimum* latent heat for the film covered surface of the solid. This minimum begins at approximately the end of the adsorption of the first monolayer, and the beginning of the deposition of the second layer.

9. Absence of an Effect of Closer Packing upon the Amount of Butane Sorbed at High Relative Vapor Pressures (Note: Added December 15, 1943).—In our work on the adsorption of butane and other vapors there had been no attempt to pack the powder tightly, so it was deemed advisable to determine whether a tighter packing would increase the amount of vapor taken up. If capillary condensation is an important factor in the process of sorption, then a significant increase should accompany the tighter packing.

An electron microscope photograph of the anatase used in this work was obtained at a magnification of 45,000 and this shows that it consists largely of aggregates. These give a very loose packing of the powder in the glass bulb where the sorption takes place. Thus with the ordinary type of packing in the bulb of 27 cu. cm. capacity, it was found in one experiment that only 3.78 cu. cm. of anatase was present, and this is approximately the average amount found. It is simpler to consider the volume of anatase per cu. cm. of capacity of the bulb. This amounts to 0.14 cu. cm. or 14%, so that the free space is 0.86 cu. cm. or 86%. Of this free space between 0.0429 and 0.0527 cu. cm. is filled up by "liquid" butane. Here 0.068 cu. cm. is the highest value attained at a pressure below that of saturation, and 0.078 cu. cm. is a value obtained at saturation. As usual the volumes given for the adsorbed film of butane do not represent its actual volume, but that of the same mass of liquid butane at −0.3° and 760 mm. pressure.

Later, additional anatase powder was packed in the bulb by tapping the bottom of the bulb on the wooden top of a desk until no tighter packing could be obtained by this means, when 4.61 cu. cm. of anatase was found to be present. The

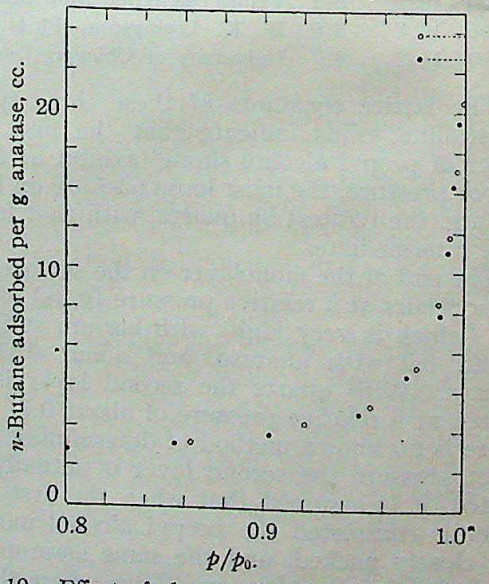

Fig. 10.—Effect of change of spacing between crystals and crystalline aggregates upon the amount of butane adsorbed at high relative pressures. Black circles indicate tighter packing, and open circles looser packing. Within the limits of experimental error the two curves are identical and no effect of packing is indicated. The dotted lines indicate the amount adsorbed at $p/p_0 = 1.0$.

(12) D. H. Bangham, *Trans. Faraday Soc.*, **33**, 805 (1937); Bangham and Razouk, *ibid.*, **33**, 1463 (1937); *Proc. Roy. Soc.* (London), **A166**, 572 (1938).

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new volume relations were per cm.^{3}: 0.171 cu. cm. of anatase in the vacuum, 0.829 cu. cm. of free space. The volumes of butane, calculated as liquid taken up just below and at saturation, were 0.0580 and 0.0673 cu. cm., respectively. These values are higher than for loose packing on account of the greater mass and area of the powder in the bulb.

The two adsorption isotherms for the looser and tighter packing, as given in Fig. 10, are the same within the limits of experimental error and give no evidence that the tighter packing increases the amount of butane sorbed. This might not be the case if the butane vapor in the bulb were kept extremely close to saturation for a very great length of time. In the determination of adsorption at lower pressures the time is extended until equilibrium is attained. For the highest pressures indicated there was no change of pressure (0.1 mm. can be detected with certainty) in four hours at $p/p_0 = 0.9990$ for the more tightly packed sample, and no change in fourteen hours at $p/p_0 = 0.9976$ for the more loosely packed sample. From this evidence it seems that capillary condensation cannot play any significant role.

While this paper deals principally with adsorption on a single solid, the writers have determined similar adsorption isotherms for more than one hundred solids, and have obtained equations for the isotherms which represent the behavior of condensed, intermediate, expanded, and gaseous films on solids. Two condensed phases have been discovered, so that we have now found five phases in films on solids. Some of these equations give remarkably accurate values of the area of the solids.

Summary

1. Almost all of the films adsorbed on the surfaces of non-porous solids, which have been investigated thus far, are highly polymolecular at vapor pressures very slightly below saturation.

2. For the first time, a determination has been made of the effect of distance on the intermolecular attraction (in energy units) between a solid and an adjacent liquid or adsorbed film. This energy of interaction is found to suffer a decay which is essentially an exponential function of the distance.

3. At 25°, the energy of vaporization of water is 10540 cal. mole^{-1}. If, however, the water is in the form of a monolayer on the otherwise clean surface of crystalline titanium dioxide (as anatase) the heat of vaporization is increased by 62%, or by 6550 cal. mole^{-1}. For the second layer this is reduced to a 13% increase, or 1380 cal. mole^{-1}, for the third to 4%, or 450 cal. mole^{-1}, while for the fourth and fifth layers, the values are of the order of 80 and 40 cal. mole^{-1}. These energy values indicate that the film of water adsorbed on titanium dioxide (anatase) should attain a minimum thickness of 5 molecular layers before saturation of the vapor is attained. Measurements of the thickness of the film just below saturation show that this is justified, since the thickness attained is over 15 Å. (five molecular layers). The measured thickness attained is 36 Å. or 10 molecular layers for nitrogen at −195.6°. Non-polar adsorbates attain considerable thicknesses. Thus *n*-butane at 0° attains a thickness of 64 Å., while the thickness of the first molecular layer is only about 4 Å., since the molecules *lie flat on the surface*. However, in the sixth or seventh layer, the degree of orientation should be small, and in the surface of the film should exhibit practically the same orientation as that in the surface of liquid butane at the same temperature. The thickness of this film is about 11 or 12 molecules.

4. The results obtained are contrary to Langmuir's theory of the general occurrence of monomolecular adsorption at vapor pressures moderately close to saturation. They also show that the combined monolayer plus capillary condensation theory, upheld by a large number of the workers in this field, is incorrect. They do not show that monomolecular adsorption cannot occur, nor are they in opposition to the idea that capillary condensation may occur in porous solids. They do show that *ad*sorbed films on plane surfaces commonly attain greater thicknesses than in porous solids. However, this should not be the case for water on hydrophobic solids, nor is it true for propyl alcohol on barium sulfate.

5. The theory of adsorption favored by these results is in agreement with the general picture indicated by the multimolecular theory of Brunauer, Emmett and Teller (BET). However, we show the incorrectness of one of the primary assumptions in their more simple theory: that the energy of vaporization of the second adsorbed layer is no greater than the energy of vaporization of the liquid, or $E_2 = E_L$. This is not offered as an adverse criticism of their theory, since this assumption was introduced by them in order to obtain a simple, two-constant adsorption isotherm. The areas given by their simple theory are surprisingly good, but the energy values ($E_1 - E_L$) are much too low. (The BET theory gives a value for $E_1 - E_L$ of 2100 cal. mole^{-1} while our experimental result corresponds to 6550 cal. mole^{-1}.) The great usefulness of their isotherm lies in the fact that it is the first and only method for the calculation of the number of molecules in a complete monolayer when the isotherm is of the sigmoid (S) or common type. The Langmuir equation also gives the number of molecules, but with non-porous solids there seems to be, unfortunately, only one known case to which it can be applied.

6. Evidence is presented which indicates that capillary condensation does not play any significant role in the sorption with a crystalline powder of the type used in this work.

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[CONTRIBUTION FROM THE WESTERN REGION, BUREAU OF MINES, UNITED STATES DEPARTMENT OF THE INTERIOR]

High-temperature Heat Contents of Magnesium Nitrate, Calcium Nitrate and Barium Nitrate[1]

BY C. HOWARD SHOMATE[2]

Thermal properties of several nitrates are of interest in connection with the hydrometallurgy of manganese, and the Pacific Experiment Station of the Bureau of Mines has undertaken studies of their low- and high-temperature specific heats and their heats of formation. The present paper reports high-temperature heat-content data of magnesium nitrate, calcium nitrate, and barium nitrate, in the anhydrous crystalline state. No previous reliable data for these substances exist.

Materials and Method

Magnesium nitrate was prepared from reagent-quality magnesium nitrate hexahydrate. The latter was heated *in vacuo*, the temperature gradually being raised from 65 to 150° over a period of forty hours. Analysis gave 16.43% Mg (calcd. 16.40%) and 0.17% MgO.

Reagent-grade calcium nitrate tetrahydrate was used for the preparation of anhydrous calcium nitrate. The tetrahydrate was melted and most of the water removed under reduced pressure. The material then was broken up and heated in a furnace at 300° for twenty-four hours. Analysis gave 24.43% Ca (calcd. 24.42%) and 0.04% CaO.

The sample of barium nitrate used was a reagent-grade material dried at 115°. Analysis gave 52.50% Ba (calcd. 52.55%).

All formula weights are in accord with the 1941 International Atomic Weights. Sample weights were corrected to vacuum, using the following densities: magnesium nitrate, 2.2; calcium nitrate, 2.36; and barium nitrate, 3.24, g./cc.

The heat content determinations of magnesium nitrate and calcium nitrate were corrected for the oxide impurities indicated above. These corrections averaged 0.15 and 0.03%, respectively.

The high temperature heat contents were determined in an apparatus previously described.[3] The calorimeter was calibrated electrically, using the defined calorie (1 cal. = 4.1833 int. joules). Each sample was enclosed in a gold-sealed platinum–rhodium alloy capsule during the measurements. The heat content of the capsule was determined in a separate series of experiments.

Results

The experimentally determined heat contents above 298.16°K. of magnesium nitrate, calcium nitrate, and barium nitrate are given in Tables I, II, and III. Determinations were made starting at about 100°, and extending up to the point where dissociation was detected. No discontinuities were found in the temperature ranges studied.

Heat content equations, given below, of the form $H_T - H_{298.16} = aT + bT^2 + c/T + d$ were derived for each of the three substances. The coefficients a, b, c and d were determined by plotting the function

$$\frac{T[(H_T - H_{298.16}) - C_{p_{298.16}}(T - 298.16)]}{(T - 298.16)^2}$$

of the experimental values against T, and drawing the best straight line through the points. The slope of this straight line is the coefficient b in the above general equation. The value of the y-intercept is $c/(298.16)^2$. The coefficient $a = c/(298.16)^2 - 596.32\ b + C_{p_{298.16}}$ and $d = (298.16)^2\ b - 2c/298.16 - 298.16 C_{p_{298.16}}$.

$$Mg(NO_3)_2: H_T - H_{298.16} = 10.68T + 0.03560T^2 - 179{,}000/T - 5{,}749 \quad (1)$$

$$Ca(NO_3)_2: H_T - H_{298.16} = 29.37T + 0.01840T^2 + 413{,}000/T - 11{,}778 \quad (2)$$

$$Ba(NO_3)_2: H_T - H_{298.16} = 30.05T + 0.01785T^2 + 401{,}000/T - 11{,}891 \quad (3)$$

Differentiating the above equations gives the following specific heat relationships

$$Mg(NO_3)_2: C_p = 10.68 + 0.07120T + 179{,}000/T^2 \quad (4)$$

$$Ca(NO_3)_2: C_p = 29.37 + 0.03680T - 413{,}000/T^2 \quad (5)$$

$$Ba(NO_3)_2: C_p = 30.05 + 0.03570T - 401{,}000/T^2 \quad (6)$$

The coefficients in these equations were chosen so that the equations would give the specific heats at 298.16°K. recently determined by Shomate and Kelley.[4] These values for $C_{p_{298.16}}$ are as follows: magnesium nitrate, 33.92; calcium nitrate, 35.69; and barium nitrate, 36.18 calories per mole, respectively. The agreement of the above heat content equations with the experimental data is shown in Tables I, II and III.

TABLE I

HIGH-TEMPERATURE HEAT CONTENT OF $Mg(NO_3)_2$ (CAL. PER MOLE)

T, °K.	$H_T - H_{298.16}$ Exptl.	Eqn. 1	Deviation	% Deviation
398.6	3,707	3,715	+ 8	+0.2
435.8	5,251	5,255	+ 4	+ .1
476.9	7,072	7,066	− 6	− .1
535.9	9,877	9,864	−13	− .1
573.6	11,757	11,778	+21	+ .2
622.5	15,328	(decomposition)		

TABLE II

HIGH-TEMPERATURE HEAT CONTENT OF $Ca(NO_3)_2$ (CAL. PER MOLE)

T, °K.	$H_T - H_{298.16}$ Exptl.	Eqn. 2	Deviation	% Deviation
402.8	4,073	4,063	−10	−0.2
456.3	6,336	6,360	+24	+ .4
499.2	8,302	8,296	− 6	− .1
560.4	11,168	11,196	+28	+ .2
621.9	14,263	14,267	+ 4	.0
677.9	17,230	17,197	−33	− .2
726.4	19,835	19,834	− 1	.0
775.1	22,556	22,574	+18	+ .1
815.0	25,190	(decomposition)		

(1) Published by permission of the Director, Bureau of Mines, U. S. Department of the Interior. Not copyrighted.

(2) Chemist, Western Region, Bureau of Mines.

(3) Southard, THIS JOURNAL, 63, 3142 (1941).

(4) Shomate and Kelley, unpublished measurements.

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TABLE III

HIGH-TEMPERATURE HEAT CONTENT OF $Ba(NO_3)_2$ (CAL. PER MOLE)

T, °K.	$H_T - H_{298.16}$ Exptl.	Equ. 3	Deviation	% Deviation
411.1	4,434	4,454	+20	+0.4
448.9	6,077	6,098	+21	+ .3
496.2	8,230	8,223	− 7	− .1
549.8	10,788	10,756	−32	− .3
626.1	14,549	14,560	+11	+ .1
693.5	18,101	18,112	+11	+ .1
769.9	22,339	22,346	+ 7	.0
820.8	25,299	25,289	−10	.0
862.1	28,363	(premelting)		

Table IV is a compilation, at 50° intervals, of the heat content and entropy above 298.16°K. of magnesium nitrate, calcium nitrate, and barium nitrate. These values have been derived from smoothed curves drawn through points representing the experimental data.

Summary

High-temperature heat content measurements of magnesium nitrate, calcium nitrate, and barium nitrate were made from about 100° up to as high a temperature as was permitted by the thermal stability of each substance.

Heat content and specific heat equations, adequately representing the experimental data, have been derived for each nitrate.

The entropy increments above 298.16°K., at 50° intervals, have been tabulated along with smoothed values of the heat contents.

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TABLE IV

HEAT CONTENTS AND ENTROPIES ABOVE 298.16°K.

	$Mg(NO_3)_2$		$Ca(NO_3)_2$		$Ba(NO_3)_2$	
T, °K.	$H_T - H_{298.16}$, cal./mole	$S_T - S_{298.16}$, cal./deg./mole	$H_T - H_{298.16}$, cal./mole	$S_T - S_{298.16}$, cal./deg./mole	$H_T - H_{298.16}$, cal./mole	$S_T - S_{298.16}$, cal./deg./mole
350	1,821	5.63	1,962	6.07	1,947	6.00
400	3,782	10.81	3,958	11.40	3,963	11.39
450	5,866	15.77	6,053	16.32	6,132	16.49
500	8,153	20.58	8,340	21.14	8,410	21.29
550	10,569	25.19	10,687	25.61	10,799	25.84
600	13,118	29.62	13,151	29.90	13,234	30.08
650			15,738	34.04	15,780	34.15
700			18,409	38.00	18,453	38.11
750			21,139	41.76	21,218	41.93
800			23,974	45.42	24,070	45.61
850					27,007	49.17

[CONTRIBUTION FROM RESEARCH LABORATORIES, MUTUAL CHEMICAL COMPANY OF AMERICA]

Crystallized Basic Zinc Chromates

BY O. F. TARR, MARC DARRIN AND L. G. TUBBS

The yellow pigment which is ordinarily produced by the reaction of acidified zinc oxide and potassium bichromate is known as zinc yellow. For almost a century there has been controversy as to whether it is a definite chemical compound, an adsorption complex or a mixture. The great variation in analyses and impurities, the selective solution of CrO_3 and K_2O, and a lack of crystalline form, led Mellor[1] to consider the various suggested formulas as representing adsorption products rather than a pure chemical compound. Although recent investigators[2,3] have reported some analyses corresponding fairly closely to molecular proportions of the combined oxides, and the major evidence[2,4] indicates the probable existence of the compound, $K_2O{\cdot}4ZnO{\cdot}4CrO_3{\cdot}3H_2O$, no prior investigator has reported the preparation of a pure crystallized compound. The authors obtained well-defined crystals having analyses corresponding to simple molecular proportions by the following procedure.

Basic Potassium Zinc Chromate

Preparation.—Zinc yellow having an analysis corresponding to the formula $K_2O{\cdot}4ZnO{\cdot}4CrO_3{\cdot}3H_2O$ was prepared by the direct reaction between an aqueous suspension of zinc oxide and a solution of potassium tetrachromate,[5] thus

$$4ZnO + K_2Cr_4O_{13} + 3H_2O \longrightarrow K_2O{\cdot}4ZnO{\cdot}4CrO_3{\cdot}3H_2O$$

On separation and drying the zinc yellow appeared to be a non-crystalline powder. When suspended in water it slowly underwent partial decomposition, releasing into solution a mixture of K_2CrO_4 and $K_2Cr_2O_7$. Equilibrium was reached when the concentration of dissolved chromate and bichromate was equivalent to about 15 g. of $K_2Cr_2O_7$ per liter.

Ten grams of the above zinc yellow was suspended in a solution containing 22.5 g. of $K_2Cr_2O_7$ in 1500 ml. of water, and brought into solution at room temperature by the addition of a minimum amount of nitric acid. This solution was slowly neutralized at 80° without mechanical agitation, with a solution containing 5 g. of potassium hydroxide and 20 g. of potassium chromate per liter. Heat was applied at the edge of the beaker and the caustic solution was added dropwise to the rising convection current. After the addition of about 300 ml., which required from six to twenty-four hours, small crystals could be seen

(1) W. Mellor, "Comprehensive Treatise on Inorganic and Theoretical Chemistry," Longmans, Green and Co., New York, N. Y., 1931, Vol. 11, p. 279.

(2) A. A. Brizzolara, R. R. Denslow, and S. W. Rumbel, *Ind. Eng. Chem.*, **29**, 656–657 (1937).

(3) I. V. Riskin and G. Pugacheva, *J. Appl. Chem.* (U. S. S. R.), **12**, 1780–1785 (1939).

(4) M. Gröger, *Sitzber. Akad. Wien*, **113**, 155 (1904).

(5) O. F. Tarr and Marc Darrin, U. S. Patent Appl., Ser. 403,707 (1941).

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in the convection stream, with larger, well-defined, transparent yellow crystals (Fig. 1) settling out loosely on the bottom of the beaker. The *p*H of the reaction solution at this time was 6.4. When the reaction was continued to a higher *p*H (about 6.7) an additional yield was obtained of smaller crystals of the same system and class. The analysis was the same for all crystals and the zinc yellow from which they were obtained. Reaction periods extending over several weeks, also long standing at various temperatures, did not increase the size of single crystals—although some agglomerates were formed. Increasing the speed of neutralization resulted in a decrease in the size of the crystals, down to the precipitation of a powder similar to the original zinc yellow.

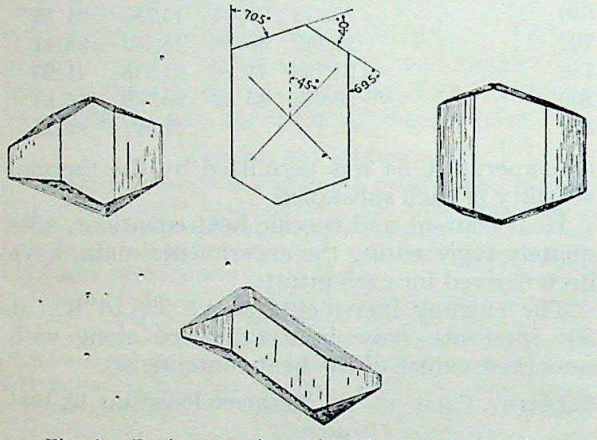

Fig. 1.—Basic potassium zinc chromate crystals.

Description.—The crystals (Fig. 1) were small, elongated, doubly-terminated, transparent yellow plates, belonging to the triclinic system, pinacoidal class. These crystals were hard but very friable. Maximum size observed for a single crystal was $10 \times 50 \times 90\ \mu$; plane angles of crystal outline measured 70.5°, 40°, 69.5°; crystals were strongly birefringent but not pleochroic. Indices of refraction were very high, being in the neighborhood of 2.0; extinction angle was about 45°, and oblique to the length of the crystal. One of the optic axes was oblique to the plate making an angle of about 21° with the normal to the plate. Dispersion was extreme, and greater at the red end of the spectrum than at the violet. Specific gravity, d^{25}_4 3.47. The crystals were soluble in alcohol, slightly soluble in water with partial decomposition to a less soluble product, and readily soluble in acids or ammonium hydroxide. They were stable in air at room temperature but lost water slowly above 100°.

Anal. Calcd. for $K_2O{\cdot}4ZnO{\cdot}4CrO_3{\cdot}3H_2O$: K_2O, 10.8; ZnO, 37.2; CrO_3, 45.8; H_2O, 6.2. Found: K_2O, 10.7; ZnO, 37.3; CrO_3, 45.4; H_2O, 6.5.

Basic Sodium Zinc Chromate

Riskin and Pugacheva[3] prepared a large variety of zinc yellows containing sodium oxide as replacement for potassium oxide, but no evidence has been presented of the existence of the pure sodium compound. By a method similar to that employed in making the potassium compound, the authors obtained quantitative yields of a new crystallized compound directly from the reaction

$$4ZnO + Na_2Cr_4O_{13} + 3H_2O \longrightarrow Na_2O{\cdot}4ZnO{\cdot}4CrO_3{\cdot}3H_2O$$

Under the microscope at 350 diameters the product appeared as small, highly refractive, transparent yellow, diamond-shaped plates, or short prisms; specific gravity, d^{25}_4 3.24. General properties were similar to those of the potassium compound. Analysis corresponded quite closely to the formula, $Na_2O{\cdot}4ZnO{\cdot}4CrO_3{\cdot}3H_2O$, as regards ratio of sodium oxide to zinc oxide to chromic anhydride; but the crystals were a little higher in water than $3H_2O$, probably due to difficulty of complete drying without decomposition.

Anal. Calcd. for $Na_2O{\cdot}4ZnO{\cdot}4CrO_3{\cdot}3H_2O$: Na_2O, 7.4; ZnO, 38.7; CrO_3, 47.5; H_2O, 6.4. Found: Na_2O, 7.4; ZnO, 38.3; CrO_3, 46.9; H_2O, 7.3.

Basic Ammonium Zinc Chromate

The ammonium compound was prepared in the same general manner as the potassium compound, but it was more difficult to obtain well-defined crystals. In preparing crystals of the ammonium compound it was found best to use a higher concentration and a little lower *p*H (5.3 to 5.7). Under the microscope at 350 diameters the crystals appeared as small, highly refractive, transparent yellow prisms, having a low order of symmetry. The product, however, did not consist entirely of crystals of this type. Mixed with these prismatic crystals were a few thin, transparent, yellow, hexagonal plates. All crystals were too small or too friable to separate by mechanical means. There was some variation in the analyses of crystals from different batches of the ammonium compound. The analysis of a typical batch of these crystals corresponded fairly closely to the formula, $(NH_4)_2O{\cdot}4ZnO{\cdot}4CrO_3{\cdot}3H_2O$, as regards percentages of zinc oxide and chromic anhydride; but the crystals were higher in ammonia with a corresponding decrease in water.

Anal. Calcd. for $(NH_4)_2O{\cdot}4ZnO{\cdot}4CrO_3{\cdot}3H_2O$: ZnO, 39.2; CrO_3, 48.1; $(NH_4)_2O$, 6.2; H_2O, 6.5. Found: ZnO, 39.8; CrO_3, 47.5; $(NH_4)_2O$, 8.0; H_2O, 4.6.

Alkali-Earth Compounds

The corresponding alkali-earth compounds were not obtained by the described method. When a solution of calcium tetrachromate, or magnesium tetrachromate, was substituted for potassium tetrachromate, the product was a basic zinc chromate containing only a trace of alkali earth.

Acknowledgment.—The authors wish to express their appreciation to J. D. N. Donnay, Institute de Geologie et de Mineralogie, Quebec, Canada, for his most helpful assistance in the crystallographic measurements of the potassium salt.

Summary

By the preparation of new, well-defined, crystals of a series of basic zinc chromates in which the oxides are combined in simple molecular proportions, it is shown that some of these products are definite chemical compounds, verifying the belief of the majority of prior investigators.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Redistribution Reactions in the Halides of Carbon, Silicon, Germanium and Tin

BY GEORGE S. FORBES AND HERBERT H. ANDERSON

The fundamental papers of Urey and co-workers on isotopic exchange equilibria[1,2,3] emphasize the fact that not even units so closely similar as isotopic atoms attain a truly random distribution among similar molecules. These investigators have set up general equations for calculation of equilibrium constants based on the distribution functions of diatomic and polyatomic molecules, and have quantitatively predicted those important deviations from random distribution which have served them so well in their separations of isotopes. One might expect *a priori* that any exchange reactions involving different organic groups, or even different halogen atoms, would exhibit substantial deviations from simple probability laws.

An important series of papers by Calingaert and co-workers[4,5,6,7,8,9] reports, however, that random exhange of organic radicals occurs within experimental error among certain alkyls, chloroalkyls and esters, likewise different halogen atoms among ethylene halides. From the laws of probability alone they work out a general equation for quantitative prediction of equilibria in such reactions, and stress the absence of chemical or energy factors affecting random distribution. They emphasize that "the redistribution reaction is adaptable as a new method of organic synthesis".[10]

It would seem that inorganic chemists have long possessed at least an instinctive realization of the possibilities of the redistribution reaction, especially in the synthesis of mixed halides containing a single atom of a quadrivalent element. For instance, Besson[11] obtained all the chloroiodides of silicon by passing iodine monochloride over silicon heated to redness. He found that if a silicon chloroiodide (plus iodine) was passed over heated silicon, silicon tetrachloride was one of the products, and he astutely remarks ". . . this is not surprising if one takes account of the partial dissociation of chloroiodides under the action of heat." Subsequently[12] he obtained mixed halides from the action of hydrogen bromide on phosphoryl chloride. He points out that the boiling point of $POClBr_2$, when distilled at normal pressure, is not fixed, since at this temperature (about 165°) it undergoes a progressive decomposition according to the equations

$$2POClBr_2 = POCl_2Br + POBr_3$$
$$\text{and } 3POClBr_2 = POCl_3 + 2POBr_3$$

Lecompte, Volkringer and Tchakirian,[13] improving a procedure of Besson,[14] heated chloroform with bromine in a sealed tube at successively higher temperatures up to 250°, allowing hydrogen bromide to escape after each heating. By fractional freezing, in addition to distillation, all the mixed halides were obtained.

Raeder[15] measured molar elevations of boiling points and molar depressions of freezing points in a great number of solutions made by dissolving a given halide of a given element from a middle group of the periodic system in excess of a second halide in the same category. By plotting $\pm\Delta T$/mole against mole per cent. of the first halide, he arrived at the following conclusions. The halides of phosphorus, arsenic, antimony, titanium, tin (and by prediction germanium as well) easily exchange their halogen atoms so as to enter into readily mobile equilibria and form mixed halides incapable of isolation in the solid or in the gaseous phase. On the other hand, the tetrahalides of carbon and silicon, which are characterized by great chemical inertness, form mixed halides only with difficulty and only under special conditions. Once formed, however, they can be isolated as pure compounds. Raeder cites Trümpy's analyses of Raman spectra of such systems[16] as confirmation of the above interpretations.

Papers of references 1 to 14 do not contain quantitative data on yields, so that closeness of approach to random distribution cannot be figured. Our interest in the stabilities of halides, cyanates and thiocyanates prompted a survey of the redistribution problem over Group IVA of the periodic system, in which at least the mixed chlorides of four elements enjoy some measure of stability. A subsequent paper by Anderson[17] describes the preparation and properties of three new compounds, $SiCl_3NCO$, $SiCl_2(NCO)_2$ and $SiCl(NCO)_3$ and shows that these, as well as mixtures of the end members of the series, attain at elevated temperatures distributions random within experimental error. In the present paper it is shown that their behavior fits into a larger scheme of relative stabilities.

Carbon Chlorobromides.—No reaction between carbon tetrachloride and tetrabromide was detected after seven hours in a sealed tube at 170°, or in a second experiment in which dry aluminum chloride was added. In the three

(1) Urey and Rittenberg, *J. Chem. Phys.*, **1**, 137 (1933).
(2) Rittenberg, Bleakney and Urey, *ibid.*, **2**, 48 (1934).
(3) Urey and Greiff, THIS JOURNAL, **57**, 321 (1935).
(4) to (7) *ibid.*, **61**, 2748, 2755, 2758, 3300 (1939).
(8) and (9) *ibid.*, **62**, 1099, 1104 (1940).
(10) Reference 4, p. 2754.
(11) Besson, *Compt. rend.*, **112**, 1314 (1891).
(12) Besson, *ibid.*, **122**, 814 (1896).
(13) Lecompte, Volkringer and Tchakirian, *ibid.*, **204**, 1927 (1937).
(14) Besson, *ibid.*, **114**, 222 (1892).
(15) Raeder, *Z. anorg. allgem. Chem.*, **210**, 145 (1933); from *Det. Kgl. Norske Vidensk Selsk. Skrifter*, **3**, 1 (1929).
(16) Trümpy, *Z. Physik*, **66**, 790 (1930); **68**, 675 (1931).
(17) Anderson, THIS JOURNAL, **66**, 934 (1944).

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TABLE I

REDISTRIBUTION OF THE CARBON CHLOROBROMIDES; $AlCl_3$ CATALYST

	Compounds	Mole, % Cl	% CCl_4	CCl_3Br	CCl_2Br_2	$CClBr_3$	CBr_4
3	CCl_4, CBr_4	0.723	obs. 29.6	38.6	23.5	6.8	1.5 ±
			calc.[4] 27.3	41.9	24.1	6.1	0.6
4	CCl_4, CBr_4	0.623	obs. 12.9	38.8	34.5	12.1	1.7 ±
			calc.[4] 15.1	36.5	33.1	13.3	2.0
5	CCl_3Br, CCl_2Br_2	0.67	obs. 19	41	28	11	1 ±
			calc.[4] 20.2	39.7	29.3	9.6	1.2

TABLE II

REDISTRIBUTION OF THE SILICON CHLOROBROMIDES; NO CATALYST

	Compounds	Mole, % Cl	% $SiCl_4$	$SiCl_3Br$	$SiCl_2Br_2$	$SiClBr_3$	$SiBr_4$
1	$SiCl_4$, $SiBr_4$	0.50	(obs. 15.3	22.5	25.1	22.5	14.6)
			calc. 6.25	25.0	37.5	25.0	6.25
2	$SiCl_3Br$	0.75	obs. 31.0	39.8	26.5	2.7	(0)
			calc. 31.6	42.2	21.1	4.7	0.4
3	$SiCl_3Br$, $SiClBr_3$	0.60	obs. 12.1	38.8	28.4	19.0	1.8 ±
			calc. 12.96	34.56	34.56	15.36	2.56

experiments listed in Table I, slightly moistened aluminum chloride was used as a catalyst, and the pressure of hydrogen chloride in the sealed tube was apparent. Random distribution was now attained within experimental error. The calculated mole percentages in Table I are figured from Calingaert's equations.[4] We have found no previous record of a direct reaction between carbon tetrachloride and carbon tetrabromide.

Experimental.—Carbon tetrabromide was precipitated from a water solution containing 25 g. of sodium hydroxide, 1 cc. of acetone and 5 cc. of bromine per liter as recommended by Wallach.[18] About 120 g. of crude product was recovered, washed, dried by suction and fused. A mixture with carbon tetrachloride in a known mole ratio was heated in a sealed tube at 170° for seven hours. Decomposition of carbon tetrabromide would have been excessive at higher temperatures or over longer periods. The reaction, if any, was less than 10% of the whole. A second experiment, with introduction of dry aluminum chloride, generated no pressure in the tube and appeared to yield no chlorobromides. In the succeeding experiments the aluminum chloride was spread out on paper, and breathed upon to activate it, presumably through formation of hydrogen chloride. Redistribution now occurred readily. After washing with caustic solution and drying with calcium chloride, the liquid mixture, 5–7 ml. in volume, was distilled using a column 30 cm. high and 7 mm. in diameter with a spiral of No. 22 copper wire having 80 turns, and was surrounded with a vapor jacket. Simultaneous readings were made of temperature, and of the depth of liquid collected in small flat-bottomed tubes backed by a millimeter scale. Satisfactory "flats" were observed at the boiling points of the first four members of the series, namely, 77°, 104°, 134°, and 160°. The cuts were made half-way between these temperatures. Small corrections were applied to the fractions for the estimated molar volumes of the respective chlorobromides. We encountered difficulties in separating the last of the chlorotribromide from tetrabromide in the last, very small, fraction. Our system was further complicated by presence of the compounds C_2Br_4 and C_2Br_6. In Experiment 3, presence of carbon tetrabromide was established qualitatively, but the figures in the last column indicate nothing beyond orders of magnitude. The other volumes, read within 0.05 ml., yielded mole percentages significant, we believe, within 2%.

Silicon Chlorobromides.—Silicon tetrachloride and tetrabromide were heated for seventy hours in a sealed tube at 140° without a catalyst. The physical properties of the fractionated products were measured, or remeasured to improve previously existing data. The figures are being submitted for separate publication in THIS JOURNAL. For redistribution studies, however, the different reactants in known mole ratios were passed through a tube at 600° approximately. Equilibrium was established quite rapidly, but the first experiment was evidently too hurried, so that mixtures 2 and 3 were passed at a half and a quarter of this rate, respectively. Table II summarizes the results. Corrections for the respective molar volumes have been applied.

Experimental.—In Experiment 1, 12 ml. of mixed liquids passed through a tube of 17-ml. volume at about 600° in forty-five minutes, but about 20% of the reactants escaped reaction. Table II shows that the second and third rates were not too rapid at the temperatures prevailing. During distillation in the apparatus described above, the temperature moved very slowly, over considerable volume intervals, in the vicinity of the boiling points of the five pure compounds, 57°, 80°, 104.5°, 128° and 153°, respectively. The last half of fraction 4 in Experiment 3 boiled at an average temperature of 132° instead of 128°, indicating the presence of some 16% of silicon tetrabromide. The volumes of tetrabromide in Experiments 2 and 3 indicate orders of magnitude only.

Since the members of the series carbon tetrachloride through carbon tetrabromide require a catalyst for rearrangement at 170°, while the members of the corresponding silicon series rearrange without a catalyst, it appears that carbon tetrahalides are much more stable with respect to rearrangement than those of silicon.

Silicon Chloroiodides.—Treatment of silicon tetrachloride with fused potassium iodide yielded a relatively small amount of $SiCl_3I$. Upon passage through a hot tube, a mixture of all five members of the series was obtained. At 58°, 114° and 172°, the boiling points of the first three members, the "flats" were especially sharp. The fractions in Table III approximate random distribution.

TABLE III

	$SiCl_4$	$SiCl_3I$	$SiCl_2I_2$	$SiClI_3$	SiI_4
Mole % observed	30.4	42.7	22.0	3.7	1.2
Mole % calculated	31.6	42.2	21.1	4.7	0.4

Silicon chlorobromides, chloroiodides and chlorocyanates attain random distribution without a catalyst. If fractionation of such mixtures is complete within a few hours,

(18) Wallach, *Ann.*, 275, 149 (1893).

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the products are separated without appreciable rearrangement.

Germanium Chlorobromides.—Booth and Morris[19] prepared the closely related germanium fluorochlorides. Held at −78°, these rearranged to the extent of 60% within two weeks. We passed an equimolar mixture of tetrachloride and tetrabromide, prepared separately from the elements, through a hot tube at 600°. Five milliliters of the liquid product was distilled through the column described above, but more rapidly than the carbon and silicon chlorides. The initial rise in the actual distillation curve (Fig. 1) is consistent with a small percentage of tetrachloride and a low reflux ratio. Next, $GeCl_4$ and $GeCl_3Br$ are formed at the expense of higher chlorobromides and bled off. The first intermediate, $GeCl_3Br$, evidently distills off at 112°, between 25 and 36 atom per cent. of bromine allowing for products already distilled. Its calculated boiling point, 109°, is one-quarter of the way between 83° and 186.5°, the boiling points of the end members. On the whole the separate existence of germanium trichlorobromide, boiling point 111 ± 3°, is supported by the data. Redistillation of 12 ml. of distillate collected between 96° and 122° yielded relatively little at 109°, and large fractions approximating the end members. Evidently rearrangement is quite rapid between these temperatures. In another distillation, still more rapid, inconclusive retardations of the temperature rise seemed to occur near 135° and 161°, but we are reluctant to offer these in evidence. The upper half of the actual distillation curve shown in Fig. 1 resembles a curve for a mixture of stable end members.

Mixed Stannic Halides.—Besson[20] found it impossible to separate stannic chlorobromides from each other by repeated fractionation even under greatly diminished pressure. He states that this would result in total decomposition of the desired products into stannic chloride and stannic bromide. By fractional freezing he then obtained three products which he held to be the three chlorobromides of tin—quite nearly pure.

Raeder's freezing point curves for the systems $SnBr_4 + SnI_4$[21] and $SnCl_4 + SnBr_4$[22] indicated continuous series of mixed crystals without compound formation. He showed[22] why Besson's procedure led to fractions having the properties observed by him. In the system $SnCl_4 + SnI_4$, however, he found evidence of the compound $SnCl_2I_2$[22] having an incongruent melting point, and stable only below −47°.

As we were disinclined to undertake a further study of this problem, we merely passed equal volumes of stannic chloride and bromide through the hot tube, and redistilled the condensate in the same apparatus as used with the other chlorobromides, over a half-hour period. The distillation curve (Fig. 1) shows no retardations of temperature increase at any of the calculated boiling points of the chlorobromides. Its initial slope suggests rapid replacement of tetrachloride at the expense of chlorobromides. It lacks the steep middle portion to be expected, in this apparatus, of two non-reacting liquids boiling at 114° and 202°, respectively. Extrapolating the findings for carbon, silicon and germanium, one would predict a random mixture of all members of the tin series, very rapidly rearranging at all the distillation temperatures, in harmony with Raeder's conclusions. It would be of interest to determine whether mixed tin halides containing one or more fluorine atoms could be isolated.

Summary

Mixtures of carbon tetrachloride and tetrabromide, as well as the carbon chlorobromides, rearrange in seven hours at 170° with slightly moistened aluminum chloride as a catalyst, until halogen atoms are distributed among the five members of the series according to the laws of probability

The corresponding rearrangements in the silicon series (chlorobromides and chloroiodides) in seven hours at 140° without catalyst are partial, but complete after passage through a tube at 600°. These random mixtures can be fully separated by fractional distillation at normal pressure without appreciable rearrangement.

Distillation curves of the hot tube product from germanium tetrachloride and tetrabromide show definite indications of the new compound $GeCl_3Br$ at 112° approximately. Upon redistillation of such a fraction, rapid redistribution takes place.

The slope of a distillation curve of the stannic chlorobromides showed no irregularities near the boiling points calculated for the mixed compounds. Some indication of redistribution was obtained, although the individual compounds could not be isolated, presumably because of redistribution during distillation.

None of the phenomena observed were inconsistent with the hypothesis that all possible members of the germanium and tin chlorobromide series coexisted in random distribution.

The stability, against rearrangement, of the chlorobromides of Group IVA decreases steadily from carbon to tin.

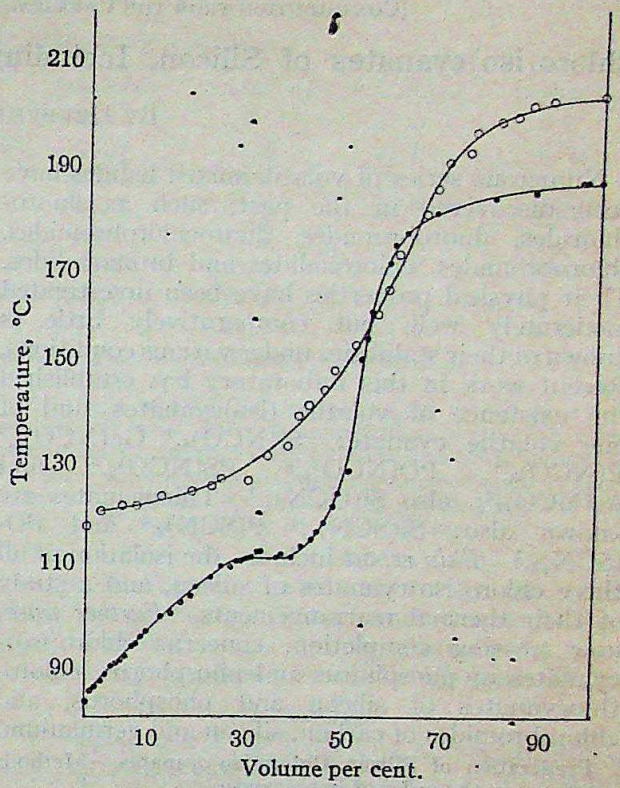

Fig. 1.—Distillation curves of germanium (●) and stannic (○) chlorobromides.

(19) Booth and Morris, THIS JOURNAL, **58**, 90 (1936).
(20) Besson, *Compt. rend.*, **124**, 683 (1897).
(21) Raeder, *Z. anorg. allgem. Chem.*, **130**, 325 (1923).
(22) Raeder, *ibid.*, **162**, 222 (1927).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

Chloro(iso)cyanates of Silicon, Including Rearrangements at High Temperatures

BY HERBERT H. ANDERSON

Numerous series of volatile mixed halides have been discovered in the past, such as fluorochlorides, fluorobromides, fluorochlorobromides, chlorobromides, chloroiodides and bromoiodides. Their physical properties have been investigated moderately well, but comparatively little is known of their stabilities under various conditions. Recent work in this Laboratory has established the existence of volatile (iso)cyanates, and of one volatile cyanate: $Si(NCO)_4$,[1] $Ge(NCO)_4$,[2] $P(NCO)_3$,[1] $PO(NCO)_3$,[3] $PS(NCO)_3$,[2] and $As(NCO)_3$[3]; also $Si(OCN)_4$.[1] Thiocyanates are known also: $Si(SCN)_4$,[4] $P(SCN)_3$,[5] and $PO(SCN)_3$.[3] *This report* includes the isolation of all three chloro(iso)cyanates of silicon, and a study of their thermal rearrangements. *Further work*, now nearing completion, concerns chloro(iso)cyanates of phosphorus and phosphorus, chlorothiocyanates of silicon and phosphorus, and chlorobromides of carbon, silicon and germanium.

Preparation of Silicon Chloro(iso)cyanates.—Methods are listed in the order of importance.

(a) **Interaction of Silicon Tetrachloride and Silicon (iso)cyanate at 600°.**—A mixture of 66 ml. of $SiCl_4$ and 70 ml. of $Si(NCO)_4$[1] was passed slowly through a hot tube. A separatory funnel with constricted outlet served in regulating the drip of the liquid over a two-hour period. The first distillation yielded crude fractions of 10 ml. of $SiCl_4$, 32 ml. of $SiCl_3(NCO)$, 45 ml. of $SiCl_2(NCO)_2$, 35 ml. of $SiCl(NCO)_3$, and 11 ml. of $Si(NCO)_4$. Boiling points were 86.8° for $SiCl_3(NCO)$, 117.8° for $SiCl_2(NCO)_2$, and 152° for $SiCl(NCO)_3$. The redistillation of each of the above fractions was limited to a two-hour period to minimize decomposition; the boiling point ranges of fractions collected for measurements did not exceed 0.5°.

(b) **Sealed Tube Method; $SiCl_4$ and $Si(NCO)_4$.**—Fifteen ml. of $Si(NCO)_4$ and 11.3 ml. of $SiCl_4$ were heated in a Carius tube for seventy hours at 135°. Products were 4.8 ml. of $SiCl_4$, 2.8 ml. of $SiCl_3(NCO)$, 3.3 ml. of $SiCl_2(NCO)_2$, 6.5 ml. of $SiCl(NCO)_3$, and 6.0 ml. of $Si(NCO)_4$. On the basis of equilibria shown later in Table II, a period of a week at 135° would be required for random rearrangement of the products.

(c) **Gradual Addition of AgNCO to a Large Excess of $SiCl_4$ in Solution.**—The possibility of making chloro(iso)cyanates by very gradual addition of silver (iso)cyanate was considered. A mixture of 90 ml. of $SiCl_4$, 35 ml. of CS_2, and 70 ml. of C_2H_5Br was used; 80 g. of silver (iso)cyanate was added in small portions, over a period of an hour, with constant and vigorous shaking. The liquid boiled slowly because of the heat of reaction. Distillation yielded 6.8 ml. of $SiCl_3(NCO)$, 5.5 ml. of $SiCl_2(NCO)_2$, and 5.7 ml. of $Si(NCO)_4$; $SiCl(NCO)_3$ was absent, or less than 0.3 ml. This method is important, although not so valuable as the high temperature method, which gives all three compounds.

Chloro(iso)cyanates as By-products in the preparation of $Si(NCO)_4$, as previously described[1]: 517 g. of AgNCO and 108 ml. (9 ml. excess) of $SiCl_4$ were used. Redistillation of the fraction boiling between 95 and 183° yielded 0.8 g. of $SiCl_2(NCO)_2$, 3.3 g. of $SiCl(NCO)_3$, 147 g. of $Si(NCO)_4$ and an estimated 5 g. of $Si(OCN)_4$. On a basis of (iso)cyanate, the yield exceeded 90%. It has been found advisable to use about this excess of silicon tetrachloride, in order to convert the silver (iso)cyanate completely into silver chloride.

Analysis.—A weighed sample was frozen and dropped beneath a 6-cm. column of absolute alcohol in a test-tube; ethyl silicate, ethyl cyanate (or isocyanate), and hydrogen chloride were the products. Water was added immediately. This method is superior to decomposition by water with the consequent formation of silica gel. Chloride was determined with standard silver nitrate solution, using potassium chromate as indicator. For $SiCl_3(NCO)$: calcd. 60.28% Cl; found 60.1, 60.5. For $SiCl_2(NCO)_2$ calcd. 38.75% Cl; found 38.6, 38.9. For $SiCl(NCO)_3$ calcd. 18.70% Cl; found 18.8, 18.9. Molecular weights were found by the Dumas method. For $SiCl_3(NCO)$ calcd. 176.45; found 176, 180. For $SiCl_2(NCO)_2$ calcd. 183.01; found 180, 188. For $SiCl(NCO)_3$ calcd. 189.57; found 193, 196.

Physical Properties.—All three chloro(iso)cyanates are colorless liquids characterized by a peculiar "isocyanate odor." Boiling points were measured to 0.5°, immediately followed by measurement of the boiling point of pure benzene or water or bromobenzene under identical conditions. Densities were measured at 25°, using a 1.7 ml. bulb with a long capillary inlet bearing a reference mark. The height of the meniscus was measured in each case.

The system was calibrated with water and probably gave densities good to two parts per thousand. The index of refraction was measured with an Abbe refractometer (calibrated with water and carbon tetrachloride) in white light at 20°.

Melting points were determined using about 3 ml. of pure sample and a toluene thermometer, with its bulb wholly immersed in the liquid. This thermometer was calibrated at 0 and −78°; melting point ranges were much less than a degree. Table I shows the trends in properties from $SiCl_4$ through to $Si(NCO)_4$.[1] The calculation of boiling points of $SiCl_3(NCO)$, $SiCl_2(NCO)_2$, and $SiCl(NCO)_3$ by linear interpolation between those of $SiCl_4$ and $Si(NCO)_4$ gave 89.6°, 121.6°, and 153.6°. The average observed value falls 2.6° lower than the calculated figure—a reasonable agreement.

TABLE I

Compound	B. p., °C.	M. p., °C.	Density, 25°	n	Molecular vol., ml.
$SiCl_4$	57.57	−70	1.469[a]	1.4126	115.7
$SiCl_3(NCO)$	86.8	−69 ± 1.5	1.445	1.4262	122.4
$SiCl_2(NCO)_2$	117.8	−80 ± 1.5	1.437	1.4380	127.3
$SiCl(NCO)_3$	152.0	−35 ± 1.5	1.437	1.4507	131.9
$Si(NCO)_4$[1]	185.6	26.0	1.434[a]	1.4610	136.8

[a] Pycnometric value recently obtained.

Boiling points and indices of refraction are the best means of physical identification of members of the series. Melting points and densities are less distinctive.

Chemical Properties.—All three chloro(iso)cyanates of silicon, like other (iso)cyanates, are vigorously decomposed by water, with the formation of gas bubbles; they react vigorously with alcohol, but no bubbles appear. The (NCO) group in this series is quite stable at 600°. Oxidation is negligible in air at 200°.

Rearrangements of Chloro(iso)cyanates of Silicon.—As shown in the section on preparation, $SiCl_4$ and $Si(NCO)_4$

(1) Forbes and Anderson, THIS JOURNAL; **62**, 761 (1940).
(2) Forbes and Anderson, *ibid.*, **65**, 2271 (1943).
(3) Anderson, *ibid.*, **64**, 1757 (1942).
(4) Reynolds, *J. Chem. Soc.*, **89**, 397 (1906).
(5) Miquel, *Ann. Chim. Phys.*, [V] II, 343 (1875); Dixon, *J. Chem. Soc.*, **79**, 541 (1901).
(6) See Mellor, "Comprehensive Treatise," Vol. VI, p. 962. Density at 20° is 1.483.

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TABLE II

REARRANGEMENTS OF SILICON CHLORO(ISO)CYANATES

Run	Initial Mixture	Atom % Cl Initial	Atom % Cl Final		$SiCl_4$	$SiCl_3(NCO)$	$SiCl_2(NCO)_2$	$SiCl(NCO)_3$	$Si(NCO)_4$
1	$\frac{1}{2}$ $SiCl_4$ + $\frac{1}{2}$ $Si(NCO)_4$	0.50	0.50	found	8	25	34	25.0	8.0
				calcd.	6.25	25.0	37.5	25.0	6.25
2	pure $SiCl_2(NCO)_2$	.50	.50	found	8	25	34	26	7
				calcd.	6.25	25.0	37.5	25.0	6.25
3	pure $SiCl_3(NCO)$	.75	.75	found	33	38	24	5	(0)
				calcd.	31.6	42.2	21.1	4.7	0.4
4	pure $SiCl(NCO)_3$	.25	.26	found	(0)[a]	5.0	26	36	33
				calcd.	0.4	4.7	21.1	42.2	31.6

[a] Too small for satisfactory measurement, although $SiCl_3(NCO)$ started to distill at 80°, instead of 87°.

react together; all five possible compounds are produced in amounts predictable by assuming random distribution of groups. Previous work on redistribution in the lead alkyl series[7] indicated random distribution of groups, and included a method of calculating the percentage occurrence of each compound. Thermal rearrangement of individual compounds ($SiCl_3(NCO)$, $SiCl_3(NCO)$, and $SiCl(NCO)_3$) was studied carefully; vapor was passed through a hot tube at 600°, at a slow rate, with later determination of products by fractional distillation. Table II summarizes the results.

Experimental Work on Rearrangements.—The redistribution between $SiCl_4$ and $Si(NCO)_4$ was done on a large scale and produced large amounts of the compounds desired, as explained at the beginning of the section on preparation. By adjusting the amounts found according to molecular volumes (Table I), the correct molecular ratios were obtained. Rearrangements of $SiCl_3(NCO)$, $SiCl_2(NCO)_2$, and $SiCl(NCO)_3$ were obtained by the passage of 5 ml. of each pure compound through a small Pyrex tube at 600°, over a period of thirty minutes. Values in Table II have been rounded off to the nearest per cent. More precise and therefore slower distillation would have led to secondary rearrangements of considerable magnitude. Amounts of less than 2% are difficult to determine, notably if the least volatile compound is involved. Volumes were measured to 0.05 ml. in calibrated receivers of the same bore and with nearly flat bottoms.

The percentages indicate random distribution within a few per cent. Secondary rearrangements are too close for attainment of theoretical ratios. Values of the chief component are a little low in all cases, but this is within experimental error, and without significance.

(7) Calingaert, Beatty and Soroos, THIS JOURNAL, 62, 1100 (1940).

A sample of $SiCl_2(NCO)_2$ rearranged to the extent of several per cent. after standing four months at room temperature. Mixtures of $Si(NCO)_4$ and $SiCl_4$, as well as the three chloro(iso)cyanates, are being set aside at room temperature with the intention of determining the distribution of products after considerable time intervals.

The author is much indebted to Professor George S. Forbes of this Laboratory for many helpful suggestions. Other work on rearrangement of mixed halides and on cyanates and thiocyanates is in progress and will be reported soon.

Summary

1. $SiCl_3(NCO)$, $SiCl_2(NCO)_2$, and $SiCl(NCO)_3$ have been prepared. The progression of several physical properties in the series $SiCl_4$ through $Si(NCO)_4$ has been tabulated. $SiCl_4$ and $Si(NCO)_4$ react rapidly at 600° to give all three chloro(iso)cyanates. Interaction is moderate in rate at 135°, and extremely slow at room temperature. Gradual addition of AgNCO to a large excess of $SiCl_4$ in solution yields $SiCl_3(NCO)$ and $SiCl_2(NCO)_2$, but no $SiCl(NCO)_3$.

2. Random distribution, such as previously found by Calingaert, Beatty and Soroos in the lead alkyl series, also applies to the rearrangement of any mixture or pure compound in the series $SiCl_4$ through $Si(NCO)_4$. No catalyst is needed.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF EMORY UNIVERSITY]

A Study of Organic Parachors. VI. A Supplementary Series of Tertiary Alcohols[1]

BY OSBORNE R. QUAYLE AND KATHERINE O. SMART

The parachor values for a series of tertiary alcohols[2] have been previously reported from this Laboratory and values for the CH_2 group in various positions have been determined and suggested as a means of calculating the parachors of other tertiary alcohols. Nine additional supplementary tertiary alcohols have been prepared and their refractive indices, densities, surface tensions and parachors have been determined. The alcohols were prepared by standard methods and were purified by successive vacuum distillations.[3] To minimize decomposition the temperatures of distillation were kept below 75°. Refractive indices were determined at 20, 25 and 35°. Densities and surface tensions were measured at 25, 45 and 55°, and the parachors were calculated for the same temperatures, using the standard formula $P = M\gamma^{1/4}/(D - d)$. The data obtained are shown in Table I. The varia-

(1) The authors wish to express their gratitude to Professor E. Emmet Reid, Research Consultant to the department, for his continued interest and suggestions in connection with this investigation.

(2) K. Owen, O. R. Quayle and E. M. Beavers, THIS JOURNAL, 61, 900 (1939).

(3) Prepared by Harry M. Stubbs of this Laboratory.

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TABLE I

PHYSICAL PROPERTIES DETERMINED FOR NINE TERTIARY ALCOHOLS

Carbinol	T	$n^{20}D^{a}$	T	D	γ	P exp.	P calcd.[b]	Dev. %
Methylethylbutyl	20	1.4284	25	0.8252	25.22	353.6	353.8	0.1
	25	1.4263	45	.8083	23.33	354.1		
	35	1.4214	55	.7999	22.41	354.3		
Methylpropylbutyl	20	1.4325	25	.8268	25.60	392.4	392.4	.0
	25	1.4301	45	.8104	23.65	392.5		
	35	1.4256	55	.8022	22.66	392.3		
Methylbutylbutyl	20	1.4350	25	.8258	26.20	430.9	430.9	.0
	25	1.4326	45	.8095	24.23	431.1		
	35	1.4280	55	.8013	23.23	430.9		
Methylmethylamyl	20	1.4238	25	.8133	24.74	357.1	357.3	.1
	25	1.4218	45	.7969	22.86	357.3		
	35	1.4172	55	.7889	21.93	357.3		
Methylethylamyl	20	1.4324	25	.8275	26.06	393.8	393.8	.0
	25	1.4301	45	.8111	24.19	394.4		
	35	1.4256	55	.8029	23.23	394.4		
Methylpropylamyl	20	1.4350	25	.8271	25.73	431.0	432.4	.3
	25	1.4332	45	.8108	24.04	432.2		
	35	1.4287	55	.8026	23.17	432.7		
Ethylbutylamyl	20	1.4424	25	.8357	26.58	506.2	506.8	.1
	25	1.4401	45	.8191	24.80	507.6		
	35	1.4356	55	.8108	23.95	508.4		
Propylbutylamyl	20	1.4420	25	.8320	26.25	545.1	545.6	.1
	25	1.4397	45	.8160	24.64	547.0		
	35	1.4354	55	.8081	23.80	547.7		
Butylbutylamyl	20	1.4458	25	.8348	26.82	584.4	584.1	.1
	25	1.4434	45	.8189	25.04	585.6		
	35	1.4390	55	.8109	24.18	586.2		

[a] Refractive indices by J. P. Sutton, Jr. [b] Calcd. P based upon values of Owen, Quayle and Beavers.[2]

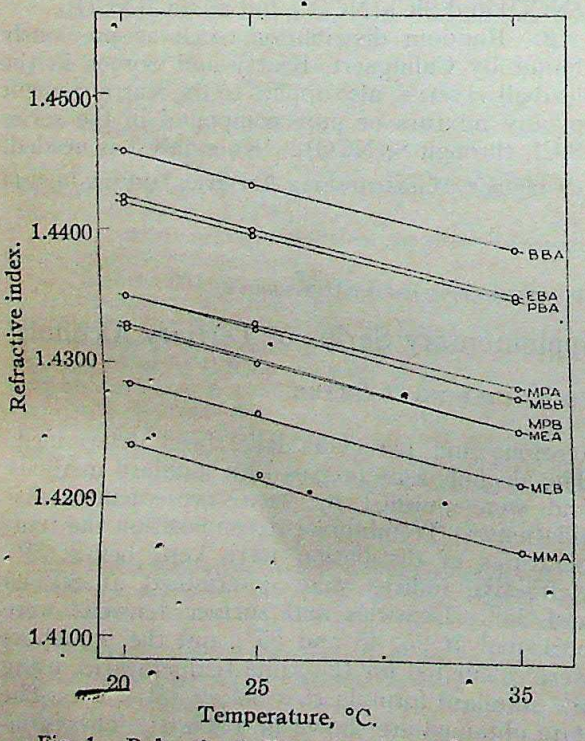

Fig. 1.—Refractive indices of tertiary carbinols.

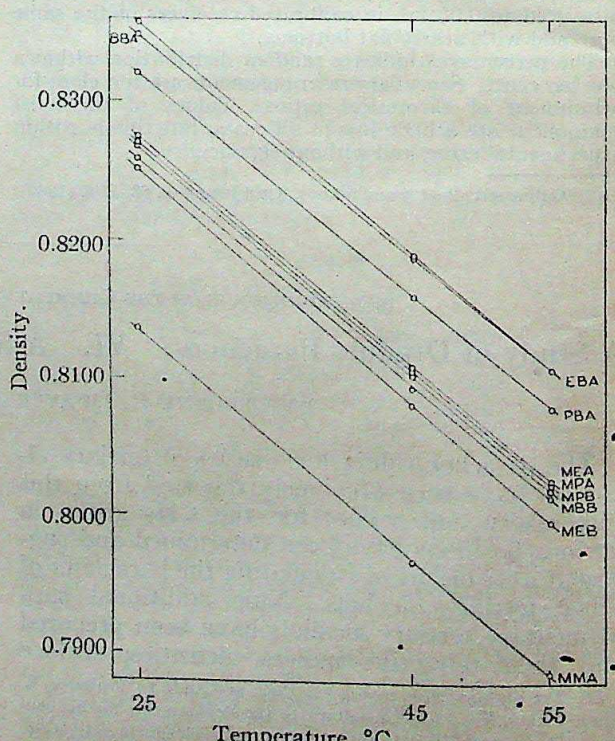

Fig. 2.—Densities of tertiary carbinols.

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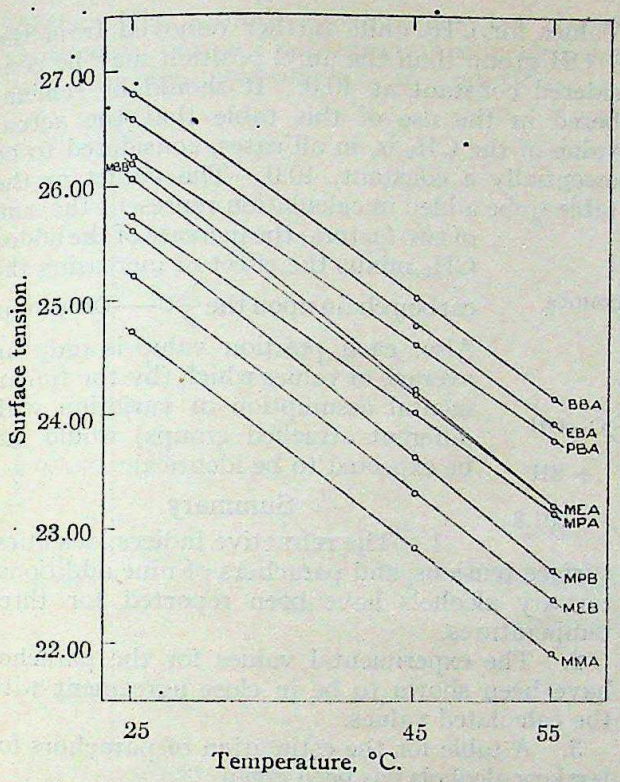

Fig. 3.—Surface tensions of tertiary carbinols.

tions of refractive indices, densities, surface tensions, and parachors with temperature are shown in Figs. 1, 2, 3, 4, respectively.

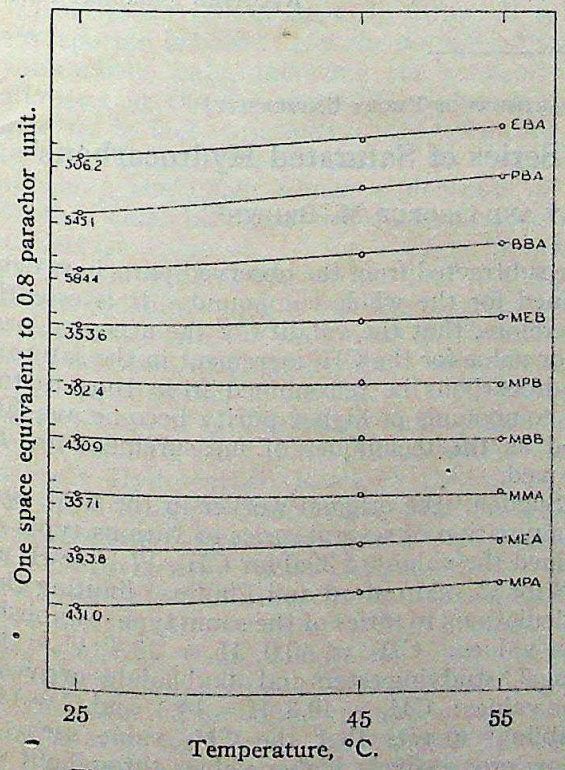

Fig. 4.—Parachors of tertiary carbinols.

Surface tensions were determined by the maximum bubble pressure method. Certain modifications were made in the design of the bubbler to ensure greater accuracy and reproducibility of readings, as well as to decrease the time necessary for measurement. It has long been recognized that it is essential that the bubbler tubes be vertical. In order to check this the tubes were attached to a cap, with an externally ground glass joint, so that they might be conveniently rotated. After a reading was completed the tubes were rotated 180° and a second reading made. If the same value, within experimental error, was obtained the tubes were considered vertical and the readings were accepted as a measurement. Each measurement was independently checked by a second observer. To avoid loss of time in readjusting the tubes to the vertical position after a change in sample, the bubbler was equipped with a heavy ground-glass flange fitting into a heavy ground collar. If the collar is securely clamped, the bubbler after being removed and replaced will seat itself in the same vertical position. In order to permit the use of samples as small as three cubic centimeters the bubbler may be slightly smaller in diameter below the flange. The design of the bubbler is shown in Fig. 5. While the modifications described may appear to be minor, the changes greatly facilitate more accurate and more rapid measurement.

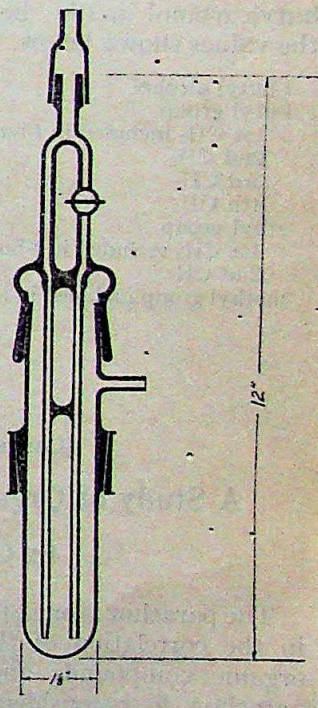

Fig. 5.—Bubbler for surface tension.

The results obtained offer an opportunity to test the values on the parachor in tertiary alcohols previously reported.[2] Using the previously reported position values for the CH_2 increments in obtaining calculated parachors, the maximum deviation between an experimental value and the corresponding calculated value was found to be 0.3% in the case of methylpropylamylcarbinol. In no other case did the deviation exceed 0.1%. The experimental error has been considered to be 0.1%. These values are given in Table I.

From the newly-determined tertiary alcohols several additional CH_2 values for various positions in tertiary alcohols may be calculated. Combining these values with those previously reported a table may be constructed for the estimation of the parachor of any tertiary alcohol having unbranched alkyl groups. Assuming the parachor value for

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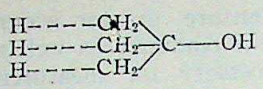
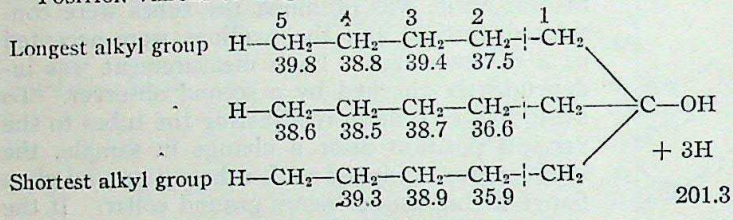


to be the determined value 201.3 of *t*-butyl alcohol, the parachor of any tertiary alcohol may be estimated by adding the CH_2 values for the various positions as given in Table II.

TABLE II

POSITION VALUES OF CH_2 IN PARACHORS OF TERTIARY ALCOHOLS



For example, the parachor for methylethyl butylcarbinol would be calculated by adding the values shown below.

t-butyl alcohol	201.3
butyl group	
1st CH_2 included in *t*-butyl linkage	———
2nd CH_2	37.5
3rd CH_2	39.4
4th CH_2	38.8
ethyl group	
1st CH_2 included in *t*-butyl linkage	———
2nd CH	36.6
methyl group included in *t*-butyl linkage	———
	———
	353.6

Values for CH_2 units further removed from the —OH group than the amyl position may be considered constant at 40.0. It should be remembered in the use of this table that the actual value of the CH_2 is, in all cases, considered to be essentially a constant, 40.0. The values in the table to be added in calculation represent the sum of two factors; the increase of the added CH_2 minus the effect of increasing the carbon chain upon the $>C—OH$ group. Also, each position value is only an average of values which (by the fundamental assumption of variation with different attached groups) would not be expected to be identical.

Summary

1. The refractive indices, densities, surface tensions, and parachors of nine additional tertiary alcohols have been reported for three temperatures.

2. The experimental values for the parachor have been shown to be in close agreement with the calculated values.

3. A table for the estimation of parachors for tertiary alcohols has been given.

4. Modifications in the bubbler for determining surface tension more accurately and rapidly have been described.

EMORY UNIVERSITY, GEORGIA

RECEIVED FEBRUARY 10, 1944

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF EMORY UNIVERSITY]

A Study of Organic Parachors. VII. A Series of Saturated Hydrocarbons[1]

BY OSBORNE R. QUAYLE, R. A. DAY AND GEORGE M. BROWN[2]

The parachor is one of the more useful constants in the correlation of the physical properties of organic compounds and their structures. The parachor, first considered an additive property, has been found to be susceptible to minor as well as to gross variations in structure. It is particularly so to any variations in the degree of unsaturation of the molecule. The parachor values in normal saturated hydrocarbons have been found to be almost unique in being additive in nature.[3] In calculating the values of other groups the alkyl residues are, therefore, considered to be of known value and are subtracted from the observed parachors determined for the whole compound. It is essential, therefore, that the validity of the accepted parachor value for the CH_2 increment in the saturated hydrocarbons be reëxamined from time to time as compounds of higher purity become available and as the techniques of measurement are improved.

Sugden,[4] the original worker in the field, upon examination of several series of various types obtained the values of 39.0 for CH_2, 17.1 for H, and 4.8 for C. Mumford and Phillips,[5] limiting their calculations to series of the same type, established the values: $CH_2 = 40.0$, H = 15.4, C = 9.2. Vogel,[6] studying esters and alkyl halides arrived at the values: $CH_2 = 40.3$, H = 14.4, and C = 11.5. Gibling[7] asserts that the CH_2 value seems to show progressively higher values throughout any homologous series due to decreasing "interference"

(1) The authors wish to express their gratitude to Prof. E. Emmet Reid, research consultant to the department, for his continued interest and suggestions in connection with the problem; to the American Petroleum Institute for samples of hydrocarbons; and to the University Center in Georgia for a grant for the purchase of a constant temperature bath.

(2) New York Community Trust Fellow, Emory University 1942–43; present address Princeton University, Princeton, N. J.

(3) Even the values for the saturated chains are not considered to be strictly additive by some observers. However, they are at least essentially so. If variations exist they appear to be of a distinctly lower order of magnitude for chains of short or moderate length.

(4) Sugden, *J. Chem. Soc.*, **125**, 1177 (1924).

(5) Munford and Phillips, *ibid.*, 2113 (1929).

(6) Vogel, *ibid.*, 333 (1934).

(7) Gibling, *ibid.*, 299 (1941).

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effects. His formula gives somewhat better agreement between observed and calculated values for high molecular weight compounds.

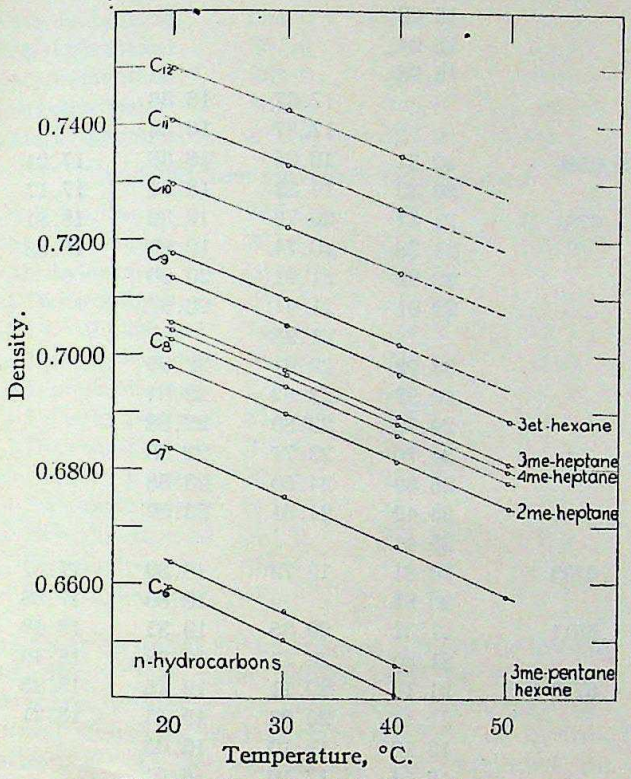

Fig. 1.—Densities of hydrocarbons.

The re-evaluation of the CH_2, C, and H values here reported is based upon the normal saturated hydrocarbons only, following the concept that variations in the apparent CH_2 value of other series are in fact variations in the values for the other non-hydrocarbon parts of the molecules. Branching the chain causes a decrease in the parachor which has been termed a strain constant. An average value of -3 for a single branching has been in general use. This does not appear to be a constant value. The hydrocarbons used in this work, with the exceptions of nonane, decane, undecane and duodecane, were prepared under the direction of Professor C. E. Boord of the Department of Chemistry of The Ohio State University as a part of the American Petroleum Institute Hydrocarbon Research Project in the Industrial Research Foundation of the University. The *n*-hexane, 2-methylpentane, 3-methylpentane and 3-ethylhexane were designated as "best liter" purity. The other A. P. I. hydrocarbons were designated as "pure." The nonane, decane, undecane, and duodecane were obtained from the Eastman Kodak Company and were refractionated. The boiling ranges of the latter samples were as follows: nonane, 148.6–148.7° at 738.0 mm.; decane, 97.8–98.4° at 69.0 mm.; undecane 108.7–109.0° at 50.5 mm.; duodecane, 66.0–66.1° at 2.3 mm.

The maximum bubble pressure method was used in the measurement of surface tension, the apparatus used being a modification[8] of that of Sugden. Surface tensions were checked by two observers. Each value reported represents a value calculated from a minimum of four observations. Where two or more values are recorded (Table I), these are entirely independent determinations made after intervening measurements, temperature changes, etc., in an endeavor to minimize any constant errors. All temperatures were maintained to within $\pm 0.05°$. The precision in the determination of surface tension was somewhat greater than one part in five hundred. The over-all precision in the determination of the parachor was in the order of one part in two thousand.

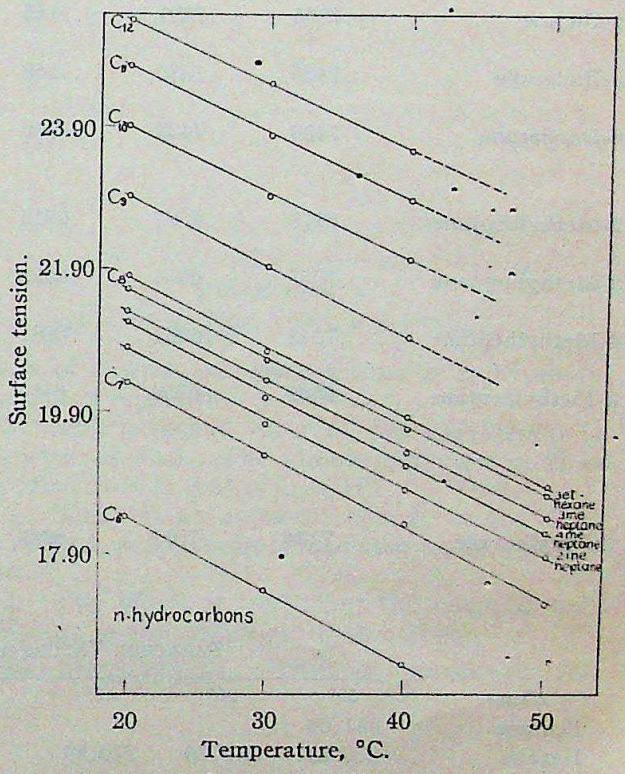

Fig. 2.—Surface tensions of hydrocarbons.

The densities and surface tensions determined are given in Table I. The parachor values were calculated by the equation $P = M\gamma^{1/4}/(D - d)$ where γ is the surface tension, M the molecular weight, D the density of the liquid, and d the density of the vapor at the same temperature. The calculated density of the vapor is relatively small and is included in the calculations only where its value is appreciable. The parachors of the normal saturated hydrocarbons and of the CH_2 increment are given in Table II. The parachors of the branched chain hydrocarbons and the values for the "strain constant" for branching are given in Table III.

The average CH_2 increment in the series of normal hydrocarbons is 40.0. There is no apparent change in this value as the chain increases within the limits here investigated. The change

(8) O. R. Quayle and L. O. Smarr, THIS JOURNAL, 66, 935 (1944).

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TABLE I

DENSITIES AND SURFACE TENSIONS OF HYDROCARBONS

Alkane	Densities at 20°	30°	40°	50°	Surface tensions at 20°	30°	40°	50°
n-Pentane	0.6260				16.00			
					15.94			
					15.98			
n-Hexane	.6593	0.6502	0.6406			17.37	16.36	
						17.37	16.34	
n-Heptane	.6837	.6752	.6668	0.6580	20.31	19.26	18.33	17.24
					20.30	19.32	18.31	17.17
n-Octane	.7027	.6945	.6862	.6781	21.81	20.76	19.82	18.81
					21.78	20.74	19.85	18.83
n-Nonane	.7175	.7097	.7020		22.92	21.91	20.96	
					22.91	21.91	20.97	
						21.95		
n-Decane	.7295	.7221	.7145		23.92	22.91	22.05	
					23.92	22.92	22.04	
n-Undecane	.7406	.7330	.7256		24.72	23.80	22.88	
					24.70	23.77	22.88	
n-Duodecane	.7496	.7423	.7349		25.39	24.50	23.58	
					25.42	24.51	23.59	
					25.41			
2-Methylheptane	.6978	.6897	.6816	.6733	20.81	19.72	18.80	17.87
					20.81		18.80	17.88
3-Methylheptane	.7055	.6974	.6892	.6811	21.32	20.35	19.31	18.40
					21.30	20.33	19.38	18.46
4-Methylheptane	.7042	.6962	.6881	.6799	21.16	20.11	19.15	18.25
					21.14	20.07	19.13	18.21
3-Methylpentane	.6639	.6550	.6460		18.10	17.10	16.05	
					18.14	17.10	16.01	
						17.06		
						17.05		
						17.09		
3-Ethylhexane	.7134	.7051	.6969	.6887	21.62	20.61	19.67	18.73
					21.62	20.61	19.64	18.69

TABLE II

PARACHOR VALUES OF NORMAL HYDROCARBONS

Alkane	Parachor at 20°	30°	40°	50°	CH_2 at 20°	30°	40°	50°	CH_2, ave.
Pentane	231.04								
Hexane	270.84	270.70	270.80		39.8				39.8
Heptane	311.34	311.21	311.36	310.58	40.50	40.51	40.56		40.5
Octane	351.13	350.96	351.28	351.00	39.79	39.75	39.92	40.42	39.8
Nonane	391.14	391.09	390.99		40.10	40.13	39.71		40.0
Decane	431.24	431.14	431.48		40.10	40.05	40.49		40.2
Undecane	470.56	470.86	471.08		39.32	39.72	39.60		39.5
Duodecane	510.14	510.76	510.86		39.58	39.90	39.78		39.8

Av. CH_2, 39.9 at 20°, 40.0 at 30°, 40.0 at 40°, over-all average 40.0

of parachor over the range of temperature studied is in no case over 0.15%. The maximum deviation from the average obtained for any calculated CH_2 increment is 1.7%; for any single compound 1.3%. It should be noted that while the value for CH_2 of 40.0 is identical with that reported by Mumford and Phillips,[5] (based on determinations of Hunten and Maass[9] primarily upon fatty acids) the value reported in the earlier work was obtained by averaging values which differed from each other by as much as 22%. Calculation from each determination of the present study gives an average atomic parachor value for H of 15.5; for C the value is 9.0.

The effect of branching the chain in the compounds studied is not uniform. The effect is increased as the branch is moved toward the center of the chain, and as the length of the branch chain is increased. Among the compounds here measured the effect is greatest in 3-ethylhexane, which has, obviously, the most symmetrical compact molecular structure. Since the parachor is a volume factor it might be expected that

(9) Henten and Maass, THIS JOURNAL, 51, 153 (1929).

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TABLE III

PARACHOR VALUES OF BRANCHED CHAIN HYDROCARBONS

Alkane	*P*, *n*-isomer	*P*, exp.	Strain per branch
2-Methylheptane	351.0	349.4	−1.6
3-Methylheptane	351.0	347.7	−3.3
4-Methylheptane	351.0	347.6	−3.4
3-Ethylhexane	351.0	345.0	−6.0
3-Methylpentane	271.0	267.9	−3.1
Calculated from previously recorded data			
3-Ethylpentane	311.0	304.2	−6.8
2-Methylhexane	311.0	309.1	−1.9
3-Methylhexane	311.0	307.3	−3.7
2,5-Dimethylhexane	351.0	347.2	−1.9
2,4-Dimethylhexane	351.0	344.9	−3.1
2,3-Dimethylhexane	351.0	344.1	−3.5
3,4-Dimethylhexane	351.0	342.6	−4.2
2,4-Dimethylpentane	311.0	307.5	−1.8
2,3-Dimethylpentane	311.0	304.3	−3.4
2,5-Dimethylheptane	391.0	384.9	−3.1
2,4-Dimethylheptane	391.0	381.1	−5.0
2,3-Dimethylheptane	391.0	373.1	−9.0
2,7-Dimethyloctane	431.0	426.4	−2.3
2,4-Dimethyloctane	431.0	422.9	−4.1

the most compact structure would have the lowest parachor. The same effect may be noted in parachor values calculated from previously recorded densities and surface tensions of hydrocarbons.[10] These values are also included in Table III. While certain regularities appear, sufficient data are not available to properly evaluate the variations in the effect of branching the chain.

Summary

1. The densities, surface tensions, and parachors of a series of hydrocarbons of high purity have been reported.

2. The parachor value of the CH_2 group is reported as 40.0. The atomic parachor of H is reported as 15.5, that of C as 9.0.

3. There is no apparent change in the CH_2 increment as the chain is increased up to duodecane.

4. The effect of branching the chain is not constant in the saturated hydrocarbons

(10) M. P. Doss, "Physical Constants of Principal Hydrocarbons," Third Edition, Texas Corp., 1942.

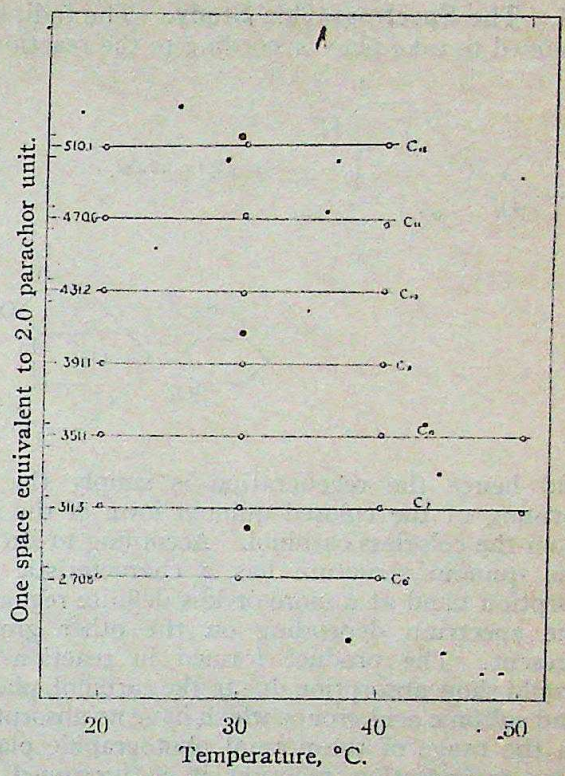

Fig. 3.—Parachors of normal hydrocarbons.

EMORY UNIVERSITY, GA. RECEIVED FEBRUARY 10, 1944

[CONTRIBUTION FROM THE CHARLES E. COATES CHEMICAL LABORATORY, LOUISIANA STATE UNIVERSITY]

A Spectrographic and Kinetic Study of the Alkaline Fading of Tetraiodophenolsulfonphthalein

BY EDWARD S. AMIS AND RALPH THEODORE OVERMAN

The alkaline form of iodo phenol blue (tetraiodophenolsulfonphthalein) has a characteristic absorption curve the intensity of which is a function of the amount of the dye present in the blue form. If an excess of the alkaline hydroxide is added to a solution of the iodo phenol blue, the dye fades to a colorless condition. The rate of fading depends upon the concentration of hydroxide present. When the colorless solution is acidified, the characteristic yellow acid form of iodo phenol blue develops progressively with time. This regeneration reaction has been studied quantitatively in the case of the brom phenol blue.[1] It is possible to study the structure of the faded and unfaded form of the dyes both spectrographically and kinetically.

In this investigation a spectrographic study was made of both the unfaded and regenerated tetraiodophenolsulfonphthalein to determine whether the two were identical. A kinetic study of the fading process in the presence of iodide salt also was made. By these methods it was hoped that definite conclusions could be reached as to the validity of proposed mechanisms for the fading and regeneration processes.

(1) Amis and Price *J. Phys. Chem.*, 47, 338 (1943).

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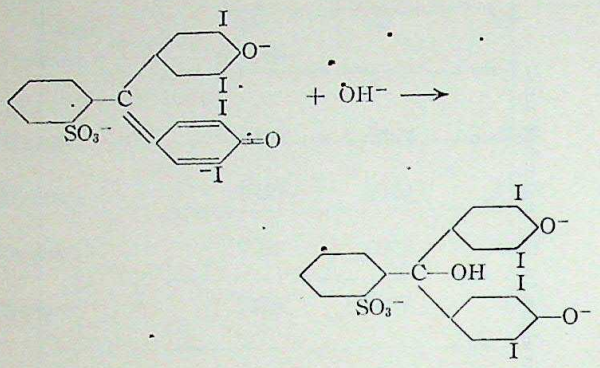
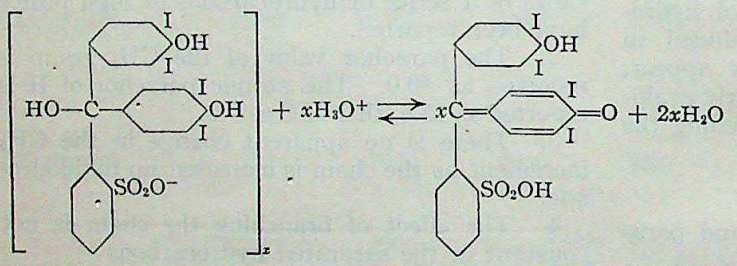
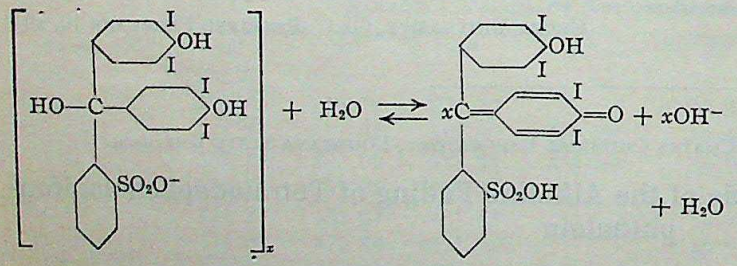
I. The Spectrographic Study.—The fading is assumed to take place according to the reaction[2,3]



and hence the regeneration is simply the reforming of the colored quinoid form of the dye from the colorless carbinol. According to Brode[4] the quinoid structure has a characteristic absorption band at a more or less definite region of the spectrum depending on the other groups present. The product formed in reaction (1) would show absorption due to the carbinol, phenol and sulfonic acid groups which have no absorption in the range of the normal photographic plate.[4] The regeneration reaction it is presumed (1) takes place according to the following mechanisms





Thus the quinoid structure of the dye is regenerated and since this material is identical with the unfaded acid form of the dye, the absorption spectrum of the regenerated material should of necessity coincide with that of the acid form of the unfaded iodo phenol blue when the two are at like *p*H.

Apparatus and Procedure.—The spectrographic data were obtained using a large Littrow spectrograph with spectrometric attachments. For these experiments dye solutions were made up to 10^{-5} molar using the same quality of dye and the same procedure employed by Amis and LaMer[3] in studying the kinetics of the fading of bromo phenol blue. The alkali for the fading was made up according to the specifications of the above authors. All measurements were made from cells with a column of absorbing medium which was 2 cm. in length. The light source for the visible region was a Mazda filament lamp and for the ultraviolet region was a hydrogen discharge tube. The setting for the visible spectra was position 3 of the glass system covering a frequency of 450–700 fresnel units. For the ultraviolet absorption of the faded dye, positions 5 and 9 of the quartz system covering a region of 450–1500 fresnel units (2000–6000 Å.) were used.

The procedure consisted of printing a millimeter scale on the plate, exposing the plate as a blank with no absorption cells in the light beam, and then interposing the cells, one being filled with distilled water and the other containing the sample being studied and measuring the absorption. The respective cells for the water and for the sample were always the same. The blank was made necessary by the fact that it was found to be impossible to equate the light intensities of the two parts of the beam visually so that they gave identical readings on the densitometer. The blank made it possible to correct for the initial difference in intensity of the two beams. The times of exposure were three, four and five seconds. The final curve was plotted from the average of the three densitometer readings corresponding to a given frequency.

The absorption as a function of the degree of fading was determined by setting the dye (10^{-5} *m*) to fade at room temperature in a known strength of alkali and at stated intervals of time measuring the absorption of the fading material. The fading was carried out in such concentrations of alkali that the short time used in taking absorption represented little change in the condition of the dye since the rate of fading was very slow.

The densitometer used was an Applied Research Laboratories Instrument which measures the density of the plate by use of a photoelectric cell. In this instrument the dark current is set to zero on the galvanometer scale and the reading of 100 as the transmission of a clear portion of the plate. The densitometer readings (D's) then ranged from zero to one hundred.

The logarithm of the ratio of the galvanometer deflection (D) for the beam which had passed through the dye to that (D_0) which had passed through the water can be related to the absorption of the incident light by the dye solution when proper corrections are made for the corresponding deflections (D' and D_0') obtained from the blank,

(2) Thiel, *Monatsh.*, **53/54**, 1008 (1929).
(3) Amis and LaMer, THIS JOURNAL, **61**, 905 (1939).
(4) Brode, "Chemical Spectroscopy," J. Wiley and Sons, Inc., New York, N. Y., 1939, pp. 127–142.

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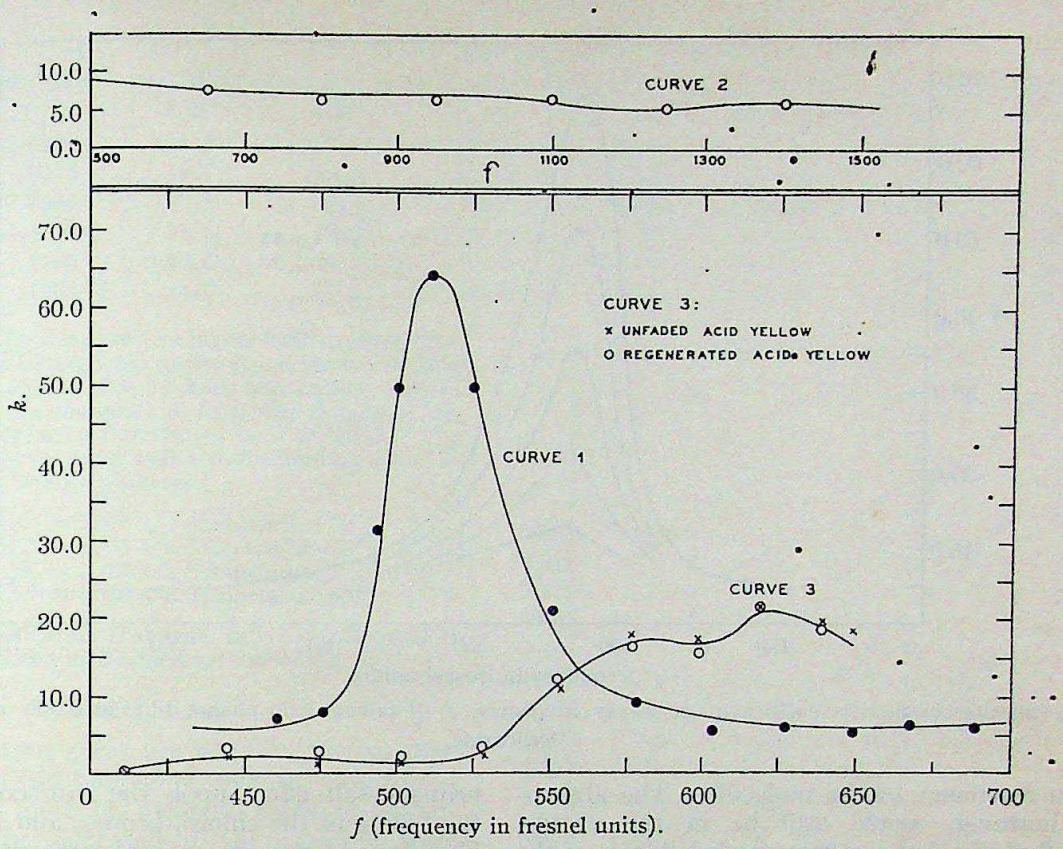

Fig. 1.—Specific extinction coefficient, k, *versus* frequency, f: Curve 1, monosodium salt of iodo phenol blue; Curve 2, iodo phenol blue faded in 0.009 molar sodium hydroxide; Curve 3, unfaded and regenerated iodo phenol blue in like strength of dilute hydrochloric acid.

and from this relationship we calculate the specific extinction coefficient, k, which according to Beer's law is given by

$$\log \frac{I}{I_0} = -kcd = \log \frac{D_0}{D} - \log \frac{D_0'}{D}$$

or

$$k = \frac{1}{cd} \log \frac{DD_0'}{D_0D'}$$

This is plotted against frequency according to the suggestion of Brode.[4]

Data and Discussion.—The specific extinction coefficients and the corresponding wave lengths of the unfaded monosodium salt of iodo phenol blue (10^{-5} molar) in solution containing no excess alkali are plotted in Curve 1 of Fig. 1 using frequency in fresnel units as abscissas and specific extinction coefficients as ordinates. This method of plotting corresponds to decreasing wave lengths of light from left to right. The dye is seen to have a sharp absorption maximum at a frequency of 510 fresnel units or 5808 Å. The specific extinction coefficient as a function of frequency for the alkaline faded iodo phenol blue in 0.009 molar sodium hydroxide is plotted in Curve 2 of Fig. 1. This absorption spectrum is typical of non-chromophoric molecules, *i. e.*, molecules containing linkages similar to those found in alcohols, acids, etc.

The specific extinction coefficient as a function of frequency of both the unfaded and of acid regenerated iodo phenol blue is likewise plotted in Curve 3 of Fig. 1, the measurements being taken in dilute hydrochloric acid solution of like concentration (pH 3) in both cases. The two spectra are identical and hence the regenerated dye corresponds exactly to the unfaded material. Thus the regeneration process is merely a change from the colorless carbinol to the yellow acid quinoid structure of the iodo phenol blue.

These spectrographic data would support the mechanism of the fading to be the formation of the colorless carbinol from the quinoid form of the dye as accepted by Thiel,[2] Biddle and Porter,[5] Kober and Marshall,[6] Kolthoff,[7] and Amis and LaMer[3] rather than the mechanism proposed by Kilpatrick and co-workers.[8,9,10] These investigators thought that the fading was due to the substitution of one of the four iodine atoms in the dye molecule by the hydroxide ion yielding iodide ion.

Now if the fading mechanism were one of substitution of a heavier iodide atom by a lighter hydroxyl radical there should be only a shifting of the absorption band to correspond to the differ-

(5) Biddle and Porter, THIS JOURNAL, **37**, 1571 (1915).
(6) Kober and Marshall, *ibid.*, **33**, 59 (1911).
(7) Kolthoff, "Acid Base Indicators," The Macmillan Co., New York, N. Y., 1937, translated by Rosenblum from the fourth, 1931, German edition; see pages 111, 116 and 218–227.
(8) Chase and Kilpatrick, THIS JOURNAL, **54**, 2284 (1932).
(9) Kilpatrick, *Chem. Rev.*, **16**, 57 (1935).
(10) Panepinto and Kilpatrick, THIS JOURNAL, **59**, 1871 (1937).

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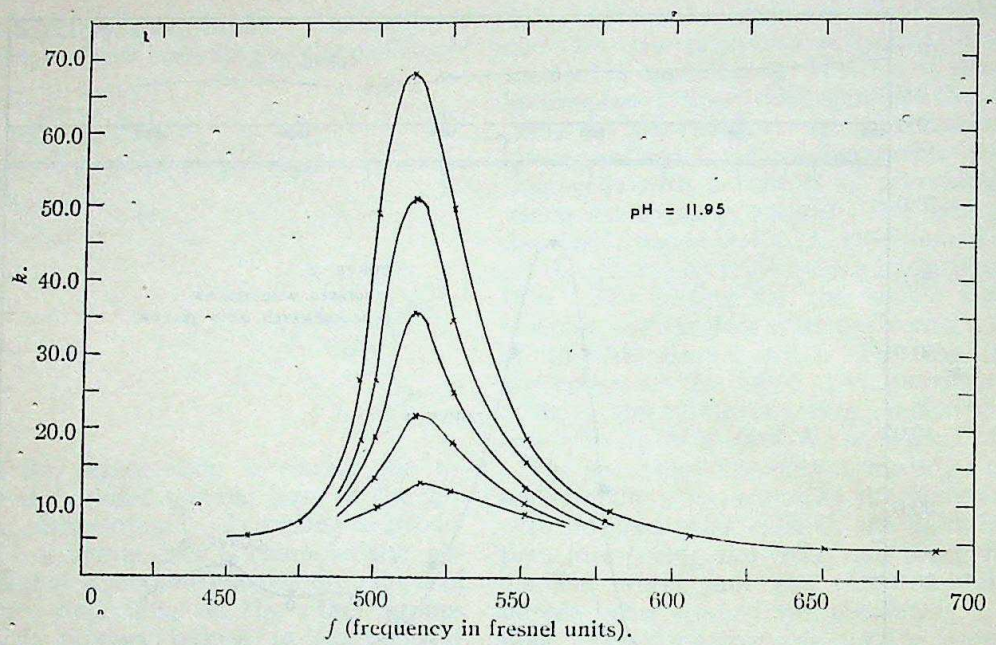

Fig. 2.—Specific extinction coefficient, k, *versus* frequency, f, of fading iodo phenol blue in 0.009 molar sodium hydroxide.

ence in resonance of the molecule. The absorption, however, would still be in the visible. Curve 2 of Fig. 1 shows that the faded form of the dye is non-chromophoric and has, therefore, lost its quinoid structure. Further, the regenerated acid form of the dye is identical in absorption with the acid form of the unfaded dye as shown by Curve 3 of Fig. 1. It appears that the acid regeneration is the removal of the hydroxyl radical from the carbinol and the reforming of the quinoid structure of the dye, rather than the re-entering by acidification of the iodine atom into the benzene nucleus.

Figure 2 represents the absorption of the iodo phenol blue as a function of the degree of fading in 0.009 molar sodium hydroxide. These curves strongly resemble the absorption of the phthalein dyes as a function of the pH of the solution.[11] And as in the case of change of pH, the absorption band does not shift greatly in wave length but simply changes in intensity, with the increased fading of the dye.

II. The Kinetic Study.—The fading of brom phenol blue as a function of hydroxide ion concentration has been carefully studied.[3] In helping to prove the mechanism of the reaction it would be pertinent to study the salt effect upon the reaction velocity. Especially would it help if the rate were run in the presence of an iodide salt, since if the mechanism proposed by Kilpatrick, *et al.*, is correct the iodide ion should exert a mass effect whereas if the fading is due to the formation of carbinol the iodide salt should exert a primary salt effect and increase the reaction rate since the reactants are both negatively charged. Panepinto and Kilpatrick[10] found a primary salt effect upon the rate constants for the fading of the chloro, bromo, and iodo phenol blue dyes in the presence of potassium chloride and bromide but found the values for the internal energy were not of sufficient accuracy to test the primary salt effect upon this function.

Materials and Procedure.—The materials and methods in these studies were essentially those used by Amis and LaMer.[3] The stock solution of iodo phenol blue was 1×10^{-4} molar. The sodium iodide (J. T. Baker analyzed) was made up before each run by weighing on an analytical balance and diluted to a suitable volume. The temperature was held constant to $\pm 0.01°$.

Ten milliliters of the 1×10^{-4} molar dye solution was placed in a volumetric flask and sufficient sodium iodide solution, sodium hydroxide solution and water were added to make a total volume of 100 milliliters of solution which was 1×10^{-5} molar with respect to the dye, 0.006 molar with respect to the sodium hydroxide and with such concentrations of sodium iodide as to give the various ionic strengths used in the studies. The time of addition of sodium hydroxide was noted and used as the initial time in the runs. A standard neutral solution of the dye (1×10^{-5} molar) was also made up and placed in the thermostat. To make a reading five milliliters of the fading dye solution was pipetted into one colorimeter cup and five milliliters of the standard unfading dye into the other colorimeter cup. Using a Klett top-reading colorimeter the amount of fading was determined as a function of time. The illumination used was a Mazda lamp with a blue filter.

The rate constants were calculated using the pseudo-unimolecular rate equation. The bimolecular rate constant was obtained by dividing the pseudounimolecular rate constant by the molarity of the sodium hydroxide which remained sensibly constant throughout a given run. The concentration was expressed in moles per liter and the time in days.

In Table I are tabulated the bimolecular rate constants at various ionic strengths and for the temperatures 25, 35 and 45°; also the energies of activation and the Arrhenius frequency factors are recorded in this table. The quantitative agreement of the data on the rate constants with the requirements of Brönsted's theory of primary salt effect can be illustrated by plotting log k *vs.* $\sqrt{\mu}$ (see Fig. 3).

(11) Brode, THIS JOURNAL, 46, 581 (1924).

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TABLE I

DATA FOR WATER WITH ALKALI HYDROXIDE AND ALKALI SALT ADDED: DYE 10^{-5} M, NaOH 0.006 N WITH ADDED NaI

		k, 25°	k, 35°	k, 45°	ΔE^*, 25–35°	ΔE^*, 35–45°	B, 25–35°	B, 35–45°
0.000	0.0000	(14.3)	(27.7)	(50.2)	12,070	11,520	10.00	9.61
.006	.0775	19.7	38.5	69.9	12,180	11,640	10.24	9.84
.008	.0895	20.8	40.6	73.9	12,190	11,660	10.28	9.87
.010	.1000	21.6	42.2	76.9	12,210	11,680	10.32	9.91
.012	.1096	22.6	44.2	80.6	12,230	11,700	10.34	9.96
.016	.1265	24.0	47.0	86.0	12,250	11,730	10.37	10.01

Log k obeys the limiting law to a higher ionic strength than would ordinarily be expected as was found for the alkaline fading of brom phenol blue by Amis and LaMer.[3] Plots can be made of the energies and Arrhenius frequency factors, respectively, as a function of ionic strength. The slopes of these curves agree well with the limiting values of the slopes given by the equations[12]

$$\Delta E^* = 1569\sqrt{\mu}\ \text{(temperature 30°)}$$
$$\Delta E^* = 1605\sqrt{\mu}\ \text{(temperature 40°)}$$
$$\Delta S^*/2.3R = 3.19\sqrt{\mu}\ \text{(temperature 30°)}$$
$$\Delta S^*/2.3R = 3.25\sqrt{\mu}\ \text{(temperature 40°)}$$

There is no indication that mass action is influential in the observed kinetics with added sodium iodide.

Conclusions

1. Absorption spectrum data on the alkaline faded iodo phenol blue show that the absorption approximates that of alcohol, acids or water. This would be expected if the carbinol were formed during the fading process.

2. Absorption spectra of the unfaded and regenerated acid solution of the dye are identical and it would appear that the fading process is reversed in acid solution.

3. The absorption of the fading dye as a function of the degree of fading, shows no marked shift in the absorption band during the fading process, but only a decrease in the intensity of absorption.

4. The influence of added sodium iodide upon the kinetics of the fading of iodo phenol blue is that of the Brönsted primary salt effect rather than a mass action effect.

5. These observations lead to the conclusion that the fading process is one of carbinol formation with the corresponding disappearance of the quinoid structure and that the regeneration process is the reconstruction of the quinoid form of the dye.

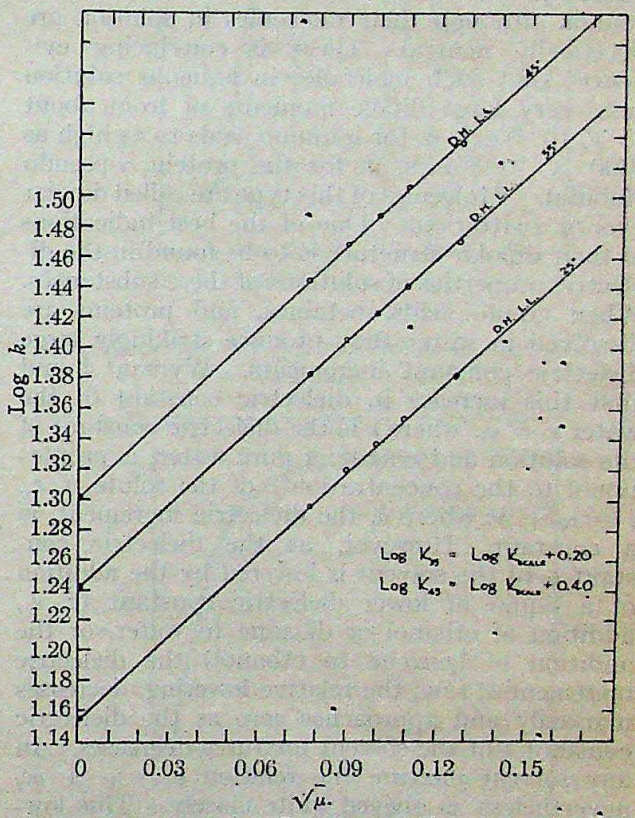

Fig. 3.—Log k *versus* $\sqrt{\mu}$ for the alkaline fading of iodo phenol blue in 0.006 molar sodium hydroxide and various concentrations of sodium iodide.

BATON ROUGE, LA. RECEIVED SEPTEMBER 7, 1943

(12) LaMer and Kamner, THIS JOURNAL, 57, 2662 (1935).

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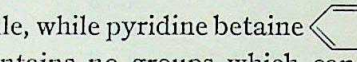
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

The Dielectric Constants of Solutions of Glycine and Pyridine Betaine in Water–Dioxane Mixtures

BY GERALD OSTER,[1] DONNA PRICE,[2] LESLIE G. JOYNER[3] AND JOHN G. KIRKWOOD

Introduction

The amino acids, betaines, and proteins exhibit certain properties similar to those of ionic compounds although their molecules in solution are electrically neutral. There is convincing evidence[4] that such molecules in aqueous solution have very large dipole moments of from about 15×10^{-18} e. s. u. for α-amino acids to as high as 1300×10^{-18} e. s. u. for the protein γ-pseudo globulin. Molecules of this type are called dipolar ions or zwitterions. One of the best indications of their dipolar structure is to be found in the dielectric properties of solutions of these substances. When amino acids, betaines, and proteins are dissolved in water they produce strikingly large dielectric constant increments. Wyman[5] found that this increase in dielectric constant of the water $\epsilon - \epsilon_0$, where ϵ is the dielectric constant of the solution and ϵ_0 that of pure water, is proportional to the concentration c of the solute, *i. e.*, $\epsilon = \epsilon_0 + \delta c$ where δ, the dielectric increment, is a constant. However, as the dielectric constant ϵ_0 of the solvent is lowered by the addition of a liquid of lower dielectric constant (*e. g.*, addition of ethanol or dioxane to water, or the addition of benzene to ethanol) the dielectric increment δ, *i. e.*, the relative lowering, decreases markedly and approaches zero as the dielectric constant ϵ of the solvent mixtures decreases. In any solvent mixture the relation $\epsilon = \epsilon_0 + \delta c$, nevertheless, is obeyed quite closely. This lowering of δ which corresponds to an apparent decrease in the dipole moment of the dipolar ions was thought to be due to an actual movement of the charged groups toward each other since lowering the dielectric constant of the solvent medium increases the coulombic attraction between the charges. It was thought that either there was an equilibrium between dipolar ions and completely uncharged molecules due to the movement of charged groups, or else a gradual decrease in dipole moment due to the distortion of chemical bond angles, so that the charges could come close together.

In order to examine these hypotheses two types of dipolar substances were examined, glycine and pyridine betaine. Glycine $^+NH_3CH_2COO^-$ offers the possibility of a shift of a hydrogen atom to the COO^- group thereby forming a nondipolar molecule, while pyridine betaine  contains no groups which can shift to form the un-ionized molecule.

Experimental

Apparatus.—The apparatus used to measure the dielectric constant was similar to that of Geddes and Kraus[6] with some modifications. The method is a resonance method due to Wyman.[7] The technique consists essentially in completely immersing in the medium a resonator of fixed inductance and capacity. The resonator is coupled inductively to an oscillator, the frequency of which is adjusted by a variable capacity until it corresponds to the natural period of the resonator. From the frequency of the resonator in vacuum (air) or in a standard of known dielectric constant and its frequency in the unknown medium the dielectric constant of the latter may be determined.

Certain features of the apparatus will be described briefly.

The resonator was of the shielded type used by Wyman for measurements in benzene. Due to the corrosive action of glycine solutions on many metals the resonator was constructed of platinum–10% iridium alloy.

The resonator was suspended in a cell containing 400 cc. of fluid. This cell was set in a double walled flask through which oil from a constant temperature bath was circulated. The double-walled flask was in turn surrounded by a Dewar flask. Thus the temperature of the solution was maintained at 25.0 ± 0.01°.

Since the dielectric constant of a water-dioxane mixture is very sensitive to the composition, it was necessary to take elaborate precautions to avoid evaporation of the dioxane during a run. A system of pipets, completely closed except for a small capillary hole, was used for filling and making dilutions. Ground glass joints were used throughout. Nitrogen was used to force the solutions into the pipets which were calibrated to ±0.01 ml.

Materials.—Practical dioxane was purified by the modified method of Vingee and Kraus.[8] Ammonia-free glycine was purified by three recrystallizations from water–alcohol solutions. The pyridine betaine was prepared by the general method of von Gerichten[9] and was purified by recrystallizations from absolute alcohol; decomposition point, 204°. Conductivity water whose specific conductivity was less than 10^{-6} ohm^{-1} was used in the solutions. The concentrations of the glycine solutions were determined to an accuracy of 0.1% by a micro-Kjeldahl analysis. Pyridine betaine exhibited greater solubility than glycine in the lower dielectric constant solvent mixtures so that its solutions were made by dissolving a known weight of the substance.

Experimental Results

In these experiments the dielectric constants of solutions of glycine and of pyridine betaine in water–dioxane (ϵ_0 from 5.7 to 78.5) were measured. The results are presented in Table I and illustrated in Figs. 1 and 2.

In the case of glycine there was some decrease in the dielectric increment δ with concentration

(1) Present address: Department of Electrical Engineering, Massachusetts Institute of Technology.

(2) Present address: Hercules Powder Co.

(3) Present address: Gulf Research Laboratory.

(4) E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publishing Corp., New York, N. Y., 1943.

(5) J. Wyman, Jr., *Chem. Rev.*, **19**, 213 (1936).

(6) J. Geddes and C. A. Kraus, *Trans. Faraday Soc.*, **32**, 585 (1936).

(7) J. Wyman, Jr., *Phys. Rev.*, **35**, 623 (1930).

(8) R. A. Vingee and C. A. Kraus, THIS JOURNAL, **55**, 21 (1933).

(9) E. von Gerichten, *Ber.*, **15**, 1251 (1882).

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TABLE I

DIELECTRIC INCREMENTS IN WATER–DIOXANE MIXTURES AT 25°

ϵ_0	δ	Range of concentration, moles/liter
	Glycine	
13.397	3.27	0.00092–0.00939
15.795	6.77	.00075– .0154
18.967	10.23	.00125– .01574
22.632	13.93	.00196– .01544
25.953	16.02	.00305– .02062
30.457	18.01	.00209– .01756
40.020	19.96	.00110– .01646
78.54	22.58	(Wyman and McMeekin)[10]
	Pyridine Betaine	
5.680	6.76	.00911– .01175
6.808	8.89	.00631– .00753
9.230	10.17	.02502– .03509
9.437	10.78	.01306– 0.1783
11.537	11.25	.02101– .02627
16.467	15.22	.01743– .02902
27.500	17.25	.0385 – .0709
78.54	18.5	(Edsall and Wyman)[11]

at very low concentrations (below 0.005 mole/liter) of glycine. The values of δ presented in Table I, therefore, represent the extrapolated values at infinite dilution. The δ values for pyridine betaine remained constant with concentration over the concentrations range measured.

Discussion

The decrease in δ with ϵ_0 for glycine and pyridine betaine are both of the general form of the decrease of that for glycine betaine and the benzbetaines in ethanol–water and ethanol–benzene mixtures as observed by Edsall and Wyman.[11] However, before seeking a common mechanism for this decrease in dielectric increment with decreasing dielectric constant of the medium it would be well to examine in the case of pyridine betaine the possibility of reversion to the un-ionized form in low dielectric constant media, thus accounting for the decrease in increment.

The positive charge in pyridine betaine is probably located near the nitrogen in the pyridine ring. Due to resonance the pyridine ring is a very stable structure and its stability is further enhanced by the resonance in the carbon–oxygen bonds of the $-CH_2-C\begin{matrix}O\\O^-\end{matrix}$ side group. Therefore it does not seem possible (except at considerably elevated temperatures) that a bond rupture between the nitrogen and a carbon atom could take place with a consequent movement of the positive charge toward the negative charge.

(10) J. Wyman, Jr., and T. L. McMeekin, THIS JOURNAL, **55**, 915 (1933).

(11) J. T. Edsall and Jeffries Wyman, Jr., *ibid.*, **57**, 1964 (1935).

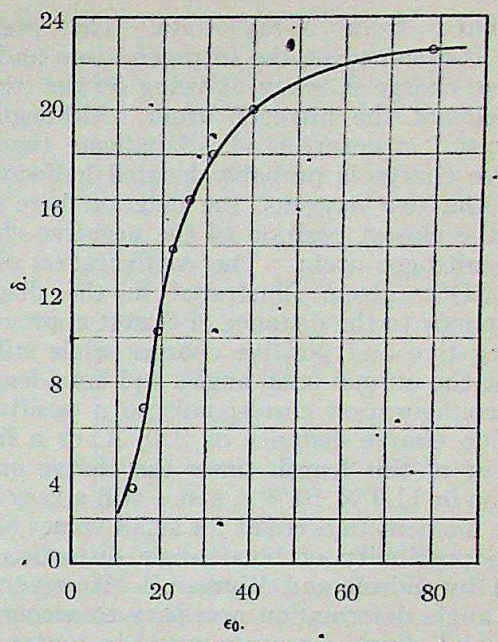


Fig. 1.—Dielectric increment of glycine in water–dioxane mixtures.

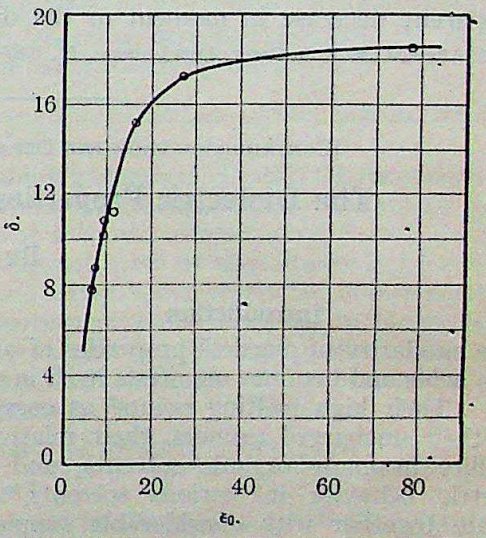
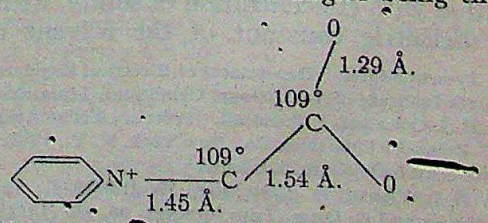


Fig. 2.—Dielectric increment of pyridine betaine in water–dioxane mixtures.

Another possibility is that since the carbon–carbon bond is $-CH_2-COO^-$ has nearly free rotation possibly by rotating the atoms about, some favorable position might be achieved in which the positive and negative charges would be very close to each other. However, from structural considerations this proves not to be the case. Below is a diagram of the pyridine betaine molecule, the atomic distances and angles being those



$$d = 1.45 \cos (180-109) + 1.54 + 1.29 \cos (180-109)$$

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determined from X-ray data. The positive charge is assumed at the nitrogen atom and the negative charge is taken as being on the oxygen atom closest the nitrogen atom. Although X-ray crystal structure studies[12] indicate that the negative charge is probably located halfway between the two oxygens, the diagram here indicates the closest position of the negative charge to the nitrogen atom. The configuration of the —C—COO⁻ group illustrated in the diagram corresponds to the distance of closest approach of the negative and positive charges while still retaining the normal bond angles and bond lengths. This configuration corresponds to a positive to negative charge distance of 2.48 Å. or a dipole moment of this length times the charge on the electron or 11.9×10^{-18} e. s. u.—still a very large dipole moment to account for small values of δ.

The possibility of bond angle distortion was raised by Edsall and Wyman.[11] However, the bond angle deformation necessary to account for such small dipole moments would be tantamount to breaking the chemical bonds.

Of course, dipole association could account for an apparent decrease in moment of the dipole. However, this would be expected to be dependent on the concentration of the dipoles giving a decrease in δ with increasing concentration. In these experiments no such effects were observed.

An explanation for the "anomalous" lowering of δ with lowering of ϵ_0 lies in the electrostatic behavior of dipoles in mixed solvents, a general theory of which is presented in the following paper.

(12) G. Albrecht and R. B. Corey, THIS JOURNAL, 61, 1087 (1939).

Summary

1. The dielectric constants of solutions of glycine and of pyridine betaine in mixtures of water and dioxane were determined.

2. The dielectric increments both of glycine and of pyridine betaine showed a regular decrease with decreasing dielectric constant of the solvent mixture. This decrease is similar to that exhibited by glycine betaine and the benzbetaines.

3. The possibility of reversion of pyridine betaine to the un-ionized was examined. Calculations show that the charged groups could approach each other (and thus account for the experimental results) only if the valence bonds were tremendously distorted.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CORNELL UNIVERSITY]

The Dielectric Properties of Dipolar Ions in Mixed Solvents

BY GERALD OSTER[1]

Introduction

The similarity of physical properties of all the amino acids and betaines manifests itself in many ways. Their high melting points[2] as compared with their uncharged isomers, their relative insolubility in many organic solvents, and their dielectric behavior in various solvents,[3a,b] all indicate together with considerable supplementary evidence,[4] the presence of a common property, namely, the existence of these substances in the form of dipolar ions.

In this paper the dielectric properties of these dipolar ions (or zwitterions, as they are sometimes called) in solution will be considered since it is these properties which are so closely similar among the various amino acids and betaines. Glycine and different betaines when in mixed solvents exhibit similar behavior of the dielectric increment, the change in dielectric constant of the solution with concentration of solute, with changing dielectric constant of the solvent mixture. With all the amino acids and betaines studied (ortho, meta and para benzbetaines,[3a] glycine, pyridine betaine)[3b] a regular decrease in the dielectric constant of the solvent mixture (alcohol–water, dioxane–water, or benzene–alcohol mixtures) was observed. A decrease in the dielectric increment corresponds to an effective decrease in dipole moment, the quantitative relation being shown below. A detailed study of the structure of one of these substances[3b] indicates that rearrangement of the charged groups within the molecule to form an uncharged molecule is probably not possible. The argument presented in reference (3b) may be carried over to other betaines and amino acids. In fact, there is further evidence[5] that the benzbetaines and glycine betaine do not exist in the uncharged form in solvent mixtures of low dielectric constant in that the known uncharged isomers (esters of these dipolar ions, prepared by heating the dipolar solid to very high temperatures) have solubility properties vastly different from the dipolar substances.

A theory of the behavior of dipolar ions in mixed solvents will now be presented in which the existence (in any appreciable quantities) of the uncharged dipolar ion need not be assumed. The

(1) Present address: Department of Electrical Engineering, Massachusetts Institute of Technology, Cambridge, Massachusetts.

(2) E. J. Cohn and J. T. Edsall, "Proteins, Amino Acids and Peptides," Reinhold Publishing Co., New York, N. Y., 1943; especially Chapter 3 by Edsall and Scatchard.

(3) (a) J. Wyman, Jr., *Chem. Rev.*, 19, 213 (1936); (b) D. Price, L. G. Joyner and G. Oster, THIS JOURNAL, 66, 946 (1944).

(4) Reference 2, Chapter 2 by J. T. Edsall.

(5) J. T. Edsall and J. Wyman, Jr., THIS JOURNAL, 57, 1964 (1935).

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theory should be equally valid for all amino acids and betaines (aminophenol being a rare exception because of its unusual molecular structure). There is abundant evidence[2] that amino acids and betaines do exist almost completely in the dipolar form in water and mixtures of water and ethanol. However, there is no direct evidence that the uncharged form is present also. It will be shown that the presence of the uncharged form, a notion incompatible with many of the properties of these substances, need not be assumed in order to explain the dielectric behavior of betaines and amino acids.

It is known from electrostatic considerations[6] that ions in mixed solvents will cause a sorting of the components of the solvent mixture so that the component of the solvent having the higher dielectric constant will gather about the ions, this being an arrangement corresponding to minimum free energy. For the same reason we would expect sorting by dipolar ions in mixed solvents. The actual evaluation of the minimized free energy will not be attempted here since the problem is quite difficult even for ordinary ions; furthermore, the exact distribution of the solvent components around the dipolar ions need not be known except that we would expect the layer of solvent immediately surrounding the dipolar ions to be made up predominantly of that solvent mixture constituent having the greater dielectric constant. Thus, we would expect water in water–dioxane or water–alcohol mixtures to gather about the dipolar ions. Alcohol in alcohol–benzene mixtures would be expected to do likewise.

From electrostatic theory it will be shown that the net effect of surrounding the dipole with a shell of material of dielectric constant greater than that of the bulk of the liquid is to reduce the effective moment of the dipolar ion. This shielding effect becomes more prominent as the difference in dielectric constant of the shell surrounding the dipolar ion and the dielectric constant of the liquid in the bulk of the solution becomes greater. This, then, accounts for the decrease in dielectric increment of the dipolar ions as the dielectric constant of the solvent mixture is decreased.

Relation of Dielectric Increment to Dipole Moment.—The dielectric increment, δ, is defined by the relation that the dielectric constant of the solution of dipolar ions of concentration c is $\epsilon = \epsilon_0 + \delta c$ where ϵ_0 is the dielectric constant of the solvent. Wyman[2] found that δ is practically independent of concentration, c.

A relation between the dielectric increment and the dipole moment of the solute may be derived from the general theory of dielectrics due to Kirkwood[7] which has been applied with some success to polar liquids by Oster and Kirkwood.[8] In the ternary system of solvents of mole fractions

(6) P. Debye and J. McAuley, *Physik. Z.*, **26**, 22 (1925); G. Scatchard, *J. Chem. Phys.*, **9**, 34 (1941).
(7) J. G. Kirkwood, *ibid.*, **7**, 911 (1939).
(8) G. Oster and J. G. Kirkwood, *ibid.*, **11**, 175 (1943).

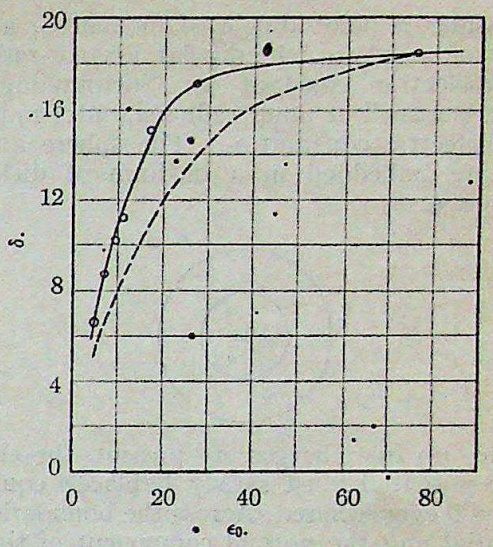

Fig. 1.—Experimental and theoretical dielectric increments of pyridine betaine in water–dioxane mixtures: ———, experimental; – – – –, theoretical.

x_2 and x_3 with solute (the dipole ions) of concentration x_1 the dielectric constant of the solution, ϵ, is related to the mean molar volume, v, the mole fractions, and polarizations P_1, P_2 and P_3 of the constituents by the formula

$$\frac{(\epsilon - 1)(2\epsilon + 1)}{9} = \frac{x_1P_1 + x_2P_2 + x_3P_3}{v} \quad (1)$$

Combining equation (1) with the formula $\epsilon = \epsilon_0 + \delta c$, where ϵ_0 is the dielectric constant of the mixture of solvents, constituents 2 and 3, and c is the concentration of the dipolar ion (constituent 1) and after some algebraic manipulation and conversion of mole fractions to moles per liter one obtains the limiting polarization of the dipolar ions due to their permanent dipole moments

$$P_1 = \frac{4\pi N}{3}\frac{\mu\bar{\mu}}{3kT} = \frac{2000}{9}\delta + \frac{(\epsilon_0 - 1)(2\epsilon_0 - 1)}{9\epsilon_0}v - R \quad (2)$$

where $\mu\bar{\mu}$ is the scalar product of the dipole moment μ of the dipolar ion and dipole moment $\bar{\mu}$ of the dipolar ion and its shell of neighbors, beyond which the dielectric constant equals the macroscopically observed dielectric constant. v is the molal volume of the dipolar ion and R is its molar refractivity.

Equation (2) is valid for most substances when the dielectric constant of the solvent, ϵ_0 is above ten. Between ten and five the first term on right side of equation (3) must be replaced by the approximation $\frac{2000}{9}\delta\left(1 + \frac{1}{2\epsilon_0^2}\right)$.

Inserting numerical values for the constants in equation (2) then for 25°

$$\delta = \frac{9}{2000}\left[20.6 \times 10^{38}\mu\bar{\mu} - \frac{(\epsilon_0 - 1)(2\epsilon_0 + 1)}{9\epsilon_0}v + R\right] \quad (3)$$

It is now necessary to calculate $\mu\bar{\mu}$ from an assumed model and so obtain values for δ which we can compare with experiment.

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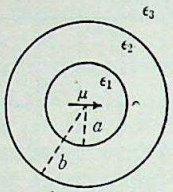
Consider a point dipole of moment μ at the center of a sphere (the dipolar ion) of radius a and dielectric constant ϵ_1. Surrounding the sphere is a shell of inner radius a, outer radius b, and dielectric constant ϵ_2. The sphere and its shell are imbedded in a medium of dielectric constant ϵ_3.



Since no free charges are present, the electrostatic potentlal must satisfy Laplace's equation, $\nabla^2\psi = 0$ everywhere. Across the boundaries the potential and the normal component of the displacement vector must be continuous, *i. e.*, at the boundaries the following conditions must be satisfied

$$\psi_1 = \psi_2 \quad \epsilon_1 \frac{\partial\psi_1}{\partial r} = \epsilon_2 \frac{\partial\psi_2}{\partial r} \quad (r = a)$$
$$\psi_2 = \psi_3 \quad \epsilon_2 \frac{\partial\psi_2}{\partial r} = \epsilon_3 \frac{\partial\psi_3}{\partial r} \quad (r = b) \tag{4}$$

From the general solution of Laplace's equation in spherical coördinates for this spherically symmetric problem, namely

$$\psi = \sum_{n=0}^{\infty} \left(A_n r^n + \frac{B_n}{r^{n+1}} \right) P_n(\cos\theta) \tag{5}$$

the simplest solutions satisfying the conditions of the problem are taken. They are

$$\psi_1 = -Ar\cos\theta + (\mu/\epsilon_1 r^2)\cos\theta \tag{6a}$$
$$\psi_2 = -Br\cos\theta + (C/r^2)\cos\theta \tag{6b}$$
$$\psi_3 = (D/r^2)\cos\theta \tag{6c}$$

Applying the conditions (4) to equations (6) yields for the field inside the sphere (region 1)

$$A = \frac{2\mu}{\epsilon_1 a^3}\left[\frac{(\epsilon_2-\epsilon_1)(\epsilon_2+2\epsilon_3) - (2\epsilon_1+\epsilon_2)(\epsilon_2-\epsilon_3)\left(\frac{a}{b}\right)^3}{(2\epsilon_2+\epsilon_1)(2\epsilon_3+\epsilon_2) - 2(\epsilon_2-\epsilon_1)(\epsilon_2-\epsilon_3)\left(\frac{a}{b}\right)^3}\right] \tag{7}$$

and for the field in the shell region (2)

$$B = \frac{6\mu}{b^3}\left[\frac{\epsilon_3-\epsilon_2}{(2\epsilon_2+\epsilon_1)(2\epsilon_3+\epsilon_2) - 2(\epsilon_2-\epsilon_1)(\epsilon_2-\epsilon_3)\left(\frac{a}{b}\right)^3}\right] \tag{8}$$

Since $\bar{\mu}$ is the moment of the molecule and its shell of neighbors, then

$$\bar{\mu} = \mu + \frac{\epsilon_2 - 1}{4\pi}\frac{4\pi}{3}(b^3 - a^3)B \tag{9}$$

The second term on the right of the equation (9) comes from the electrostatic formula for the moment M of a region of volume v and dielectric constant ϵ in a field of intensity E, namely

$$M = \frac{\epsilon - 1}{4\pi} vE$$

In equation (9) μ does not equal the moment μ_0 of the molecule in free space, but rather

$$\mu = \mu_0 + \frac{\epsilon_1 - 1}{4\pi}\frac{4\pi}{3}a^3 A \tag{10}$$

Now μ and $\bar{\mu}$ act in the same direction so that $\mu\bar{\mu}$ is simply the product of equations (9) and (10). The equation for $\mu\bar{\mu}$ is considerably simplified if we take $\left(\frac{a}{b}\right)^3 << 1$. If, due to sorting, the outer radius of the shell is only three times that of its inner radius the quantity $(a/b)^3$ is sufficiently small so that the following equation holds to a good degree of approximation

$$\mu\bar{\mu} = \mu^2\left[1 - \frac{2(\epsilon_2-1)(\epsilon_2-\epsilon_3)}{(2\epsilon_2+\epsilon_1)(2\epsilon_3+\epsilon_2)}\right] \tag{11a}$$

where

$$\mu = \frac{\mu_0}{1 - \frac{2(\epsilon_1-1)(\epsilon_2-\epsilon_1)}{3\epsilon_1(2\epsilon_2+\epsilon_1)}} \tag{11b}$$

Equation (11b) shows that μ is practically independent of ϵ_3. It will be noticed from equation (11a) that $\mu\bar{\mu}$ is decreased when the dielectric constant of the shell, ϵ_2, is greater than that of the outer medium, ϵ_3. $\mu\bar{\mu}$ equals μ^2 only when $\epsilon_2 = \epsilon_3$ as would be the case for dipolar ions in a single solvent, for, example, pure water. As the dielectric constant of the medium ϵ_3 (written ϵ_0 in equations (2) and (3)) is reduced, $\mu\bar{\mu}$ approaches zero (ϵ_2 is generally large compared with unity and $\epsilon_1 = n^2$, the square of the refractive index of the solute) and so by equation (3) δ should approach zero (the other two terms in equation (3) not containing δ are relatively small). The effect on ϵ_3 of the sorting out of the higher dielectric constant constituent of the solvent mixture to form a shell about the dipolar ion has been neglected. This is a small effect, however, since the concentrations of the dipolar ions in the systems studied are very small compared with the concentration of the high dielectric constant constituent of the solvent mixture, so that the dielectric constant of the solvent would hardly be expected to be altered appreciably by this sorting process.

The media 1, 2 and 3 have been treated as continuous right up to the surface of the adjacent media. It is known[7,8] that in order to account for the dielectric properties of pure polar liquids it is necessary to examine a region near the surface of a molecule of the liquid where the dielectric constant cannot be considered equal to that of the bulk of the liquid. It turns out, however, that the cruder continuum model proves to be sufficiently detailed so as to agree with the general features of the observed dielectric properties of dipolar ions in mixed solvents.

Application of the Theory

In order to test the theory, the dielectric increment of pyridine betaine in mixtures of water and dioxane have been calculated. This may be evaluated by combining equations (3) and (11a) to

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solve for δ. From the observed δ for pyridine betaine in pure water we calculate its dipole moment μ to be 16.9×10^{-18} e. s. u. In equation (11a) ϵ_1 is replaced by the square of the refractive index of pyridine betaine which is determined from a calculated molar refractivity R. The molar volume of pyridine betaine in water is $v = 99.6$ cc./mole.[6] The dielectric constant of water, ϵ_2, has the value 78.54.

The theoretical and experimental[3b] results are illustrated in the figure.

The deviations of the theoretical results from the observed suggest that the sorting of the water molecules by the dipolar ions is not complete and therefore the actual shielding effect is not as great as would be expected for a shell made up entirely of water molecules.

The writer wishes to thank Professor J. G. Kirkwood for his helpful suggestions.

Summary

A theory of the decrease in dielectric increment of dipolar ions with decrease in dielectric constant of the solvent mixture is presented. On the basis of electrostatic theory dipolar ions would be expected to sort out the solvent constituent of higher dielectric constant. The shell of material of higher dielectric constant thereby produced serves to act as an electrostatic shield thus decreasing the effective dipole moment (and therefore the dielectric increment) of the dipolar ion. The shielding effect becomes more prominent as the difference in dielectric of the shell surrounding the dipolar ion and that of the liquid in the bulk of the solution becomes greater.

This continuum treatment leads to results which reproduce the general features of the observed results.

CAMBRIDGE, MASS. RECEIVED NOVEMBER 5, 1943

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF HARVARD UNIVERSITY AND RADCLIFFE COLLEGE.]

Syntheses of Tyrosyltyrosyltyrosine and Tyrosyltyrosyltyrosyltyrosine.

BY ARCHIE E. BARKDOLL[1] AND WILLIAM F. ROSS[2]

In relation to certain protein studies in progress in this Laboratory, there were desired polypeptides containing three, four and additional residues of the amino acid *l*-tyrosine[3] bound one to another with none but tyrosyl residues within the chain. For this reason the syntheses of tyrosyltyrosyltyrosine and tyrosyltyrosyltyrosyltyrosine have been carried out according to the procedures to be described in this paper.

The starting material was the compound O-acetyl-N-carbobenzoxytyrosyltyrosine ethyl ester, I, prepared according to the method of Bergmann, *et al.*,[4] which involves the coupling of O-acetyl-N-carbobenzoxytyrosyl chloride with the ethyl ester of tyrosine. This product may be applied in several ways toward the synthesis of the desired polypeptides. Its hydrogenation yields tyrosyltyrosine ethyl ester, II, to the free amino group of which additional tyrosine residues may be coupled through the action of the chloride or azide of a suitable tyrosine derivative.

The preparation of O-acetyl-N-carbobenzoxytyrosyl-O-acetyltyrosyl chloride, which after reaction with II would lead directly to a derived tetrapeptide, was first investigated. O-Acetyl-N-carbobenzoxytyrosyl-O-acetyltyrosine was obtained in good yield by the saponification and subsequent acetylation of I, but attempts to convert it satisfactorily into the chloride failed. The reaction of the free acid with phosphorus pentachloride yielded an oil, which in exploratory experiments with tyrosine ethyl ester gave no useful products. It appears probable that the failure of this approach was due to an attack on the peptide linkage by the phosphorus pentachloride. Similar results were obtained by Pacsu and Wilson,[5] who studied the action of phosphorus pentachloride and of thionyl chloride on carbobenzoxyglycylglycine.

The azide of N-carbobenzoxytyrosyltyrosine coupled with II, would also yield a derivative of the tetrapeptide. This line of approach was next investigated. N-Carbenzoxytyrosyltyrosine hydrazide was obtained readily by the action of hydrazine hydrate on I. The corresponding azide was prepared and, without isolation, added in ethyl acetate solution to a similar solution of the ester, II. The failure to isolate any definite product and the inaccessibility of the two reagents employed led finally to the simple, direct approach of adding single tyrosine residues stepwise to peptide esters of increasing length.

This procedure, although laborious and time-consuming, led finally to the desired products. For its consummation O-acetyl-N-carbobenzoxytyrosyl chloride was coupled with tyrosyltyrosine ethyl ester, to give O-acetyl-N-carbobenzoxytyrosyltyrosyltyrosine ethyl ester, III. The latter was converted by hydrolysis to the carbobenzoxytripeptide, IV, which was catalytically reduced to the desired tripeptide, V. Repeating this process, addition of another

(1) Present address: Experimental Station, du Pont Company, Wilmington, Delaware.

(2) Present address: Shell Oil Company, Inc., Wood River, Illinois.

(3) *l*-Tyrosine was used throughout; consequently all of the compounds described in the text contain tyrosine of this configuration.

(4) Bergmann, Zervas, Salzmann and Schleich, *Z. physiol. Chem.*, **224**, 17 (1934).

(5) Pacsu and Wilson, *J. Org. Chem.*, **7**, 117 (1942).

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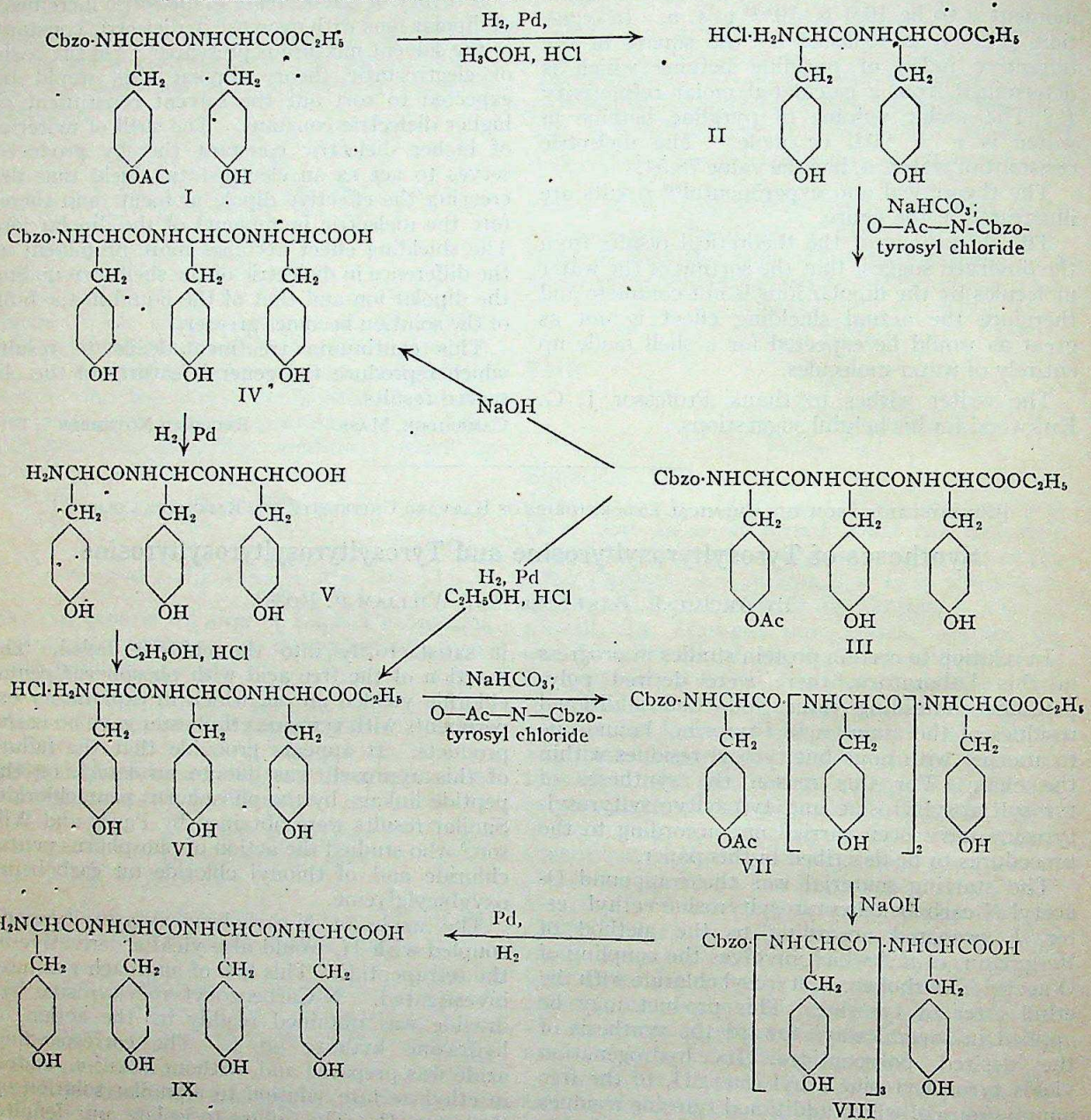
TABLE I

SYNTHESES OF TYROSYLTYROSYLTYROSINE AND TYROSYLTYROSYLTYROSYLTYROSINE



tyrosine residue to the tripeptide ester, VI, yielded the tetrapeptide, tyrosyltyrosyltyrosyltyrosine, IX. An outline of the entire procedure is given in Table I.

It will be noted that catalytic reduction of O-acetyl-N-carbobenzoxytyrosyltyrosine ethyl ester, III, in absolute ethanol containing hydrogen chloride leads directly to an unacetylated product. A parallel case was observed by Bergmann and Fruton[6] in the reduction of O-acetyl-N-carbobenzoxytyrosylglycine ethyl ester, and analogous behavior of derivatives of oestrone has been observed by Miescher and Scholz.[7] The removal of the O-acetyl group during reduction has been verified by the synthesis of tyrosyltyrosine ethyl ester hydrochloride by an unambiguous method. O-Acetyl-N-carbobenzoxytyrosyltyrosine ethyl ester, I, was saponified to N-carbobenzoxytyrosyltyrosine and this was esterified with diazoethane. The resulting ester was reduced to tyrosyltyrosine ester hydrochloride, II, identical with that obtained by the reduction of the acetylated derivative, I. In addition, the dipeptide ester hydrochloride was prepared by the esterification of tyrosyltyrosine.

The O-acetyl group was lost also during the reduction of O-acetyl-N-carbobenzoxytyrosyltyrosyltyrosine ethyl ester, III, to tyrosyltyrosyl-

(6) Bergmann and Fruton, *J. Biol. Chem.*, **118**, 405 (1937).
(7) Miescher and Scholz, *Helv. Chim. Acta*, **20**, 263 (1937).

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tyrosine ethyl ester hydrochloride, VI. The same product was formed by the direct esterification of tyrosyltyrosyltyrosine with absolute ethanol and dry hydrogen chloride. This esterification is of interest in view of the report of Pacsu and Wilson[8] that attempts to prepare the ester hydrochlorides of several tripeptides were unsuccessful because of cleavage of the peptide chain. For example, alanylglycylglycine on esterification was converted to a mixture of the ester hydrochlorides of glycine and alanylglycine.

The O-acetyl group, however, is not removed when glacial acetic acid is substituted for methanolic hydrogen chloride, the carbobenzoxy derivative reduced, and gaseous hydrogen chloride then added. In this way, O-acetyl-N-carbobenzoxytyrosine methyl ester gave O-acetyltyrosine methyl ester hydrochloride, and O-acetyl-N-carbobenzoxytyrosine gave O-acetyltyrosine hydrochloride.

The availability of the series consisting of tyrosine, tyrosyltyrosine, tyrosyltyrosyltyrosine and tyrosyltyrosyltyrosyltyrosine makes possible a comparison of the physical and chemical properties of the various members. Most striking is the change in solubility with the number of tyrosine residues within the molecule. Tyrosine itself is almost insoluble in water, tyrosyltyrosine and the tripeptide are freely soluble, but the tetrapeptide only slightly soluble in the cold. There is an increasing solubility in either ethyl or methyl alcohol as the number of residues is increased. Both the tri- and tetrapeptides give positive tests with Millon reagent.

The absorption spectra of the first three members of the series have also been determined.[9] All three compounds contain the same chromophoric group, the phenolic ring, so that little qualitative difference would be anticipated. This expectation is confirmed by the experimental curves of Fig. 1 and the data of Table II. There is only a slight quantitative shift toward the red with increasing molecular weight; this may be associated with the increasing size of the molecule to which the chromophores are bound in each case. The proportionality between the extinction coefficient and the number of tyrosine residues per molecule is also evident from the last column of the table.

TABLE II

For these experiments buffered solutions of *p*H 4.5 were employed. The value of 2750 Å. for λ max of tyrosine agrees with that of Enselme and Pozzi[10] for this amino acid in a solution of *p*H 5.95.

Substance	Mol. wt.	$E_{molar,\ max.}$	λ max, Å.	$E_{molar,\ max./1350}$
l-Tyrosine	181.2	1350	2750	1.00
Tyrosyltyrosine	344.4	2850	2760	2.11
Tyrosyltyrosyl-tyrosine dihydrate	543.6	4160	2765	3.08

(8) Pacsu and Wilson, *J. Org. Chem.*, **7**, 126 (1942).

(9) We are especially grateful to Dr. R. Norman Jones for his cooperation in making these determinations.

(10) Enselme and Pozzi, *Bull. soc. chim. biol.*, **17**, 283 (1935).

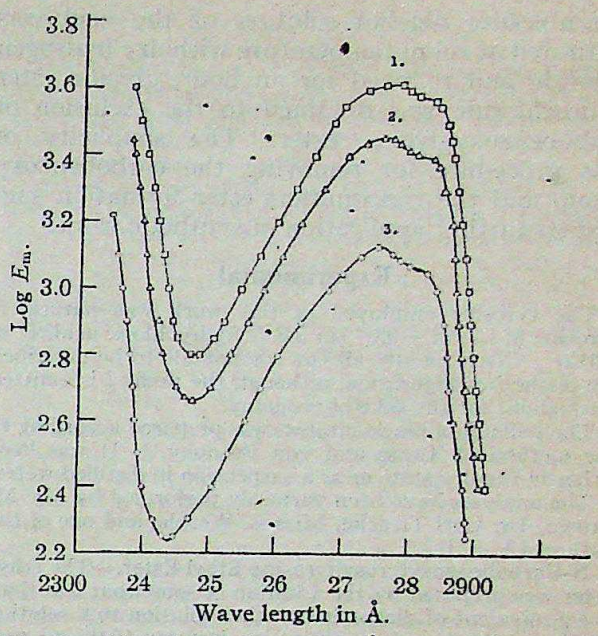

Fig. 1.—Ultraviolet absorption spectra of *l*-tyrosyl-*l*-tyrosyl-*l*-tyrosine dihydrate, □, (1); *l*-tyrosyl-*l*-tyrosine, △, (2); and *l*-tyrosine, O, (3); all in a buffer solution of *p*H 4.5.

The Removal of the Carbobenzoxy Group by Alcoholic Hydrogen Chloride.—In addition to the usual catalytic hydrogenation method for the removal of the carbobenzoxy group from amino acids and polypeptides, several others have been found valuable for special cases such as the reduction of sulfur containing carbobenzoxy derivatives. Thus sodium in liquid ammonia has been employed by Sifferd and du Vigneaud,[11] and phosphonium iodide in glacial acetic acid by Harington and Mead.[12] Also, White[13] removed the carbobenzoxy group by treatment with aqueous hydrogen chloride at 60°. We have observed that the action of an absolute ethanol solution of hydrogen chloride also serves to liberate the carbobenzoxy group, with the simultaneous formation of the corresponding ester hydrochloride.

In an attempt to prepare N-carbobenzoxytyrosyltyrosine ethyl ester by the action of absolute ethanol and dry hydrogen chloride at 0° on N-carbobenzoxytyrosyltyrosine, it was found that a major portion of the acid had been converted by esterification of the peptide carboxyl and fission of the carbobenzoxy group to tyrosyltyrosine ethyl ester hydrochloride, while only a small amount of the desired carbobenzoxy ester was obtained. A similar experiment with O-acetyl-N-carbobenzoxytyrosyltyrosine ethyl ester gave the same products.

The action of absolute ethanolic hydrogen chloride on carbobenzoxyglycine at 0° likewise yielded a mixture of glycine ester hydrochloride and carbobenzoxyglycine ethyl ester. But, if

(11) Sifferd and du Vigneaud, *J. Biol. Chem.*, **108**, 753 (1935).

(12) Harington and Mead, *Biochem. J.*, **29**, 1602 (1935).

(13) White, *J. Biol. Chem.*, **106**, 143 (1934).

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the absolute alcohol solution of the acid was saturated at room temperature with dry hydrogen chloride and refluxed for an hour, glycine ester hydrochloride was obtained to the exclusion of carbobenzoxyglycine ester. The simplicity of this procedure for removing the carbobenzoxy group and the concomitant ester formation suggest its further application in synthetic work.

Experimental

The tyrosine employed in this work was natural *l*-tyrosine of $(\alpha)^{20}D$ −9.0° (in 5.8 *N* hydrochloric acid, $C = 3.613$). Consequently all the compounds to be described are of the *l* configuration, although the prefix *l* is omitted throughout for the sake of economy.

The palladium black catalyst was prepared according to the method of Tausz and von Putnoky.[14] It was kept either in the dry state or as a suspension in distilled water.

The analyses have been variously performed by Mr. M. Brown, Dr. Carl Tiedcke, Miss E. Werble, and one of the authors (A. E. B.).

N-Carbobenzoxytyrosyltyrosine Ethyl Ester.—The ethyl ester was prepared by the addition of somewhat less than one equivalent of diazoethane–ether solution to a solution of N-carbobenzoxytyrosyltyrosine hydrate (0.97 g.) prepared by the method of Bergmann,[4] in 15 cc. of methanol. The sirupy residue remaining after concentration of the solution *in vacuo* was dissolved in ethyl acetate and unreacted acid extracted with dilute sodium bicarbonate. The ethyl acetate solution was dried over anhydrous sodium sulfate, the solvent removed *in vacuo*, and the residue recrystallized several times from ethyl acetate–petroleum ether to yield 260 mg. of the pure ester in the form of colorless, silky needles melting at 159–160.5°.

Anal. Calcd. for $C_{28}H_{30}O_7N_2$: C, 66.38; H, 5.97; N, 5.53. Found: C, 65.96, 65.88; H, 6.11, 6.17; N, 5.62.

All melting points are uncorrected.

Tyrosyltyrosine Ethyl Ester Hydrochloride.—Five grams of O-acetyl-N-carbobenzoxytyrosyltyrosine ethyl ester, prepared by the method of Bergmann,[4] was dissolved in 110 cc. of 0.2 *N* absolute ethanolic hydrogen chloride and reduced at atmospheric pressure in the presence of 1.4 g. of palladium black catalyst. The product, recovered after concentration by the addition of ether, represented an almost quantitative yield. For analysis it was recrystallized twice from absolute alcohol–absolute ether in the form of microscopic clusters of platelets; it melted at 216° (dec.).

Anal. Calcd. for $C_{20}H_{25}O_5N_2Cl$: C, 58.50; H, 6.16; Cl, 8.68. Found: C, 58.25, 58.41; H, 6.05, 6.23; Cl, 8.55.

An identical product was obtained by dissolving 100 mg. of tyrosyltyrosine[4] in 10 cc. of absolute ethanol saturated with dry hydrogen chloride at 0°. After two days at 7° the crystalline ester hydrochloride was obtained by concentration and addition of ether. It melted at 217° and showed no depression of the decomposition point when mixed with the product described above.

The same product, melting at 216°, was obtained by the catalytic reduction of N-carbobenzoxytyrosyltyrosine ethyl ester in absolute ethanolic hydrogen chloride.

N-Carbobenzoxytyrosyltyrosine Methyl Ester.—Methylation of N-carbobenzoxytyrosyltyrosine hydrate with diazomethane in methyl alcohol solution gave the ester, which, after several recrystallizations from ethyl acetate–ligroin, formed small needles and rosets melting at 174–175°.

Anal. Calcd. for $C_{27}H_{28}O_7N_2$: C, 65.84; H, 5.73; N, 5.68. Found: C, 65.62; H, 5.57; N, 6.27.

Tyrosyltyrosine Methyl Ester Hydrochloride.—Obtained by the catalytic reduction of N-carbobenzoxytyrosyltyrosine methyl ester, this product melted at 210° after three recrystallizations from absolute methanol–absolute ether.

Anal. Calcd. for $C_{19}H_{23}O_5N_2Cl$: C, 57.79; H, 5.87; Cl, 8.98. Found: C, 57.84, 57.49; H, 6.09, 6.03; Cl, 9.17.

O-Acetyl-N-carbobenzoxytyrosyl-O-acetyltyrosine.—Three grams of finely powdered O-acetyl-N-carbobenzoxytyrosyltyrosine ethyl ester was added to 21 cc. of 1 *N* sodium hydroxide. After shaking for an hour at room temperature, the solution was filtered, and 1.11 cc. of acetic anhydride in 12 cc. of dioxane added. After fifteen minutes at room temperature, the solution was acidified to congo red with 1 *N* hydrochloric acid. The solid thus formed was collected on the filter, washed with water and recrystallized three times from hot acetone–water, to give white tufts of needles melting at 209–210°. The acid was insoluble in cold acetone, and in either hot or cold water, but was moderately soluble in boiling acetone.

Anal. Calcd. for $C_{30}H_{30}O_9N_2$: C, 64.05; H, 5.37; N, 4.98. Found: C, 63.94, 63.82; H, 5.20, 5.35; N, 5.30.

O-Acetyl-N-carbobenzoxytyrosyltyrosyltyrosine Ethyl Ester.—Tyrosyltyrosine ethyl ester hydrochloride (4.24 g.) was dissolved in 35 cc. of water, 25 cc. of pure ethyl acetate was added and the mixture cooled in ice. The free ester was liberated by the addition of 1.70 g. of sodium bicarbonate. It settled out as a thick paste after several minutes of shaking. This was filtered off, pressed as dry as possible on the filter, and then dissolved in 75 cc. of purified dioxane. To this solution 25 cc. of ethyl acetate was added and the resulting solution dried for an hour at 0° over anhydrous potassium carbonate. After filtration the solution was stored at 0° for about an hour, during the preparation of O-acetyl-N-carbobenzoxytyrosyl chloride.

The latter was prepared essentially according to the procedure of Bergmann[4]: 7.20 g. of the finely powdered free acid was suspended in 72 cc. of anhydrous ether, and cooled in an ice–salt-bath; to the suspension was then added 4.20 g. of finely powdered phosphorus pentachloride. The flask was shaken in ice until the white crystalline acid chloride had completely formed. This was filtered off, washed with a 1:2 mixture of anhydrous ether–petroleum ether and dried in an evacuated desiccator at 0° over phosphorus pentoxide. It was used for coupling with the ester as soon as possible.

For this purpose, 2.28 g. of O-acetyl-N-carbobenzoxytyrosyl chloride dissolved in 20 cc. of purified, anhydrous ethyl acetate was added to the tyrosyltyrosine ethyl ester solution as prepared above. Immediate formation of a precipitate of tyrosyltyrosine ester hydrochloride occurred. After standing at room temperature for nine hours, the latter was removed, and the solution concentrated *in vacuo* to a thick yellow sirup which was crystallized by the slow addition of ethyl acetate. After two recrystallizations from hot acetone–ether the product was obtained as a white microcrystalline powder, m. p. 211°. The yield of the crude product, calculated from the weight of amino acid ester hydrochloride recovered, was 78%.

Anal. Calcd. for $C_{39}H_{41}O_{10}N_3$: C, 65.81; H, 5.81; N, 5.90. Found: C, 65.94, 65.80; H, 6.35, 6.15; N, 5.92.

Tyrosyltyrosyltyrosine Ethyl Ester Hydrochloride.—A sample of 2.06 g. of O-acetyl-N-carbobenzoxytyrosyltyrosyltyrosine ethyl ester was dissolved in 40 cc. of anhydrous dioxane by warming, and 160 cc. of absolute ethanol, 7 cc. of 2 *N* absolute ethanolic hydrogen chloride and 2 g. of palladium black catalyst were added. After completion of the hydrogenation, which followed, the filtered solution was concentrated *in vacuo* to a thick sirup which was taken up in 15 cc. of water and treated with 10 cc. of ethyl acetate and 0.8 g. of sodium bicarbonate in order to transfer the ester to the organic phase. After washing the aqueous phase with several additional 10-cc. portions of ethyl acetate, the combined ethyl acetate extracts were dried thirty minutes at 0° over anhydrous potassium carbonate and filtered. When dry hydrogen chloride gas was passed over the surface of the filtrate, the hydrochloride formed as a light yellow sirup which slowly

(14) Tausz and von Putnoky, *Ber.*, **52**, 1573 (1919).

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crystallized. The yield of product was 66%. In order to purify a sample for analysis it was necessary to repeat the procedure of transferring the liberated ester to ethyl acetate and adding hydrogen chloride. Hemispherical nodules of crystals ranging up to 2 mm. in diameter were obtained; m. p. 231–231.5° (dec.) with previous coloring and sintering. Attempts to crystallize the compound directly from alcohol–ether gave an oil which crystallized but slowly and retained any impurities present.

Anal. Calcd. for $C_{29}H_{34}O_7N_3Cl$: C, 60.88; H, 5.99; Cl, 6.11. Found: (dried at 100° *in vacuo*) C, 60.67, 60.20; H, 6.82, 6.25; Cl, 6.12.

The same product was obtained by esterification of 150 mg. of tyrosyltyrosyltyrosine in absolute ethanol solution with hydrogen chloride. The procedure was similar to that followed for tyrosyltyrosine ethyl ester, except that the viscous sirup obtained on concentration of the solution was crystallized by allowing it to stand under ethyl acetate for several days; yield, 158 mg. The m. p. was 230–231° (dec.) and a mixture of the product with the tripeptide ester hydrochloride, of m. p. 231–231.5° (dec.), prepared by the reduction of O-acetyl-N-carbobenzoxytyrosyltyrosyltyrosine ethyl ester, gave no depression.

N-Carbobenzoxytyrosyltyrosyltyrosine.—This derivative was obtained by saponification of 1.5 g. of O-acetyl-N-carbobenzoxytyrosyltyrosyltyrosine ethyl ester in 8.5 cc. of 1.1 *N* sodium hydroxide. It formed as a gel when the solution was acidified to congo red, and was finally crystallized as sheaves and rosets of needles from warm methanol; m. p. 182–183°, yield, 1 g.

Anal. Calcd. for $C_{35}H_{35}O_9N_3$: C, 65.51; H, 5.49; N, 6.55. Found: C, 65.45, 65.49; H, 5.56, 5.61; N, 6.49.

Tyrosyltyrosyltyrosine Dihydrate.—To a solution of 400 mg. of N-carbobenzoxytyrosyltyrosyltyrosine in 20 cc. of methanol were added 30 cc. of water, 0.4 g. of palladium black catalyst and a small drop of glacial acetic acid. Removal of the carbobenzoxy group was complete after hydrogenation for thirty minutes. The filtered solution was concentrated *in vacuo* at a bath temperature not exceeding 35°. The peptide crystallized in the form of microscopic white prisms after the removal of approximately half of the solvent. After further concentration, the solid was removed and recrystallized twice from hot water to give fine prisms of m. p. 181–182° in a yield of 150–200 mg.

Anal. Calcd. for $C_{27}H_{29}O_7N_3 \cdot 2H_2O$: C, 59.65; H, 6.11; N, 7.73; H_2O, 6.65. Found: C, 59.54, 59.53; H, 5.92, 6.14; N, 7.90; H_2O, 6.63.

The tripeptide was slightly soluble in cold alcohol and water, somewhat soluble in hot alcohol and quite soluble in hot water. The anhydrous material, formed by drying at 100° over phosphorus pentoxide *in vacuo*, was hygroscopic, tending to revert to the dihydrate on exposure to the air.

N-Carbobenzoxytyrosyltyrosine Hydrazide Hydrate.—The hydrazide was obtained from O-acetyl-N-carbobenzoxytyrosyltyrosine ethyl ester by reaction with hydrazine hydrate in ethanol solution. It melted at 246° (dec.) after recrystallization from pyridine, and lost one molecule of water on drying over phosphorus pentoxide for one hour at 100° (1 mm.).

Anal. Calcd. for $C_{26}H_{28}O_6N_4 \cdot H_2O$: C, 61.16; H, 5.94; N, 10.97; H_2O, 3.53. Found: C, 61.13; H, 5.96; N, 11.09; H_2O, 3.42.

It has already been pointed out that attempts to use the corresponding azide in coupling experiments with tyrosyltyrosine ethyl ester were without success.

O-Acetyl-N-carbobenzoxytyrosyltyrosyltyrosyltyrosine Ethyl Ester.—O-Acetyl-N-carbobenzoxytyrosyl chloride was prepared as described in the preparation of the O-acetyl-N-carbobenzoxy tripeptide, except that in this case it was desirable to have extremely pure chloride on account of the difficulty of purifying the tetrapeptide. Therefore, just as the crystals of chloride began to form, the solution was filtered, the precipitate discarded and the chloride to be used in the coupling obtained from further crystallization in the filtrate.

374 mg. of O-acetyl-N-carbobenzoxytyrosyl chloride was dissolved in 10 cc. of anhydrous ethyl acetate and the solution added to that containing the ester from 1.14 g. of tyrosyltyrosyltyrosine ethyl ester hydrochloride. The latter had been prepared in the same manner as the tyrosyltyrosine ester in the synthesis of the tripeptide. The solution became turbid, and an oil deposited. After standing for two days, this oil had solidified and was found to be a mixture of the tripeptide ester hydrochloride and the desired O-acetyl-N-carbobenzoxy tetrapeptide ester. The two were separated by extraction of the former from the solid with 0.5 *N* hydrochloric acid and crystallization of the tetrapeptide ester from hot acetone–ether. The yields were 233 mg. and 624 mg., respectively. The m. p. of the latter was 235.5–236.5° (dec.).

Anal. Calcd. for $C_{48}H_{50}O_{12}N_4$: C, 65.89; H, 5.76; N, 6.40. Found: C, 65.53; H, 5.80; N, 6.43.

N-Carbobenzoxytyrosyltyrosyltyrosyltyrosine.—A sample of 590 mg. of finely powdered O-acetyl-N-carbobenzoxytyrosyltyrosyltyrosyltyrosine ester was saponified by treatment with 6 equivalents of 1 *N* sodium hydroxide for thirty minutes at room temperature. The free acid was precipitated as an amorphous jell on acidification to congo red. After filtering, washing, and drying, it weighed 530 mg. It was finally obtained as a white solid, appearing under the microscope as ill-formed rosets of crystals, by the slow concentration of a methanol solution in a partially evacuated desiccator over phosphorus pentoxide. The final yield was 201 mg. and the product melted at 224–225° (dec.) with previous darkening at 220°. The acid contained a molecule of methanol which was lost on drying over phosphorus pentoxide at 100° (1 mm.).

Anal. Calcd. for $C_{44}H_{44}O_{11}N_4 \cdot CH_3OH$: CH_3OH, 3.83. Found: (dried *in vacuo* at 100°) 3.70. Calcd. for $C_{44}H_{44}O_{11}N_4$: C, 65.65; H, 5.51; N, 6.96. Found: C, 65.35; H, 5.62; N, 6.38.

On standing in the air, the dried acid rapidly absorbed 1% of its weight of moisture. The acid was insoluble in water and 5% sodium bicarbonate, but soluble in 1 *M* sodium hydroxide and hot methanol.

Tyrosyltyrosyltyrosyltyrosine.—A sample of 118 mg. of N-carbobenzoxy tetrapeptide methyl alcoholate was catalytically hydrogenated in methyl alcohol solution containing a small drop of acetic acid. Concentration of the filtered solution gave a viscous sirup which formed a noncrystalline glassy solid on standing. The latter we were unable to obtain in a clearly crystalline form in spite of many efforts. The analytical sample was obtained as a glass-like solid by treating the tetrapeptide in methanol solution with activated carbon, followed by concentration *in vacuo* and drying over phosphorus pentoxide one hour at 65° (1 mm.).

Anal. Calcd. for $C_{36}H_{38}O_9N_4$: C, 64.46; H, 5.71; N, 8.35. Found: C, 63.45; H, 5.72; N, 7.15.

The tetrapeptide was insoluble in cold water, hot and cold dioxane, ethyl acetate, and acetone, but was soluble in cold 5% sodium carbonate, 0.5 *N* hydrochloric acid, absolute methanol and ethanol, and glacial acetic acid. It could be precipitated from absolute ethanol solution in an amorphous condition by the addition of ether.

Purification of Materials for Determination of Absorption Spectra.—A. Tyrosine: Six grams of tyrosine, obtained from the University of Illinois, was recrystallized five times from boiling distilled water, carbon being employed during the first two recrystallizations: yield 2.42 g. The material was dried for two hours over phosphorus pentoxide at 100° (1 mm.).

B. Tyrosyltyrosine: The dipeptide was prepared by the method of Bergmann, *et al.*[4] After two recrystallizations from hot ethanol–water, the peptide was obtained in the form of small, colorless prisms melting at 285–288° (dec.), with preliminary sintering. The material was dried over phosphorus pentoxide for two hours at 100° (1 mm.).

C. Tyrosyltyrosyltyrosine Dihydrate: An analytical sample of tripeptide dihydrate (300 mg.) which gave correct analyses but which had a very faint yellow tint, was

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recrystallized three times from hot distilled water, 25 mg. of activated carbon being used in the first recrystallization. There was obtained 220 mg. of white clusters of prisms, m. p. 180–181°. As the anhydrous tripeptide was quite hygroscopic, the stable hydrate was air-dried to constant weight and employed for the spectral analysis.

O-Acetyl-N-carbobenzoxytyrosine Methyl Ester.—A 9.91-g. sample of recrystallized O-acetyl-N-carbobenzoxytyrosine was esterified in methyl alcohol with diazomethane. The product after two recrystallizations from ether melted at 73–74.5°.

Anal. Calcd. for $C_{20}H_{21}O_6N$: C, 64.66; H, 5.70; N, 3.77. Found: C, 64.68, 64.77; H, 6.00, 5.81; N, 4.13.

Tyrosine Methyl Ester Hydrochloride from the Reduction of O-Acetyl-N-carbobenzoxytyrosine Methyl Ester.—Three grams of O-acetyl-N-carbobenzoxytyrosine methyl ester, dissolved in 30 cc. of 0.27 *N* absolute methanolic hydrogen chloride, was reduced in the presence of palladium black catalyst. From the reaction solution was obtained 1.75 g. of fine needles, which after two recrystallizations from absolute methanol–absolute ether melted at 187° (dec.). A mixed melting point with authentic tyrosine methyl ester hydrochloride showed no depression.

Anal. Calcd. for $C_{10}H_{14}O_3NCl$: C, 51.83; H, 6.09. Found: C, 51.63, 51.55; H, 6.15, 6.31.

O-Acetyltyrosine Methyl Ester Hydrochloride.—One gram of O-acetyl-N-carbobenzoxytyrosine methyl ester was dissolved in 40 cc. of glacial acetic acid and hydrogenated in the presence of palladium black catalyst. The filtered solution was saturated with dry hydrogen chloride and concentrated *in vacuo* at a bath temperature of 25° until the hydrochloride crystallized. There was obtained 0.68 g. of O-acetyltyrosine methyl ester hydrochloride, which melted at 201° (dec.), after two recrystallizations from hot glacial acetic acid–ether.

Anal. Calcd. for $C_{12}H_{16}O_4NCl$: C, 52.65; H, 5.89; Cl, 12.95. Found: C, 52.47, 52.50; H, 5.77, 5.97; Cl, 12.8.

O-Acetyltyrosine Hydrochloride.—O-Acetyl-N-carbobenzoxytyrosine dissolved in glacial acetic acid was reduced with palladium black catalyst in the usual manner. The reduction product separated as a white, flocculent precipitate which was dissolved by saturating the solution with dry hydrogen chloride and heating on the steam-bath. The solution was filtered and the hydrochloride obtained as small white needles by cooling the filtrate and resaturating it with hydrogen chloride. Three recrystallizations from glacial acetic acid–hydrogen chloride gave a product melting at 223° (dec.).

Anal. Calcd. for $C_{11}H_{14}O_4NCl$: C, 50.87; H, 5.43; Cl, 13.65. Found: C, 50.81, 50.66; H, 5.53, 5.40; Cl, 13.21.

Action of Absolute Alcoholic Hydrogen Chloride on N-Carbobenzoxytyrosyltyrosine.—Anhydrous N-carbobenzoxytyrosyltyrosine (1.16 g.) was dissolved in 15 cc. of absolute ethanol, and the solution saturated at 0° with dry hydrogen chloride and stored in ice for thirty-one hours. By concentrating the alcohol solution and diluting it with ether, altogether 590 mg. of tyrosyltyrosine ethyl ester hydrochloride, m. p. 214°, was obtained. By allowing the mother liquor and washings to evaporate spontaneously overnight white needles of N-carbobenzoxytyrosyltyrosine ethyl ester were formed; weight 189 mg. After recrystallization from ethyl acetate–petroleum ether the latter melted at 159°, and gave no depression on admixture with an authentic sample.

Action of Absolute Alcoholic Hydrogen Chloride on O-Acetyl-N-carbobenzoxytyrosyltyrosine Ethyl Ester.—Five grams of O-acetyl-N-carbobenzoxytyrosyltyrosine ethyl ester was treated with 90 cc. of ethanolic hydrogen chloride as described in the preceding section. The product consisted of 2.0 g. of tyrosyltyrosine ethyl ester hydrochloride, m. p. 216° (dec.) and 1.2 g. of an impure product melting at 132–160°. The latter, which appeared to be composed of the starting material and N-carbobenzoxytyrosyltyrosine ethyl ester, we were unable to purify further.

N-Carbobenzoxyglycine Ethyl Ester.—The ester from 14 g. of glycine ethyl ester hydrochloride was coupled in ethyl acetate solution with 20.2 g. of carbobenzoxy chloride, employing the customary technique. The product was purified by vacuum distillation, b. p. 147–151° (0.5–1.0 mm.), and 17.8 g. was obtained. It formed beautiful long needles which were readily recrystallized from aqueous ethanol, m. p. 35.5–36.5°.

Anal. Calcd. for $C_{12}H_{15}O_4N$: C, 60.74; H, 6.37; N, 5.90. Found: C, 60.45, 60.72; H, 6.26, 6.46; N, 5.96.

Action of Absolute Alcoholic Hydrogen Chloride on Carbobenzoxyglycine.—A solution of 3 g. of carbobenzoxyglycine[15] in 15 cc. of absolute ethanol was saturated with dry hydrogen chloride at 0° and stored at this temperature for 42 hours. By cooling and seeding the solution there was obtained altogether 1.25 g. of glycine ester hydrochloride, which melted at 144.5–145° alone and at 143.5–144.5° when mixed with an authentic sample. The concentrated mother liquor was dissolved in ether, and the resulting solution dried over sodium sulfate and concentrated on the steam-bath. The light yellow residual oil was crystallized from alcohol–water to give 0.86 g. of carbobenzoxyglycine ester, m. p. 35.5°. This gave no depression in a mixed m. p. determination with an authentic sample.

An ethanolic hydrogen chloride solution of 10 g. of carbobenzoxyglycine was refluxed for one hour while a slow stream of dry hydrogen chloride was passed through the solution. 5.80 g. of glycine ester hydrochloride melting at 143–144° was obtained, and no carbobenzoxyglycine ester could be recovered from the mother liquor. This represents an 87% yield.

Summary

1. Tyrosyltyrosyltyrosine and tyrosyltyrosyltyrosyltyrosine have been synthesized.

2. The ultraviolet absorption specta of tyrosine, tyrosyltyrosine and tyrosyltyrosyltyrosine are compared.

3. The use of alcoholic hydrogen chloride for the removal of the carbobenzoxy group is described.

RECEIVED FEBRUARY 10, 1934

(15) Bergmann and Zervas, *Ber.*, **65**, 1192 (1932).

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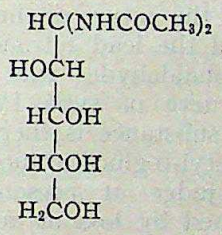
[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, No. 297]

Lead Tetraacetate Oxidations in the Sugar Group. VIII.[1] The Preparation and Proof of Structure of N-Acetyl-D-glucofuranosylamine[2]

BY ROBERT C. HOCKETT AND LEONARD B. CHANDLER[3]

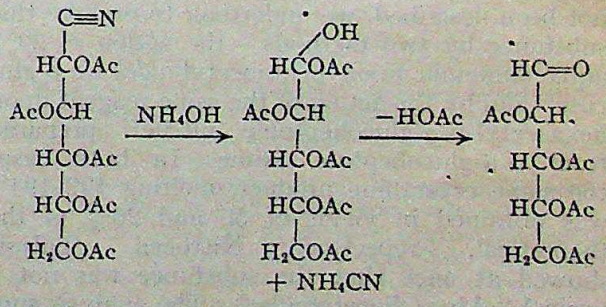
In 1893, Alfred Wohl[4] published his method of degrading an aldose to the next lower member of the series. The action of acetic anhydride and fused sodium acetate upon the D-glucose oxime which had been described by Jacobi[5] produced an acetylated D-gluconic acid nitrile which in turn lost CN^- when treated with an ammoniacal solution of silver oxide. This unusual hydrolysis of a cyanide group as a pseudohalogen instead of to the carboxyl group, produced a compound with one less carbon atom. However, instead of obtaining D-arabinose directly in a free state, Wohl obtained the pentose in a combination with two molecules of acetamide. This product, usually called by the unsatisfactory name "D-arabinose diacetamide," showed a composition and properties consistent with the formula



The open-chain structure was accepted as a matter of course in the era[4] when both sugars and their oximes were regarded as compounds of this type. As the realization grew, however, that the majority of sugar derivatives have cyclic structures,[6] these acetamide condensation products eventually became recognized as representatives of the relatively rare class of acyclic sugar derivatives.[7] The absence of a ring has been further confirmed in several cases by observation of the number of acetyl groups introduced on complete acetylation[8,9] as well as by study of the behavior of the substances toward lead tetraacetate.[10]

It was shown by Maquenne[11] that silver ions are not necessary for the removal of the cyanide group and that aqua ammonia alone will bring about the reaction in one instance. In this Laboratory Maquenne's observation has been confirmed and the effectiveness of 29% ammonia alone has been shown in a number of other cases.[8]

Interesting questions arise concerning the mechanisms of the several reactions which convert pentaacetyl-D-gluconic nitrile into "D-arabinose diacetamide." It is noteworthy that no tendency of free sugars to condense directly with acetamide has been observed either in this Laboratory or elsewhere[7] in spite of a number of efforts to effect such a combination under various conditions. The implication is that some form of sugar other than the pyranose is present at the instant of combination with acetamide. Such a form of D-arabinose could conceivably be the tetraacetyl *aldehydo*-D-arabinose which might be present in a transitory manner, *if* the hydrolysis of nitrile group proceeds at a greater speed than ammonolysis of the acetate groups. The latter, so long as present, will prevent cyclization to furanose or pyranose.



There are two objections to this theory. First, we have been unable to combine pentaacetyl *aldehydo*-D-glucose with acetamide in this Laboratory under any conditions found so far. Second, in the Wohl reaction no acetamide is present until it has been formed by the action of ammonia upon acetate groups in the molecule. We must therefore assume that two acetyl groups are converted to acetamide prior to condensation. If acetyl groups must also serve to prevent cyclization until after condensation has occurred, we must also assume that the groups at the two and three positions undergo ammonolysis more rapidly than those in the four and five positions. Thus 4,5-diacetyl *aldehydo*-D-arabinose may be the true intermediate.

(1) Number VII of this series, THIS JOURNAL, 66, 472 (1944).

(2) Parts of this paper are taken from a thesis submitted by Leonard B. Chandler to the Graduate School of the Massachusetts Institute of Technology in partial fulfillment of the requirements for the degree of Doctor of Philosophy in October, 1939. A similar paper was read before the Division of Organic Chemistry at the Cincinnati meeting of the American Chemical Soicety in April, 1940.

(3) Present address: Nylon Division, E. I. du Pont de Nemours and Company, Wilmington, Delaware.

(4) Wohl, *Ber.*, 26, 730 (1893); *cf.* Wohl and List, *ibid.*, 30, 3101 (1897); Wohl, *ibid.*, 32, 3668 (1899).

(5) Jacobi, *ibid.*, 24, 696 (1891); *cf.* Rischbieth, *ibid.*, 20, 2673 (1887).

(6) Irvine and Gilmour, *J. Chem. Soc.*, 93, 1429 (1908); *cf.* Wolfrom and Thompson, THIS JOURNAL, 53, 622 (1931).

(7) Brigl, Mühlschlegel and Schinle, *Ber.*, 64, 2921 (1931).

(8) Hockett, THIS JOURNAL, 57, 2265 (1935); Hockett, Deulofeu, Sedoff and Mendive, *ibid.*, 60, 278 (1938).

(9) Deulofeu, *J. Chem. Soc.*, 2973 (1932).

(10) Hockett, Dienes, Fletcher and Ramsden, THIS JOURNAL, 66, 467 (1944).

(11) Maquenne, *Compt. rend.*, 130, 1402 (1900).

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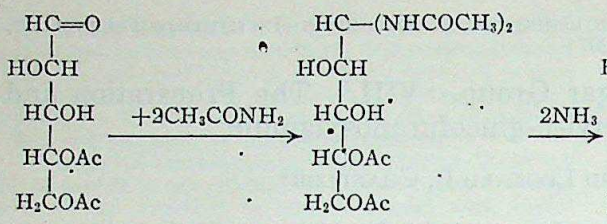


The non-combination of the fully acetylated aldehydo sugars with acetamide may indicate either (1) that removal of acetyls from positions two and three activates the carbonyl in a necessary manner or, (2) that an alkaline medium is necessary for the condensation. If this is true, the "sugar diacetamide" is obviously formed as a result of a delicate balance among the rates of several concurrent reactions.

In either case, fully acetylated *aldehydo*-sugars ought to be converted by aqua ammonia into the open-chain diacetamide condensation products. Deulofeu[9] obtained "L-erythrose diacetamide" by the action of ammonia in ethanol upon triacetyl-aldehydo-L-erythrose and Brigl, Mühlschlegel and Schinle[7] obtained an analogous "D-glucose dibenzamide" by the action of ammonia in methanol upon pentabenzoyl-*aldehydo*-D-glucose. An attempt in this Laboratory, to prepare "D-xylose diacetamide" has resulted in failure. The action of aqua ammonia upon crystalline tetraacetyl-*aldehydo*-D-xylose,[12] has yielded no crystalline products. Neither have we been able to obtain D-gulose oxime or pentaacetyl-D-gulonic nitrile in a crystalline state.

Since "D-glucose diacetamide" had apparently not been described, we undertook to prepare this substance by two methods: the action of 29% aqua ammonia upon pentaacetyl-*aldehydo*-D-glucose[13] and by the action of the same reagent upon hexaacetyl-D-α-glucoheptonic nitrile[14] prepared from D-α-glucoheptose oxime. In both cases the same crystalline product, melting 192–194°, was obtained in yields of 56 and 26% of the theoretical, repectively. Nitrogen analysis showed at once that the substance was not a typical "aldose diacetamide." The analysis supported formulation as an N-acetyl-D-glucosylamine. Such a compound had previously been reported by Brigl and Keppler and by Niemann and Hays.[15] Their product, prepared by the action of ketene upon D-glucopyranosylamine, was shown by oxidation with periodic acid and hypobromite to a dibasic acid with one less carbon atom, to contain a pyranose ring.

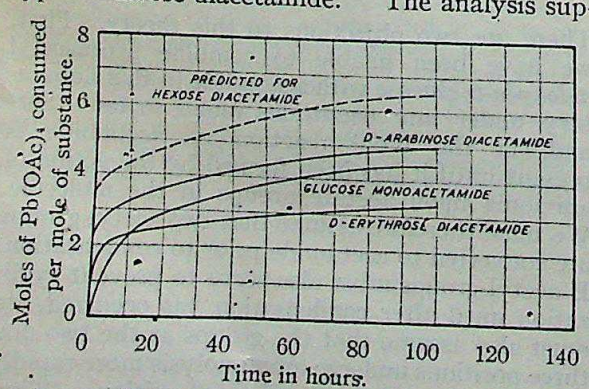


Fig. 1.

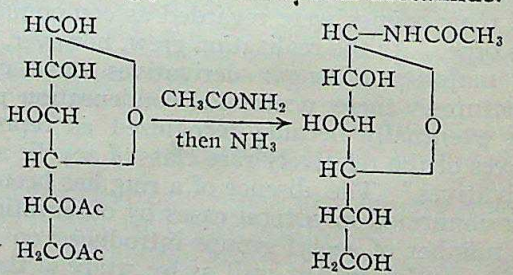
COMPARISON OF N-ACETYL-D-GLUCOSYLAMINES

	Melting point, °C. (uncor.)	Specific rotation
Hockett and Chandler	192–194	+86.9 (*C*, 1.584; H_2O; 25°)
Niemann and Hays (Brigl and Keppler)	255	−22.4 (*C*, 1.24; H_2O)

COMPARISON OF PENTAACETYL-D-GLUCOSYLAMINES

Hockett and Chandler	82.5–84.5	+32.7 (*C*, 1.062; $CHCl_3$; 25°)
Niemann and Hays (Brigl and Keppler)	160–161	+17.7 (*C*, 0.76; $CHCl_3$; 22°)

To determine the nature of the ring in our isomer, we applied the lead tetraacetate oxidation method.[16] Formaldehyde was produced and an oxidation curve of type IV was obtained (Fig. 1). The substance is therefore considered to be an N-acetyl-D-glucofuranosylamine. It is impossible to judge at present whether this product is formed by loss of acetamide from a typical "hexose diacetamide"[17] or by direct condensation of a glycofuranose with acetamide.



We describe D-α-glucoheptose oxime apparently for the first time. It was previously prepared in this Laboratory by Mr. André Laus (unpublished research) in 1936.

We wish to thank Professor M. L. Wolfrom of The Ohio State University for seed crystals of three compounds used in this study and Dr. Morris Zief of this Laboratory for optical measurements on glucoheptose oxime.

Experimental

N-Acetyl-D-glucofuranosylamine from Pentaacetyl-*aldehydo*-D-glucose.—A sample of 6.9 g. (0.0177 mole) of

(12) Wolfrom, Newlin and Stahly, THIS JOURNAL, **53**, 4379 (1931).
(13) Wolfrom, *ibid.*, **51**, 2188 (1929).
(14) *Cf.* Zemplén and Kiss, *Ber.*, **60**, 165 (1927).
(15) Brigl and Keppler, *Z. physiol. Chem.*, **180**, 38 (1929); Niemann and Hays, THIS JOURNAL, **62**, 2060 (1940).
(16) Hockett, Reeder and Nickerson, *ibid.*, **66**, 472 (1944).
(17) *Cf.* Schneider, Sepp and Stiehler, *Ber.*, **51**, 220 (1918); Pacsu, *ibid.*, **58**, 509 (1925); Montgomery, Hann and Hudson, THIS JOURNAL, **59**, 1124 (1937).

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pentaacetyl-*aldehydo*-D-glucose (m. p. 110–118°), prepared by the method of Wolfrom[13] was treated with 110 cc. of 29% aqua ammonia at 50–60° for three hours. The solvents were then removed under reduced pressure and the remaining sirup was treated again with 110 cc. of ammonia solution. After concentration to a sirup, the latter was treated with 50 cc. of absolute ethanol which caused separation of fine crystals weighing 2.2 g.; yield, 56%. Recrystallized from about five parts of water with addition of eighteen parts of absolute alcohol, the crystals reached a maximum melting point of 189–191° (uncor.) (with decomposition) when heated at the rate of two degrees a minute. They rotated[18] +86.7° (*C*, 3.937; H_2O; 22.4°). A slow mutarotation[15] to +85.8° occurred in ten days. The compound is moderately soluble in hot water, slightly soluble in ice-cold water and in hot dry methanol, and insoluble in absolute ethanol, ether, pyridine, acetone and chloroform. It reduced Fehling solution only slowly on continued boiling.

Anal. Calcd. for $C_8H_{15}O_6N$: C, 43.3; H, 6.84; N, 6.34. Found: C, 42.4, 42.2, 43.2; H, 6.39, 6.73, 6.26; N, 6.34, 6.49.

Pentaacetyl-D-glucofuranosylamine.—A sample of 1.56 g. (0.00707 mole) of N-acetyl-D-glucofuranosylamine was treated with a mixture of 7.5 cc. (0.0789 mole) of acetic anhydride and 6 cc. (0.0740 mole) of pyridine at 75–80° for three hours. Solution was complete in thirty minutes and then slight discoloration occurred. After three hours, 5 cc. of pyridine was added and the solution was concentrated under diminished pressure (bath temp., 55°) to a sirup. This sirup was several times dissolved in absolute alcohol and reconcentrated to get rid of pyridine. The resulting yellow sirup was dissolved in 10 cc. of acetone and filtered through carbon to decolorize. The filtrate was treated with 10 cc. of dry ether and then with petroleum ether to turbidity. Crystals weighing 1.46 g. (53% of the theoretical) separated in a refrigerator. These prisms, once recrystallized from the same solvents, melted 82.5–84.5° (uncor.) and rotated[18] +32.7° (*C*, 1.620; $CHCl_3$; 25°). They are readily soluble in acetone, chloroform, methanol and ethanol, somewhat soluble in warm water, very slightly soluble in boiling ether or cold water, and insoluble in petroleum ether.

Anal. Calcd. for $C_{16}H_{23}O_{10}N$: N, 3.60; acetyl, 44.3. Found: N, 3.76, 3.77; acetyl, 44.2.

Pentaacetyl-D-glucofuranosylamine was also made by heating at 90° for ninety minutes with four parts of acetic anhydride and one-quarter part of anhydrous sodium acetate. The mixture was poured on ice, and the product was dissolved in chloroform, which was shaken repeatedly with sodium bicarbonate solution, was washed with water, dried over sodium sulfate and evaporated. The sirup remaining was crystallized as described above.

Attempted Condensation of Pentaacetyl-*aldehydo*-D-glucose with Acetamide.—After ten hours of boiling under reflux, a solution of the glucose derivative and of acetamide in chloroform was found to contain the starting materials unchanged.

D-α-Glucoheptose Oxime.—Nineteen grams (0.0906 mole) of D-α-glucoheptose (m. p. 188–190°) made as described by Haworth, Hirst and Stacey,[19] was treated with a methanol solution of 0.129 mole of hydroxylamine overnight at room temperature. A little unreacted sugar remaining the next morning was dissolved by warming a short time on the steam-bath. The solution was then concentrated to a sirup (diminished pressure) and was dissolved in a minimum volume of dry methanol. A crystalline product weighing 17 g. (85% of the theoretical) soon separated which melted at 89–91.5°. Recrystallized from water, it melted at 100–101° (uncor.).

Anal. Calcd. for $C_7H_{15}O_7N$: N, 6.22. Found: N, 6.33, 6.30.

The substance shows a slight mutarotation in water. The initial rotation[18] of −6.3° (*C*, 1.589; H_2O; 22°) reaches 0.9° in seventy hours. Because of the low magnitude of these rotations, no accurate rate constant has been obtained.

Hexaacetyl-D-α-glucoheptonic Nitrile.—Thirteen grams (0.0578 mole) of D-α-glucoheptose oxime (m. p. 89–91°) was treated with 69 cc. of acetic anhydride and 5 g. of anhydrous sodium acetate. Heat was evolved as the oxime dissolved. Finally the mixture was digested for an hour at 100° and then poured on ice. The precipitated gum soon solidified after excess acetic acid had been neutralized with sodium bicarbonate. Filtered, decolorized, and recrystallized from hot ethanol, 13.5 g. of product (51% of the theoretical) was obtained. After recrystallization to constant properties, the elongated prisms melted 85.5–87.5° (uncor.) and rotated[18] +24.3° (*C*, 3.893; $CHCl_3$; 24.8°). Zemplén and Kiss, who prepared the compound by another method,[14] reported a melting point of 112.5–113.5° but a closely agreeing rotation +24.6° at 21°. Possibly two crystal modifications exist.

Anal. Calcd. $C_{19}H_{25}O_{12}N$: C, 49.5; H, 5.44; N, 3.05. Found: C, 49.8, 49.8; H, 5.47, 5.47; N, 3.26. Acetyl determination by the method of Kunz and Hudson[20] resulted in hydrolysis of the cyanide group as well as the acetyls: calcd. for seven CH_3CO, 65.6; found, 63.6 (60 min.), 64.7 (75 min.) and 65.6 (120 min.).

N-Acetyl-D-glucofuranosylamine from Hexaacetyl-D-α-glucoheptonic Nitrile.—A sample of 10.5 g. (0.0229 mole) of the nitrile was heated for three hours at 50° with 125 cc. of 29% aqua ammonia. The solution was then concentrated to a sirup (diminished pressure) which was given a second treatment with ammonia. The sirup obtained by a second concentration was dried by adding absolute alcohol and redistilling solvent-free. The dried sirup was dissolved in a little absolute ethanol and ether was added to turbidity. Crystals separated in a yield of 1.3 g. or 26%. Recrystallized as described above, the small prisms attained a melting point of 192–194° (uncor.) and rotated[18] +86.9° (*C*, 1.584; H_2O; 25.1°). The two samples when mixed showed no depression of melting point.

Anal. Calcd. for $C_8H_{15}O_6N$: C, 43.4; H, 6.84; N, 6.34. Found: C, 43.4, 43.8; H, 6.94, 7.12; N, 6.25.

Rate of Oxidation of N-Acetyl-D-glucofuranosylamine by Lead Tetraacetate.—The measurement was carried out under the standard conditions described by Hockett, Dienes and Ramsden.[21]

Detection of Formaldehyde on Oxidation of N-Acetyl-D-glucofuranosylamine by Lead Tetraacetate.—A sample of 0.10 g. (0.0005 mole) of the glucose derivative was dissolved in 10 cc. of water in a small distilling flask. A volume of 15 cc. of approximately 0.05 molar lead tetraacetate in glacial acetic acid was added from a buret. After ten minutes, a receiver was attached and packed in dry-ice. The liquids were distilled under reduced pressure into this receiver. To the distillate was added 30 cc. of a saturated solution of 2,4-dinitrophenylhydrazine in 2 *N* hydrochloric acid (about 0.2 g. of the hydrazine). The precipitate of formaldehyde 2,4-dinitrophenylhydrazone melted at 166° (cor.).

Summary

An N-acetyl-D-glucofuranosylamine has been prepared in two ways: by the action of aqua ammonia upon pentaacetyl-*aldehydo*-D-glucose and upon hexaacetyl-D-α-glucoheptonic nitrile. The physical properties of the new compound are recorded along with those of the corresponding pentaacetyl-D-glucofuranosylamine and of D-α-glucoheptose oxime.

(18) All rotations in this paper refer to specific rotations of the D line of sodium at 20° unless otherwise stated. Concentrations are stated in grams of solute in 100 cc. of solution.

(19) Haworth, Hirst and Stacey, *J. Chem. Soc.*, 2864 (1931); *cf.* Fischer, *Ann.*, **270**, 64 (1892), and Philippe, *Ann. chim. phys.*, **26**, 289 (1912).

(20) Kunz and Hudson, THIS JOURNAL, **48**, 1932 (1926).

(21) Hockett, Dienes and Ramsden, *ibid.*, **65**, 1474 (1943).

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The ring structure of N-acetyl-D-glucofuranosylamine has been determined by its behavior when oxidized by lead tetraacetate. The new reactions give further insight into the mechanism of the Wohl degradation of sugars.

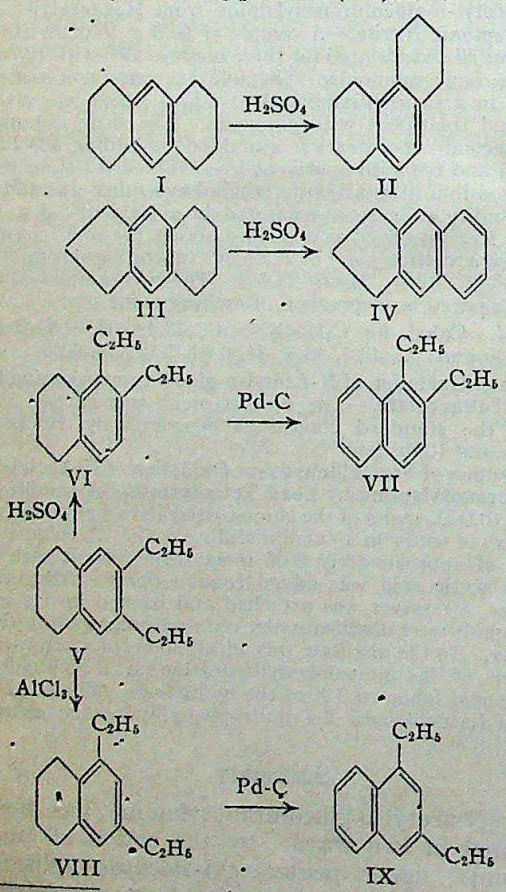
CAMBRIDGE, MASS. RECEIVED FEBRUARY 23, 1944

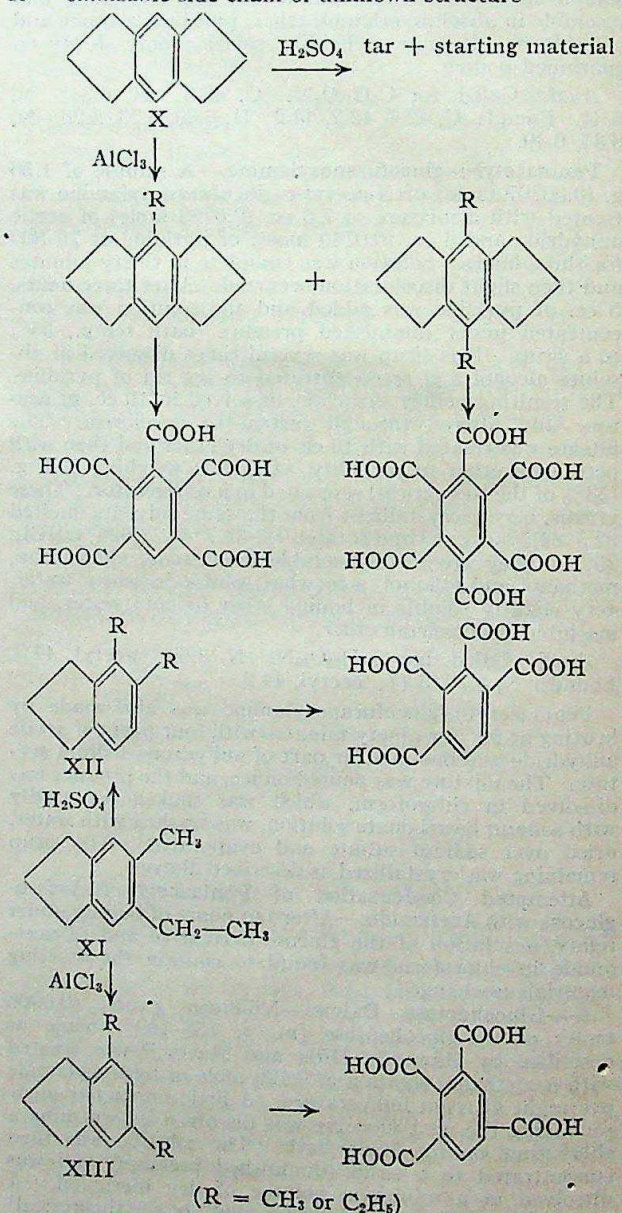
[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

The Jacobsen Rearrangement. VIII.[1] Cyclic Systems; Mechanism

BY RICHARD T. ARNOLD AND RODERICK A. BARNES[2]

For many purposes it is convenient to regard hydrindene and tetralin as *o*-dialkylbenzenes. If this view is accepted, then one might suppose that the tri- and tetramethylene rings in these substances would undergo rearrangement when the molecule is subjected to conditions which bring about a migration of simple alkyl groups. Therefore it was of interest to study the Jacobsen rearrangement of hydrocarbons derived from tetralin and hydrindene. During the course of this investigation octahydroanthracene (I), 5,6,7,8-tetrahydrobenz[f]indan (III),[3] 6,7-diethyltetralin (V), 5-ethyl-6-methylhydrindene (XI), and *s*-hydrindacene (X) (Ring Index 1459) have been prepared and their reactions with sulfuric acid and aluminum chloride (in three cases) investigated.





The only example of a Jacobsen rearrangement involving a cyclic system which so far has been

(1) VII, THIS JOURNAL, 62, 2631 (1940). The Authors desire to thank Dr. Lee Irvin Smith for his interest in this work and for the authentic samples of benzene tetracarboxylic-acids used as reference compounds.

(2) Abstracted from a thesis by Roderick A. Barnes, presented to the Graduate Faculty of the University of Minnesota in partial fulfillment of the requirements for the Ph.D. degree, November, 1943.

(3) Sen-Gupta, *J. Ind. Chem. Soc.*, 16, 89 (1939).

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reported is the conversion of octahydroanthracene into octahydrophenanthrene.[4] The results obtained in our work are in charts.

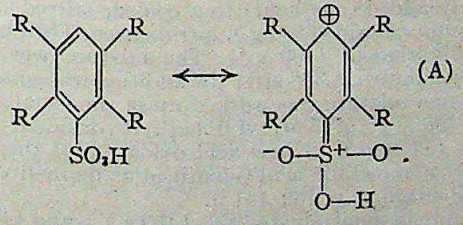
Discussion

No satisfactory and adequate explanation has yet been proposed for the mechanism of the Jacobsen rearrangement.[5]

In their original paper, Mills and Nixon[6] pointed out that in hydrindene the two bonds linking the trimethylene group to the benzenoid ring are probably distorted toward one another and that such a distortion should affect the aromatic character of the benzenoid ring. A very important result which must accompany such a deflection of these valence bonds is the reduction in the steric influence of the methylene groups adjacent to the benzene ring.[7]

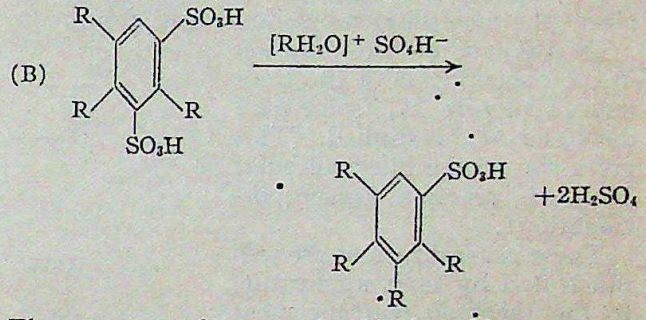
As the chart of reactions shows, successful Jacobsen rearrangements have been effected with compounds I, V and XI to give products with the expected orientations (*i. e.*, 1, 2, 4, 5- to 1, 2, 3, 4-). Compound III was not rearranged but was dehydrogenated by the action of sulfuric acid. No products from the rearrangement of X could be detected. In every case where possible (V and XI), aluminum chloride brought about a change in the orientation of the alkyl groups from the 1, 2, 4, 5-position to the 1, 2, 3, 5-position in a manner identical to that observed with simple tetraalkylbenzenes.

The evidence so far accumulated indicates that the Jacobsen rearrangement proceeds via an initial sulfonation and that it is the sulfonic acid which undergoes the rearrangement.[5] If the statement at the close of the footnote[7] is accepted, then it becomes apparent that in the sulfonic acids derived from I, V and XI, the sulfonic acid group is sterically more hindered than it is in the sulfonic acids from III and X. This steric factor is important because it controls in part the contribution of structure "A" to the resonance.[8,9]



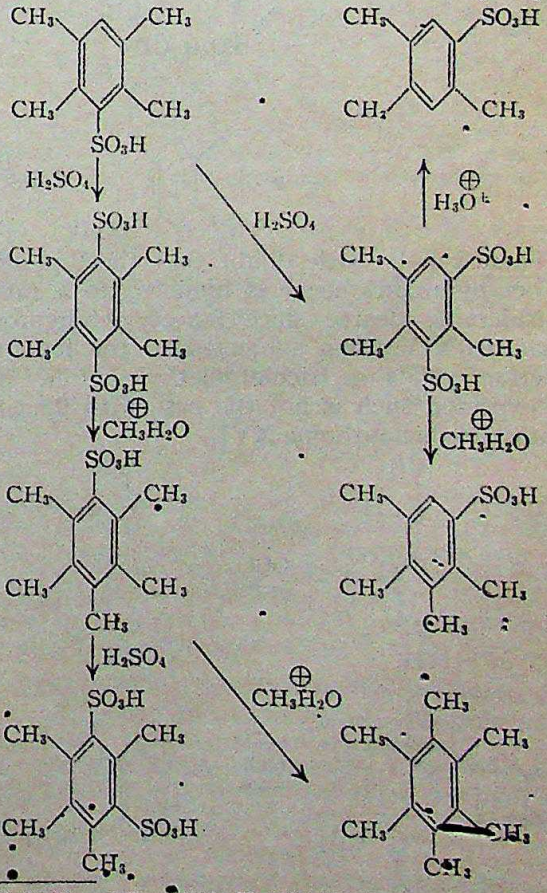
(A)

The contribution of "A" to the resonance is less in the sulfonic acids derived from I, V and XI than it is in the sulfonic acids derived from III and X. As a result the benzene rings in the former compounds are more susceptible to attack by cationoid reagents than are those in the latter compounds. Furthermore, it has been shown[10] that the most hindered sulfonic acid groups are those most readily hydrolyzed by acid solutions. It follows, therefore, that in a disulfonic acid of type "B" the sulfonic acid grouping subject to the greatest hindrance will be the one to be preferentially replaced by cationic reagents.



The entrance of a second sulfonic acid group and the replacement of the original sulfonic acid group by an alkyl cation is an essential feature of the Jacobsen rearrangement. This conclusion together with the other considerations mentioned above lead to the following generalizations with regard to the mechanism of the Jacobsen reaction:

(1) The rearrangement of alkyl groups can occur only if the initial sulfonic acid group is



(4) Schroeter and Gotzsky, *Ber.*, **60**, 2035 (1927).

(5) Smith, "Organic Reactions," J. Wiley and Sons, New York, N. Y., 1943, pp. 370–384.

(6) Mills and Nixon, *J. Chem. Soc.*, 2510 (1930).

(7) A systematic investigation of the relative steric influence of the methylene group when present in a methyl group, a six-membered ring (as in tetralin), and a five-membered ring (as in hydrindene) has been under way for some time in this Laboratory and will be continued as conditions permit. This work has already indicated that the steric effect of these groups decreases in the order in which they are mentioned above.

(8) Kumler and Daniels, THIS JOURNAL, **65**, 2190 (1943).

(9) Kumler and Halverstadt, *ibid.*, **63**, 2182 (1941).

(10) Smith and Guss, *ibid.*, **62**, 2631 (1940).

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sufficiently hindered sterically by two ortho substituents so that the contribution of form "A" to the resonance is diminished.

(2) The resulting steric inhibition of resonance allows for the formation of a disulfonic acid.

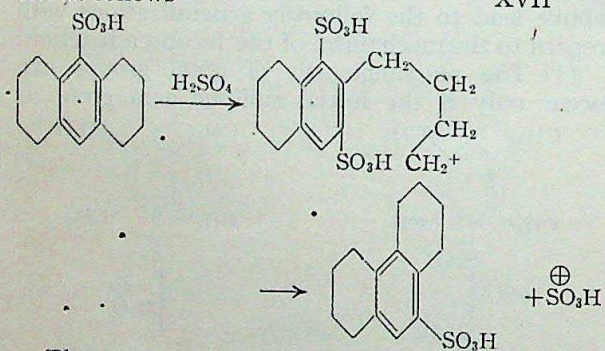
(3) This latter reaction takes place preferentially in the meta position to the first sulfonic acid group and leads to the elimination of an alkyl cation or the opening of a saturated ring to form an intermediate having a cationic terminal carbon atom.

(4) The cationic alkyl group preferentially replaces the most hindered sulfonic acid group.

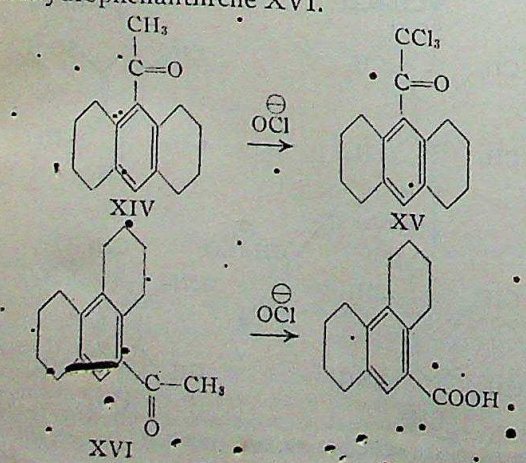
(5) Because of a diminution in the contribution of the resonance structure "A," some para disulfonic acid is formed. This gives rise to the intermolecular Jacobsen reaction (disproportionation).

These generalizations are well illustrated by their application to the Jacobsen rearrangement of durene already shown.

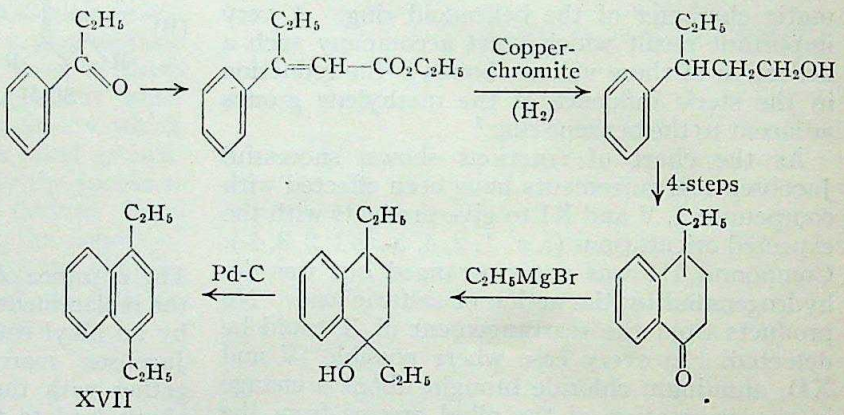
When applied to the specific case of octahydroanthracene, the rearrangement can be written as follows



There can be little doubt that the 9-position in octahydroanthracene is hindered to a rather considerable degree since 9-acetyloctahydroanthracene XIV when subjected to the haloform reaction yields a trichloromethyl ketone XV. As expected such is not the case with 9-acetyloctahydrophenanthrene XVI.



Incidental to this study, all of the possible diethylnaphthalenes having the two alkyl groups in a single ring have been synthesized. The 1,2-, 2,3- and 1,3-diethylnaphthalenes resulted from the catalytic dehydrogenation of the corresponding tetralins (VI, V and VIII) by means of palladium–charcoal catalyst. The structures of the tetralins employed were established by nitric acid oxidation to the known benzenetetracarboxylic acids; these were identified as their tetramethyl esters. 1,4-Diethylnaphthalene was prepared via the following sequence of reactions



The resulting hydrocarbon XVII (m. p. 16.5–17°) formed a picrate melting at 91–93°. These physical properties are quite different from those reported for 1,4-diethylnaphthalene by Frösche and Harlass.[11]

Experimental

5-Methylhydrindene.—A mixture of freshly distilled 5-chloromethylhydrindene (50 g.), absolute alcohol (200 cc.) and palladium on barium sulfate catalyst (1.5 g.) was shaken with hydrogen (45–50 lb. pressure) at room temperature. When the reaction was complete (twenty minutes), the catalyst was removed by filtration. From four such runs there was obtained on fractionation 154 g. of hydrocarbon (96%); b. p. 86–88° (19 mm.). Platinum oxide also is an effective catalyst.[12]

5-Ethyl-6-methylhydrindene.—Acetic anhydride (102 g.) was slowly added (one hour) to a cooled, stirred mixture of aluminum chloride (223 g.), nitrobenzene (500 cc.) and 5-methylhydrindene (100 g.). The mixture was stirred for ninety minutes at 30° after the addition was completed. The reaction mixture was worked up in the usual manner to give 106.8 g. of 5-acetyl-6-methylhydrindene; b. p. 152–158° (11 mm.). Nitric acid oxidation of the ketone gave only pyromellitic acid (identified as its methyl ester; m. p. and mixed m. p. 139–141°).

A mixture of amalgamated zinc (450 g.), water (450 cc.), concentrated hydrochloric acid (900 cc.), acetic acid (450 cc.) and the ketone (100 g.) was refluxed for fifty hours during which time 800 cc. of hydrochloric acid was added in portions. There was obtained 70.7 g. of hydrocarbon; b. p. 112–116° (11 mm.).

Anal. Calcd. for $C_{12}H_{16}$: C, 89.93; H, 10.07. Found: C, 89.70; H, 10.25.

5-Propionylhydrindene.—Propionic anhydride (130 g.) was added to a cooled, stirred mixture of aluminum chloride (292 g.), nitrobenzene (500 cc.) and hydrindene (118 g.). The mixture was worked up as described above for 5-acetyl-6-methylhydrindene. There was obtained 139 g. of ketone; b. p. 159° (12 mm.).

(11) Frösche and Harlass, *Monatsh.*, **59**, 282 (1932).

(12) Plattner and Ronigen, *Helv. Chim. Acta*, **25**, 593 (1942).

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Anal. Calcd. for $C_{12}H_{14}O$: C, 82.72; H, 8.10. Found: C, 82.97; H, 8.33.

The oxime melted at 95–96°.

Anal. Calcd. for $C_{12}H_{15}ON$: C, 76.15; H, 7.99. Found: C, 76.26; H, 7.78.

Diethyl 5-Hydrindenylmethylmalonate.—Sodium (46 g.) was dissolved in one liter of absolute ethanol. Malonic ester (320 g.) was added and this was followed by the slow addition (two hours) of 5-chloromethylhydrindene (200 g.). The mixture was gently refluxed for five hours, made acidic (litmus) with 1:1 hydrochloric acid, and then the alcohol was removed by distillation. The residue was poured into water, separated, and distilled; b. p. 158–165° (3 mm.); weight 225 g.

Anal. Calcd. for $C_{17}H_{22}O_4$: C, 70.30; H, 7.65. Found: C, 70.28; H, 7.77.

β-5-Hydrindenylpropionic Acid.—(a) A mixture of 5-propionylhydrindene (35 g.), dioxane (110 cc.), sulfur (14 g.) and concentrated ammonia saturated with hydrogen sulfide (140 cc.) was heated in a closed iron pipe at 150–155° for twenty-four hours. The residue after removing the solvents was refluxed for two hours with potassium hydroxide (200 cc., 15%). The alkaline solution was treated with norite, filtered, and acidified. The liberated acid was extracted with benzene. Distillation in a sausage flask at 4 mm. pressure followed by recrystallization from dilute acetic acid gave 26 g. of acid; m. p. 85–86°.

Anal. Calcd. for $C_{12}H_{14}O_2$: C, 75.76; H, 7.41. Found: C, 75.64; H, 7.45.

(b) Saponification of diethyl 5-hydrindenylmethylmalonic ester followed by decarboxylation gave the same acid in a more impure condition; yield 91%; m. p. 78–80°. It was impossible to raise this melting point appreciably by recrystallization. A mixed melting point determination of the two samples gave m. p. 82–84°.

5-Hydrindacene-1-one.—Phosphorus pentachloride (5.21 g.) was added in portions to a solution of pure β-5-hydrindenylpropionic acid (4.76 g.) in dry benzene (50 cc.). Upon cooling to room temperature stannic chloride (3.7 cc.) dissolved in benzene (6 cc.) was added dropwise during an interval of forty-five minutes. Decomposition with dilute hydrochloric acid gave the ketone; yield 3.84 g.

Anal. Calcd. for $C_{12}H_{12}O$: C, 83.68; H, 7.03. Found: C, 83.36; H, 7.18.

***s*-Hydrindacene.**—A mixture of amalgamated zinc (140 g.), water (115 cc.), hydrochloric acid (230 cc.), acetic acid (86 cc.), toluene (115 cc.) and 5,6-cyclopenteno-1-indanone (20 g.) was refluxed for thirty-six hours during which time an additional 200 cc. of hydrochloric acid was added. There was obtained on distillation of the toluene layer 15.1 g. of hydrocarbon; b. p. 116–120° (9 mm.). Recrystallization from ethanol gave long prisms; m. p. 52–54°.

Anal. Calcd. for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 90.92; H, 8.59.

This hydrocarbon on nitric acid oxidation gave only pyromellitic acid (methyl ester; m. p. 139–141°).

6,7-Diethyltetralin.—This hydrocarbon was prepared essentially by the method of Fleischer and Siefert.[13] Proof of its structure was established by nitric acid oxidation to pyromellitic acid.[14]

5,6,7,8-Tetrahydrobenz[f]indan.—This hydrocarbon was prepared according to the directions published by Sen-Gupta.[15]

4,9-Dibromo-5,6,7,8-tetrahydrobenz[f]indan.—The hydrocarbon (1.0 g.) was dissolved in acetic acid and a solution of bromine in acetic acid was added dropwise until a permanent reddish solution resulted. After a few minutes sodium bisulfite (0.2 g.) in 50 cc. of water was added. The white precipitate was collected and recrystallized from ethanol; m. p. 141.5–142.5°.

Anal. Calcd. for $C_{13}H_{14}Br_2$: C, 47.3; H, 4.27. Found: C, 47.5; H, 4.36.

3-Phenylpentanol-1.—Ethyl β-ethylcinnamate (200 g.) was hydrogenated at 250° with an initial pressure of 2800 pounds in the presence of 35 g. of copper chromite (37 KAF). The reduction was complete in six hours. Fractionation gave 137.4 g. of 3-phenylpentanol-1; b. p. 145–148° (26 mm.).[16]

1-Ethyltetralone-4.—This cyclic ketone was prepared from 3-phenylpentanol-1 by use of the method of Levy.[16]

1,4-Diethylnaphthalene.—A solution of the above ketone (5.6 g.) dissolved in dry ether (25 cc.) was slowly added to a solution of ethylmagnesium bromide prepared from 5.5 g. of ethyl bromide. After thirty minutes the mixture was decomposed with dilute hydrochloric acid. The ether layer, after removal of the ether, left a residue of crude carbinol (6.4 g.). This carbinol was heated for two hours at 225° with palladium-charcoal (0.2 g., 10%) in a current of carbon dioxide. After cooling, the product was taken up in ethanol (50 cc.), filtered, and treated with 5 g. of picric acid while the solution was warm. On cooling, the picrate separated; m. p. 91–93°. The hydrocarbon was regenerated by shaking the picrate with ether and ammonia. Evaporation of the ether layer and distillation gave 4.1 g. of hydrocarbon; b. p. 165° (25 mm.); m. p. 16.5–17°.

Anal. Calcd. for $C_{14}H_{16}$: C, 91.25; H, 8.75. Found: C, 91.70; H, 9.04.

9-Acetyl-1,2,3,4,5,6,7,8-octahydrophenanthrene.—In the preparation of 6-acetyltetralin from tetralin (132 g.) acetic anhydride (82 g.), aluminum chloride (300 g.) and dry carbon bisulfide (400 cc.) there were obtained 69.2 g. of 6-acetyltetralin and 11 g. of 9-acetyloctahydrophenanthrene (m. p. 50.5–51.5).[17] The structure of the latter was established by conversion to the corresponding 9-octahydrophenanthrene carboxylic acid; m. p. 236–238°. Schroeter[18] reports 239–240°.

9-Acetyloctahydroanthracene.—A solution of acetic anhydride (11.3 g.) in tetrachloroethane (25 cc.) was added slowly to a cooled solution of aluminum chloride (30 g.) and octahydroanthracene (9.3 g.) in tetrachloroethane (100 cc.). The solution was stirred in an ice-bath for two hours after the addition was completed, and the mixture was decomposed with dilute hydrochloric acid. Fractionation gave 7.8 g. of ketone; b. p. 169° (3 mm.). Crystallization from methanol gave a white solid; m. p. 72–72.5°.

Anal. Calcd. for $C_{16}H_{20}O$: C, 84.16; H, 8.83. Found: C, 84.09; H, 8.86.

9-Trichloroacetyloctahydroanthracene.—An aqueous solution of potassium hypochlorite from 15 g. of bleaching powder (H. T. H.) was shaken vigorously with 1.0 g. of acetyloctahydroanthracene. The solution became warm and, on cooling, a precipitate (1.4 g.) melting at 123.5–124.5° was isolated. The trichloro ketone crystallized with one molecule of water.

Anal. Calcd. for $C_{16}H_{17}OCl_3 \cdot H_2O$: C, 57.59; H, 5.14. Found: C, 57.61; H, 5.17.

2,3-Diethylnaphthalene.—One gram of 6,7-diethyltetralin was heated with palladium-charcoal (0.1 g., 10%) at 200–240° for three hours. The product was taken up in a small quantity of ethanol, filtered, and treated with a saturated solution of picric acid in ethanol. The precipitated picrate melted at 126–128°. The regenerated hydrocarbon was liquid at room temperature.

Action of Sulfuric Acid on the Hydrocarbons

(A) Octahydroanthracene.—The reported rearrangement to octahydrophenanthrene[4] was confirmed.

(B) 5,6,7,8-Tetrahydrobenz[f]indan.—The hydrocarbon (11.8 g.) and concentrated sulfuric acid (47 g.) were heated at 118°. Sulfur dioxide was continuously evolved.

(13) Fleischer and Siefert, *Ber.*, **53**, 1255 (1920).

(14) Campbell, Soffer and Steadman, THIS JOURNAL, **64**, 425 (1942).

(15) Sen-Gupta, *J. Ind. Chem. Soc.*, **16**, 89 (1939).

(16) Levy, *Compt. rend.*, **197**, 772 (1933).

(17) Bergmann and Bergmann, *J. Chem. Soc.*, 1364 (1939).

(18) Schroeter, *Ber.*, **57**, 2003 (1924).

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On cooling the mixture was poured into 250 cc. of water and treated with calcium oxide (27 g.). After filtering, the filtrate was treated with sodium carbonate to remove the excess calcium ion. Evaporation of the aqueous filtrate gave a semicrystalline mass. This was steam distilled at 145–150° in the presence of dilute sulfuric acid. One gram of starting hydrocarbon and one gram of benz[f]-indan (m. p. 92–93°) were recovered. The latter formed its well known picrate, m. p. and mixed m. p. 116–118°.

(C) **6,7-Diethyltetralin.**—Eighteen grams of the hydrocarbon in sulfuric acid (80 cc.) was heated gradually while being stirred. At 60° complete solution was effected. The mixture was then heated at 95° for fifteen minutes and allowed to cool. Steam distillation at 150° gave 4.9 g. of liquid hydrocarbon. Oxidation of a portion of this material with nitric acid gave only mellophanic acid (methyl ester—m. p. and mixed m. p. 129–131°). Dehydrogenation of the hydrocarbon with palladium-charcoal gave 1,2-diethylnaphthalene a liquid hydrocarbon whose picrate melted at 105.5–107°.

(D) **5-Ethyl-6-methylhydrindene.**—Ten grams of the hydrocarbon was heated with 40 cc. of sulfuric acid at 90° for thirty minutes. Steam distillation as described above gave 1.4 g. of volatile hydrocarbon. Nitric acid oxidation gave only mellophanic acid (methyl ester—m. p. and mixed m. p. 129–131°).

(E) ***s*-Hydrindacene.**—Three grams of the hydrocarbon and 20 g. of sulfuric acid were heated at 70° for three minutes. More drastic conditions (*i. e.*, higher temperatures, etc.) gave only unidentifiable tarry materials. The solution was cooled and a solid sulfonic acid separated. To the total contents of the flask acetic acid (2 cc.) and sulfuric acid (5 cc.) were added and the temperature was raised to 98° and held there for one hour. Steam distillation gave the starting hydrocarbon (m. p. 52–53°) as the sole product. Considerable tarry residue remained in the distilling flask.

Action of Aluminum Chloride on the Hydrocarbons

(A) **6,7-Diethyltetralin.**—Thirteen grams of hydrocarbon and aluminum chloride (1 g.) was heated on the steam-bath for two and one-half hours and then allowed to stand several days at room temperature. After decomposition with water followed by ether extraction there was obtained on fractionation at 11 mm. three cuts boiling at 124–140°, 142–152°, and 155–168°. The first cut on oxidation with nitric acid gave impure prehnitic acid (identified as its methyl ester—m. p. and mixed m. p. 109–110°). Fraction II (b. p. 142–152°) gave fairly pure prehnitic acid. Dehydrogenation of this fraction with palladium–charcoal gave a naphthalenic hydrocarbon whose picrate melted at 100–101°. This hydrocarbon must be 1,3-diethylnaphthalene.

(B) **5-Ethyl-6-methylhydrindene.**—Treatment of 20 g. of hydrocarbon with aluminum chloride (2.0 g.) as described above gave on fractionation at 15 mm. the following cuts: I, 80–100° (1 g.), II, 100–120° (7 g.), III, 120–140° (10 g.), IV, 140–180° (0.5 g.) and V, 215–230° (0.8 g.). Fraction III gave prehnitic acid on nitric acid oxidation (identified as its methyl ester) and fraction V gave benzenepentacarboxylic acid (pentamethyl ester—m. p. and mixed m. p. 146–148°).

(C) ***s*-Hydrindacene.**—The hydrocarbon (1.5 g.) was treated with aluminum chloride (0.5 g.) as described above. The reaction product was oxidized with nitric acid and the resulting carboxylic acid mixture was esterified with diazomethane. Penta- and hexacarbomethoxybenzenes were isolated; m. p. 146–148° and 184–186°, respectively.

Summary

1. The Jacobsen rearrangement has been studied with cyclic hydrocarbons related to hydrindene and tetralin.

2. The action of aluminum chloride on 6,7-diethyltetralin, 5-ethyl-6-methylhydrindene, and *s*-hydrindacene is reported.

3. A new and convenient synthesis of pure 1,4-diethylnaphthalene is described.

4. A mechanism for the Jacobsen rearrangement is proposed and discussed.

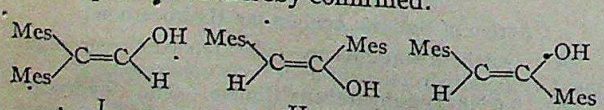
MINNEAPOLIS, MINNESOTA RECEIVED FEBRUARY 14, 1944

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Vinyl Alcohols. IX.[1] Esters of 1,2-Dimesitylvinyl Alcohols

BY REYNOLD C. FUSON, L. J. ARMSTRONG[2] AND W. J. SHENK, JR.

For the dimesitylvinyl alcohol produced by the dehydration of hydromesitoin or isohydromesitoin[1] three structures are possible—1,1-dimesitylvinyl alcohol (I) and the *cis* (II) and *trans* (III) forms of 1,2-dimesitylvinyl alcohol. The present paper is concerned with the last two of these. Although it has not been possible to prepare these enols, evidence has been accumulated which shows both to be unstable and thus entirely different from the dehydration product. The structure, 1,1-dimesitylvinyl alcohol, (I), previously assigned to this product is thereby confirmed.



One of the methods employed in attempts to make enols II and III consisted in the condensation of mesitylmagnesium bromide with mesitylketene (IV). The possibility of preparing enols from ketenes was suggested by the work of Gilman and Heckert,[3] who found that the enolate formed by the addition of the Grignard reagent to diphenylketene was converted by the action of benzoyl chloride to the corresponding enol benzoate. Hydrolysis of this ester produced the enol, which immediately ketonized. It seemed possible that a more stable enol could be made by the condensation of a Grignard reagent with mesitylketene. Although this ketene could not be isolated it was prepared in solution and to the solution was added mesitylmagnesium bromide. The enolate (V) reacted with benzoyl chloride to yield a benzoate (VI) of desoxymesitoin (VII). The structure of the benzoate was established by

(1) For the preceding communication in this series see Fuson and Rowland, THIS JOURNAL, 65, 992 (1943).

(2) Present address, Rohm and Haas Company, Philadelphia, Pennsylvania.

(3) Gilman and Heckert, THIS JOURNAL, 42, 1010 (1920).

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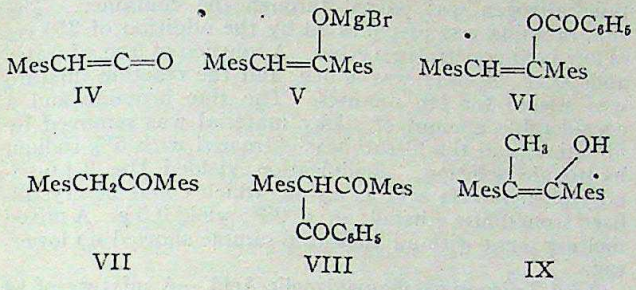
hydrolysis, which generated desoxymesitoin. That the benzoylation product was not the 1,3-diketone (VIII) was shown by its failure to



generate methane in the Kohler–Richtmyer apparatus.[4]

An attempt to synthesize the new benzoate from desoxymesitoin led to an interesting result. Desoxymesitoin was treated with ethylmagnesium bromide, and benzoyl chloride was added to the solution of the resulting enolate. The benzoate formed in this way was not identical with that from the ketene. It had similar chemical properties, however. It likewise gave no gas in the Grignard machine[4] and yielded desoxymesitoin when hydrolyzed. Evidently the two benzoates are *cis–trans* isomers. It also becomes certain that neither the *cis* (II) nor the *trans* (III) 1,2-dimesitylvinyl alcohol is stable with respect to the keto form. This result stands in marked contrast to the stability of the propenol, IX,[5] and that of 1,1-dimesitylvinyl alcohol (I).

Two acetates have also been prepared from desoxymesitoin. One of these had been made earlier by Barnes, Cooper, Tulane and Delaney[6] by heating desoxymesitoin with acetic anhydride and potassium acetate. It melted at 106° and, presumably, has the *trans* configuration. A low-melting acetate (67–68°), presumably the *cis* modification, was prepared by the action of acetyl chloride on the enolate formed by treating desoxymesitoin with ethylmagnesium bromide.

As might be expected, the synthesis of highly hindered ketenes offered difficulty. Mesitylketene was obtained in solution by the action of zinc on α-bromomesitylacetyl bromide. However, attempts to isolate it yielded only the dimer.

An attempt to prepare 2,4,6-triethylphenylketene by the same method led to similar results. The ketene could not be isolated. However, when water was added to the solution the hydration product of the ketene, 2,4,6-triethylphenylacetic acid, was formed.

An attempt to prepare mesitylketene from mesitoyldiazomethane likewise gave only the hydration product, mesitylacetic acid. Similar results were obtained in attempts to prepare 2,4,6-triisopropylphenylketene.

(4) Kohler and Richtmyer, THIS JOURNAL, **52**, 3736 (1930).

(5) Fuson, Corse and McKeever, *ibid.*, **62**, 3250 (1940); Fuson, Byers and Rabjohn, *ibid.*, **63**, 2639 (1941).

(6) Barnes, Cooper, Tulane and Delaney, *J. Org. Chem.*, **8**, 153 (1943).

Experimental

α-Bromomesitylacetyl Bromide.—A mixture of 50 g. of mesitylglycolic acid[7] and 30 cc. of phosphorus tribromide was heated on the steam-bath for six hours. The lower layer was removed and distilled *in vacuo;* b. p. 138–139° (9 mm.); yield 65%.

Mesitylketene Dimer.—A solution of 26 g. of α-bromomesitylacetyl bromide in 50 cc. of absolute ether was added rapidly, with stirring, to a suspension of 15 g. of granulated zinc in 150 cc. of boiling absolute ether. The mixture was boiled for thirty minutes. The zinc bromide was precipitated from the yellow solution by the addition of 700 cc. of low-boiling petroleum ether. The solution was filtered and the solvent evaporated rapidly. The ketene dimer was purified by recrystallization first from a chloroform–petroleum ether mixture and then from methanol. It formed colorless crystals, melting at 197–200°, which were insoluble in 5% sodium hydroxide solution and in 5% hydrochloric acid.

Anal.[8] Calcd. for $C_{22}H_{24}O_2$: C, 82.48; H, 7.56; mol. wt., 320. Found: C, 82.36; H, 7.85; mol. wt. (ebullioscopic in chloroform), 325.

***trans*-1,2-Dimesitylvinyl Benzoate.**—A solution of mesitylketene was prepared according to the foregoing directions from 55 g. of α-bromomesitylacetyl bromide and 25 g. of zinc in 200 cc. of dry ether. After the reaction mixture had been heated under reflux for ten minutes, 800 cc. of low-boiling petroleum ether was added to precipitate the zinc bromide formed during the reaction. To the resulting solution was added a solution of mesitylmagnesium bromide prepared from 20 g. of bromomesitylene and 2.4 g. of magnesium in 50 cc. of dry ether. The reaction mixture was stirred for twenty minutes at room temperature. Twenty cubic centimeters of benzoyl chloride was then added, and stirring was continued for an hour at room temperature. The solution was filtered and shaken with 200 cc. of 5% sodium hydroxide solution and 20 cc. of alcohol to remove the excess benzoyl chloride. The ether–petroleum ether layer was washed successively with water, 10% potassium bicarbonate solution and water. It was dried over calcium chloride, and most of the solvent was removed by evaporation. When allowed to stand overnight the solution deposited the benzoate in clusters of white needles. These were collected on a filter, washed with low-boiling petroleum ether and recrystallized from methanol; m. p. 147–148°; yield, 5 g.

Anal. Calcd. for $C_{27}H_{28}O_2$: C, 84.34; H, 7.34. Found: C, 84.09; H, 8.00.

The benzoate was insoluble in 5% sodium hydroxide solution and 5% hydrochloric acid. Analysis in the Grignard machine[4] showed the absence of active hydrogen. When treated with copper acetate in ether the benzoate failed to yield a copper derivative.

Hydrolysis of the Benzoate.—One gram of the benzoate was dissolved in a solution made from 40 cc. of ethanol, 2 g. of sodium and 2 cc. of water. This solution was heated under reflux for two and one-half hours, cooled, diluted with an equal volume of water and extracted twice with ether. The ether solution was washed with water and dried over calcium chloride. Evaporation of the solvent left a solid residue. It was recrystallized from a mixture of methanol and water; m. p. 91–92°; yield 0.5 g. A mixture with an authentic specimen of desoxymesitoin showed no lowering of the melting point.

Enolization of Desoxymesitoin.[9]—Desoxymesitoin yielded 0.96 mole of methane in the Grignard machine,[4] but when the reaction mixture was treated with water the original ketone was recovered. Enolizing agents such as alcoholic alkali, sodium ethoxide and sodium amide likewise failed to produce a stable enol.

***cis*-1,2-Dimesitylvinyl Benzoate.**[9]—To the Grignard reagent, prepared from 0.7 g. of magnesium, 1.9 g. of ethyl

(7) Fuson, Emerson and Gray, THIS JOURNAL, [illegible] (1939).

(8) The microanalyses reported in this paper were carried out by Miss Theta Spoor and Miss Dorothy Schneider.

(9) This experiment was performed by Dr. Stanley P. Rowland.

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bromide and 20 cc. of dry ether, was added a solution of 2.3 g. of desoxymesitoin in 25 cc. of dry ether. The mixture was heated under reflux for one hour. An ether solution of 2 cc. of benzoyl chloride was added, and the refluxing continued for three hours. The decomposition of the mixture and the isolation of the product were conducted in the usual way. The benzoate was purified by recrystallization from methanol. It formed fine, white platelets melting at 104–105.5°.

Anal. Calcd. for $C_{27}H_{28}O_2$: C, 84.34; H, 7.34. Found: C, 84.31; H, 7.34.

cis-1,2-Dimesitylvinyl Acetate.[9]—The preceding synthesis was repeated, acetyl chloride being used in place of benzoyl chloride. The vinyl acetate boiled at 188–193° (4 mm.) and melted at 68–69°. It was purified by recrystallization from methanol.

Anal. Calcd. for $C_{22}H_{26}O_2$: C, 81.94; H, 8.12. Found: C, 81.91; H, 8.26.

Mesitylglyoxal Monohydrazone.—This compound was prepared by the procedure used by Nenitzescu and Solomonica[10] for the synthesis of the monohydrazone of benzil. A solution of hydrazine acetate, prepared from 54 g. of hydrazine sulfate and 77 g. of anhydrous sodium acetate in 250 cc. of water, was boiled for five minutes. The sodium sulfate was precipitated by the addition of 250 cc. of ethanol and removed by filtration. The hydrazine acetate solution was added rapidly from a dropping funnel to a warm solution of 58 g. of mesitylglyoxal in 100 cc. of ethanol. The mixture was heated for ten minutes under reflux. When cold it deposited the hydrazone in white crystals. The yield of crude product was 90%. The monohydrazone was purified by recrystallization from a mixture of ether and low-boiling petroleum ether; m. p. 129–131°.

Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.44; H, 7.42. Found: C, 69.40; H, 7.60.

Mesitoyldiazomethane.—A mixture of 5 g. of mesitylglyoxal monohydrazone and 6 g. of yellow mercuric oxide was added to a flask containing a mixture of 500 cc. of low-boiling petroleum ether, two drops of saturated alcoholic potassium hydroxide solution and 3 g. of finely ground calcium sulfate. The mixture was stirred for three hours at ice-bath temperatures. The solid material was removed by filtration and washed with a little ether. Evaporation of the solvent from the filtrate and washings left the diazomethane in yellow crystals. The yield of crude product was 75%. It crystallized from methanol in fine, yellow needles; m. p. 59–61°, with decomposition.

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.21; H, 6.43. Found: C, 70.36; H, 6.19.

In an attempt to prepare mesitylketene a solution of 5 g. of mesitoyldiazomethane in 50 cc. of dry benzene was dropped slowly into a 10-cc. modified Claisen flask placed in a metal bath held at 100–110°. After the benzene had been distilled nitrogen was passed in and the residue distilled *in vacuo*. No sharp fraction could be obtained; the material in the receiver was a yellow, resinous mass.

Mesitylacetic Acid.—One gram of mesitoyldiazomethane was treated for thirty minutes with 100 cc. of boiling water. The solution was allowed to cool, 3 g. of potassium carbonate was added and the mixture extracted twice with ether. Acidification of the carbonate solution yielded 0.3 g. of mesitylacetic acid; m. p. 165–166°.

2,4,6-Triethylphenylacetic Acid.—Thirty-five grams of 2,4,6-triethylphenylglycolic acid[5] was mixed with 15 cc. of phosphorus tribromide and the mixture allowed to stand overnight on the steam-bath. An additional 5 cc. of phosphorus tribromide was added and the heating continued for twelve hours. The organic layer was distilled *in vacuo*, yielding 27 g. of α-bromo-2,4,6-triethylphenylacetyl bromide; b. p. 140–142° (5 mm.).

A solution of 20 g. of α-bromo-2,4,6-triethylphenylacetyl bromide, 50 cc. of dry ethyl ether and 50 cc. of dry butyl ether was added dropwise, with stirring, to a mixture of 5 g. of granulated zinc and 30 cc. of dry ethyl ether. The addition required five minutes, and the mixture was stirred and warmed for ten minutes longer. During this time nitrogen was passed through the container. The zinc bromide was precipitated by the addition of 350 cc. of low-boiling petroleum ether. A solution of 5 cc. of water and 50 cc. of ether was added, and the reaction mixture was stirred for ten minutes. The zinc bromide and a considerable amount of sticky material was removed by filtration, and the filtrate was extracted with 5% sodium hydroxide solution. Acidification yielded the 2,4,6-triethylphenylacetic acid as an oil, which could be crystallized from dilute ethanol; m. p. 98°; yield 0.5 g. A mixed melting point with an authentic sample showed no lowering.

2,4,6-Triisopropylphenylglycolic Acid.—A mixture of 84 g. of selenium dioxide and 700 cc. of 95% ethanol was heated at 50° until the solid had dissolved. Methyl 2,4,6-triisopropylphenyl ketone (153 g.)[11] was added and the mixture heated under reflux, with stirring, for seven hours. The selenium was removed by filtration, and the solvent was distilled. The 2,4,6-triisopropylphenylglyoxal distilled at 138–143° (7.5 mm.). The yield was 77% of the theoretical.

A mixture of 95 g. of the glyoxal and 1 l. of 10% potassium hydroxide solution was heated on a steam-bath for twenty-four hours and acidified with hydrochloric acid. The 2,4,6-triisopropylphenylglycolic acid dissolved with difficulty in dilute potassium hydroxide solution. The solution was washed repeatedly with ether and acidified with hydrochloric acid. The glycolic acid was recrystallized twice from 66% acetic acid; m. p. 163–164° (cor.); yield 73%.

Anal. Calcd. for $C_{17}H_{26}O_3$: C, 73.34; H, 9.42. Found: C, 73.60; H, 9.62.

Methyl 2,4,6-Triisopropylphenylglycolate.—This ester was obtained in 65% yield by heating the acid for three hours with methanol which had been saturated previously with hydrogen chloride. It was recrystallized from ligroin; m. p. 94–95°.

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.93; H, 9.65. Found: C, 73.80; H, 9.73.

Saponification with aqueous alkali converted it to the original acid.

Dioxolone from 2,4,6-Triisopropylphenylglycolic Acid.—A mixture of 9 g. of the acid, 40 cc. of acetone and 2 cc. of concentrated sulfuric acid was stirred for thirty minutes at ice-bath temperatures. The dioxolone was obtained in beautiful, white crystals melting at 165–165.5°; yield 75%.

Anal. Calcd. for $C_{20}H_{30}O_3$: C, 75.43; H, 9.50. Found: C, 75.59; H, 9.82.

Treatment of the dioxolone with hydrazine hydrate converted it to the corresponding hydrazide. A solution of 1.5 g. of the dioxolone, 50 cc. of absolute ethanol and 2 g. of hydrazine hydrate was heated for four hours under reflux. The product was recrystallized from a ligroin–benzene solution (7:3). It formed white crystals melting at 156–157°.

Anal. Calcd. for $C_{17}H_{28}O_2N_2$: C, 69.82; H, 9.65; N, 9.58. Found: C, 70.22; H, 9.32; N, 9.85.

The Hydrazone of 2,4,6-Triisopropylphenylglyoxal.[12]—The procedure was similar to that given for the mesityl analog. From 62.4 g. of the glyoxal there was obtained 59 g. (90%) of the hydrazone, melting at 147–151°, with decomposition. It was recrystallized repeatedly from dilute ethanol. The hydrazone formed white cubes melting at 153–154°, with decomposition.

Anal. Calcd. for $C_{17}H_{26}N_2O$: C, 74.41; H, 9.55. Found: C, 74.38; H, 9.65.

2,4,6-Triisopropylphenylacetic Acid.—(a) A finely ground mixture of 7 g. of yellow mercuric oxide, 2.5 g. of

(10) Nenitzescu and Solomonica, "Org. Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 496.

(11) Fuson, Bottorff and Speck, THIS JOURNAL, 64, 1450 (1942).

(12) This compound was prepared by Dr. Quentin F. Soper.

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anhydrous calcium sulfate and 5 g. of the hydrazone of 2,4,6-triisopropylphenylglyoxal was covered with 75 cc. of dry ether and stirred for twelve hours at room temperature. The ether was decanted through a filter paper and the black residue washed by decantation with a total of 100 cc. of dry ether. Removal of the ether left the diazo compound as a yellow powder, which decomposed explosively at 125°. After recrystallization from methanol it was found to decompose at 104°; yield 4.5 g.

It was covered with water and a pinch of silver oxide was added. The mixture was boiled for thirty minutes. Eight grams of potassium hydroxide pellets was added and the boiling continued for fifteen minutes. A solid was removed by filtration and recrystallized from ether. It formed pale yellow crystals melting at 204–205°. This substance was not identified. When the filtrate was acidified the 2,4,6-triisopropylphenylacetic acid was precipitated. It was recrystallized from 75% acetic acid and then from ligroin; m. p. 146–146.5°. A mixture with an authentic specimen of the acid (see below) showed no depression in melting point.

(b)[13] The hydrolysis of 2,4,6-triisopropylbenzyl cyanide could not be effected satisfactorily with 50–80% sulfuric acid. The method of Redemann and Lucas[14] for the saponification of esters, however, was found to be suitable. A mixture of 67 g. of the pure nitrile, 500 cc. of diethylene glycol, 100 g. of potassium hydroxide and 20 cc. of water was heated under reflux for twelve hours and poured into water. The 2,4,6-triisopropylphenylacetic acid, precipitated by acidification of the mixture, was recrystallized from aqueous ethanol; m. p. 144–145°; yield 85%.

Anal. Calcd. for $C_{17}H_{26}O_2$: C, 77.80; H, 9.99. Found: C, 78.08; H, 9.67.

Hydrolysis of the nitrile with potassium hydroxide and ethanol produced 2,4,6-triisopropylphenylacetamide. It was recrystallized from ethanol; m. p. 170–171°.

Anal. Calcd. for $C_{17}H_{27}NO$: C, 78.11; H, 10.41. Found: C, 78.15; H, 10.57.

2,4,6-Triisopropylbenzyl Cyanide.[11]—2,4,6-Triisopropylbenzyl chloride, prepared by the chloromethylation of 1,3,5-triisopropylbenzene,[15] was converted to the corresponding cyanide by treatment with cuprous cyanide. A mixture of 149 g. of the chloride, 57.8 g. of cuprous cyanide and 60 cc. of dry pyridine was heated at 210–220° for ninety minutes. When the mixture had cooled to 150° it was poured into a mixture of 500 g. of ice and 200 cc. of ammonium hydroxide. The mixture was allowed to stand overnight, and the crude nitrile was collected on a filter and distilled, b. p. 129–130° (4 mm.); m. p. 81–82°; yield 64%.

Anal. Calcd. for $C_{17}H_{25}N$: C, 83.89; H, 10.35. Found: C, 83.40; H, 10.26.

Summary

Methods of synthesis of hindered aldoketenes have been studied.

The *cis* and *trans* enol benzoates of desoxymesitoin have been prepared. Hydrolysis was found to convert them to desoxymesitoin, showing that the *cis* and *trans* enols of desoxymesitoin were unstable and ketonized rapidly. The corresponding *cis* and *trans* acetates were also prepared. These results confirm the conclusion reached earlier that the dehydration product of hydromesitoin or isohydromesitoin is 1,1-dimesitylvinyl alcohol.

(13) This preparation was carried out by Dr. M. L. Ward.

(14) Redemann and Lucas, *Ind. Eng. Chem., Anal. Ed.*, **9**, 521 (1937).

(15) Fuson, Horning, Ward, Rowland and Marsh, THIS JOURNAL, **64**, 30 (1942).

URBANA, ILLINOIS RECEIVED MARCH 13, 1944

The Relation of Estrogenic Activity to Structure in Some 4,4′-Dihydroxydiphenylmethanes[1]

BY E. EMMET REID AND EDITH WILSON[2]

Estrogenic activity has been noted by Dodds and Lawson[3] in some 4,4′-dihydroxydiphenylmethanes, $(HOC_6H_5)_2CRR'$. It seemed worthwhile to prepare a number of these to see how the estrogenic activity varies with the size and character of the groups R and R′. Two series have now been made: one, in which R is methyl and R′ varies from methyl to hexyl, and the other, in which R and R′ are identical and vary from methyl to amyl. Besides these several compounds of different types, including the double one, $(HOC_6H_4)_2C(CH_3)CH_2CH_2C(CH_3)(C_6H_4OH)_2$, from acetonyl-acetone have been studied. In order to have comparable estrogenic data, the known compounds have been prepared and tested along with the new. For better chemical characterization the benzoates of all of them have been prepared. The results are in Table I. The activities of the members of the second series are plotted in Fig. 1. When our work was nearly completed, an article by Campbell[4] covering part of the same ground appeared.

The activity reaches a peak in the first series with the methyl-propyl and in the second series a much higher peak at the propyl-propyl, which is ten times as potent as any of the others. The activities for ethyl-propyl and for propyl-butyl are borrowed from Campbell. For comparison the data for the corresponding *trans*-4,4′-dihydroxy-α,β-dialkylstilbenes[5] are plotted in Fig. 1, but they are in rat units per milligram while ours are in the same units per gram. The ethylene derivatives are around a thousand times as active as the methane derivatives, yet the shapes of the two curves are strikingly alike except that the maximum is at the ethyl-ethyl in the one and at the propyl-propyl in the other. The rise is gradual through the methyl-ethyl in the one and through the ethyl-propyl in the other. In both

(1) Original manuscript received October 20, 1942.

(2) Present address: Biochemical Research Foundation, Newark, Del.

(3) Dodds and Lawson, *Proc. Roy. Soc.* (London), **B125**, 222 (1938).

(4) N. R. Campbell, *ibid.*, **B129**, 528 (1940).

(5) Dodds, Goldberg, Lawson and Robinson, *ibid.*, (London), **B127**, 140 (1939).

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TABLE I

MELTING POINTS AND ACTIVITIES

R	R′	M. p., °C.	Rat u./g.	Benzoate m. p., °C.
Methyl	Methyl[3,6,7,8]	155	28	161
Methyl ethyl	[6,8,9,10,11]	124	80	143
Methyl	Propyl[6,8,10,11,12]	149	200	120
Methyl	Butyl[7]	Liq.	40[2]	72
Methyl	Amyl	101	35	118
Methyl	Hexyl	88	50	114
Methyl	*i*-Propyl	194	50	204
Methyl	*i*-Butyl[6,11]	153	200	116
Ethyl	Ethyl[6,10,12]	204	200	163
Propyl	Propyl[6,12]	154	2000	142
Butyl	Butyl[6]	170.5	20	129.5
Amyl	Amyl	148.5	10	94
c-Pentanone[6,8,11]		157	66	205
c-Hexanone[6,11,13,14]		184	50	198
4-Me-Hexanone[10,11,13]		179	200	149.5
Methyl	Phenyl[6,11,14,15]	188	0	150.5
Methyl	*p*-MeO phenyl	245	55	221
Benzyl	Benzyl[16]	193	0	223
$(CH_3C{\cdot}CH_2{\cdot})_2$[17]		302 d	200	247

the activities drop off sharply as soon as the maxima are passed. Symmetry seems to play an important part; the maxima are at ethyl-ethyl and propyl-propyl. So far as the same compounds are concerned our results agree well with those of Campbell except that our value for propyl-propyl is much higher.

The methyl-*i*-butyl is considerably more active than the methyl-*n*-butyl. A methyl group in the 4-position in the cyclohexanone derivative raises its activity, so does the *p*-methoxy group in the methyl-*p*-methoxyphenyl. The double compound from acetonyl-acetone shows as much activity as any except the propyl-propyl. This is remarkable considering its high molecular weight and low solubility.

The estrogenic activities were determined by Dr. Geschickter and Dr. Byrne by the standard method.

The melting points of the compounds of the two series show alternation, as do those of their benzoates.

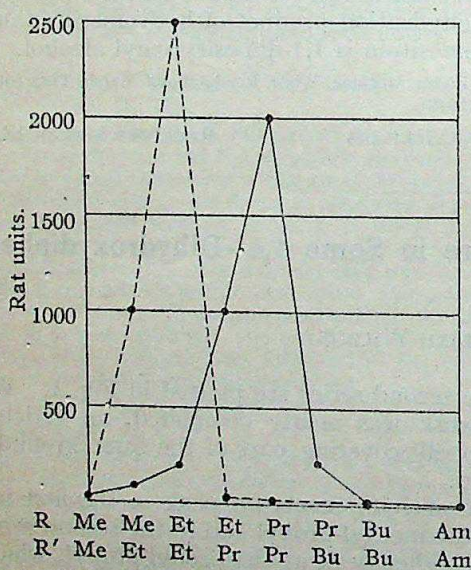

Fig. 1.—Estrogenic activity related to sizes of R and R′: —●——●—, rat u./g. $(HOC_6H_4)_2CRR'$; – –●– – – –●– –, rat u./mg. $HOC_6H_4CR{:}CR'C_6H_4OH$.

(6) Campbell gives m. p. of Bu-Bu 165°.
(7) Zincke, *Ann.*, **343**, 85 (1905).
(8) v. Braun, *ibid.*, **472**, 1 (1929).
(9) Zincke, *ibid.*, **362**, 205 (1908).
(10) Easson, Harrison, McSwiney and Pyman, *Quart. J. and Year Book of Pharmacy*, **7**, 509 (1934).
(11) McGreal, Niederl and Niederl, THIS JOURNAL, **61**, 345 (1939).
(12) Dianin, *J. Russ. Phys.-Chem. Soc.*, **28**, 488, 523, 601 (1891).
(13) Schmidlin and Lang, *Ber.*, **43**, 2806 (1910).
(14) I. G. Farbenind., German patent 467,728 (1927); [*Chem. Abs.*, **23**, 1729 (1929).]
(15) I. G. Farbenind., German patent 604,406 (1932); [*Chem. Abs.*, **29**, 855 (1935).]
(16) Zincke, *Ann.*, **363**, 255, 280 (1908).
(17) Amann and Fonrobert, U. S. patent 1,614,172 (1927); [*Chem. Abs.*, **21**, 805 (1927).]

Experimental

The method of preparation was the same for all. The ketone and three equivalents of phenol were put into a glass-stoppered bottle and concentrated hydrochloric acid equal to about one-fifth of the phenol added. The mixture stood, with occasional shaking, until the reaction seemed to be complete, which took from a day or two for the simpler ketones up to twenty weeks for some others. Hydrogen chloride was passed into the slow ones from time to time. The condensations went much faster if, instead of using aqueous hydrochloric acid, the ketone–phenol mixture was saturated with hydrogen chloride, but the products so obtained were harder to purify. The mixtures turned red in any case, but the purified compounds were colorless. The reaction product was poured into hot water, the unused reactants driven off with steam, and the residue filtered off or collected in ether according to its physical state. The yields were high, 90% or better, even with the higher ketones if they were given time enough. Acetic acid, chloroform, acetone and toluene were used as solvents. The low melting compounds were hard to purify as they tended to separate from solvents as liquids. Some could be obtained pure only by saponification of the recrystallized benzoates. The benzoates were made by the Schotten–Baumann method. All melting points were determined with the aid of a thermometer calibrated for 3-inch immersion. The analyses of new compounds are in Table II.

TABLE II

ANALYSES

R R′	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
Methyl amyl	80.28	79.41	8.45	8.51
Methyl hexyl[a]	80.54	78.50	8.72	8.64
Benzoate	80.61	79.91	6.77	6.53
Amyl amyl	81.17	80.98	9.41	9.50
Methyl *i*-propyl	79.69	79.53	7.81	7.99
4-Methyl-*c*-hexanone	81.13	81.10	7.47	8.02
Methyl *p*-MeO-phenyl	78.75	78.39	6.25	6.45
Benzyl benzyl	85.26	85.70	6.31	6.34
$(CH_3CCH_2—)_2$	79.19	79.30	6.60	6.79

[a] The low carbon is probably due to adsorbed water. On account of the low m. p. the compound was difficult to dry. The benzoate gave satisfactory figures.

Summary

A number of 4,4′-dihydroxy-diphenylmethanes, $(HOC_6H_4)_2CRR'$, have been prepared and their

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estrogenic activities determined in order to relate their activities to the size and character of the groups R and R′.

For characterization their benzoates have been made.

BALTIMORE, MD. RECEIVED MARCH 31, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MISSOURI]

Single Bond Energies. V. The Association of Ketyls

BY H. E. BENT AND A. J. HARRISON[1]

The compound formed by the addition of an alkali metal to an aromatic ketone is highly colored and by some investigators[1a] has been assigned the formula

$$R_2{=}C(\text{—}O\text{—}Na)\text{—}$$

although evidence has been advanced[2] to show that the compound should not be considered to be a free radical but is associated and should be represented as a pinacolate

$$\begin{aligned} R_2{=}C\text{—}O\text{—}Na \\ | \\ R_2{=}C\text{—}O\text{—}Na \end{aligned}$$

We have attacked this problem by the method used in studying hexaphenylethane and triphenylmethyl reported by Ziegler and Ewald.[3] They found that on diluting a solution of hexaphenylethane the deviations from Beer's law could be explained satisfactorily by assuming an equilibrium between the ethane and the free radical and also assuming only the free radical to be colored.

Benzophenone was chosen as the first compound to be studied since it is the simplest aromatic ketone. Fluorenone was chosen as the second compound due to the presence of a five-membered ring. Peculiarities in five-membered rings have been found in the acidity of very weak acids,[4,5] the dissociation of free radicals[6] and the addition of sodium to single bonds.[7]

A solution of the ketyl is prepared by shaking the ketone in ether solution with 0.6% sodium amalgam. A portion of this solution is used to rinse the apparatus, removing adsorbed water. Fresh solution is then poured into the cell in which the optical density is to be determined. In order to avoid the errors inherent in an analysis one sample is used for a whole series of measurements, dilution being accomplished by means of the apparatus shown in Fig. 1. This device is carefully calibrated to determine the amount of hold up in the annular space when a solution is poured through it. The total volume of ether is determined at the beginning of the experiment. This permits one to pour a known fraction of the solution through the dilution device and then to distill the ether back, condensing it in the solution which had been retained in the annular space, thus diluting the solution by a known fraction. Two or three dilutions may be carried out with one cell before the solution becomes too dilute to measure with precision. Another sample of the solution is removed and the sodium determined analytically.

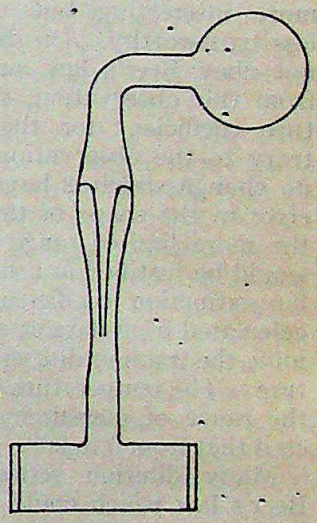

Fig. 1.—Dilution device. The solution is diluted without exposing to air by inverting the whole apparatus. A certain fraction of the liquid is retained in the annular space around the capillary. The apparatus is then returned to its original position without pouring solution back from the flask. On cooling the cell solvent distills from the flask back into the cell.

Measurements of the optical density were carried out with a spectrophotometer, previously described,[8] which illuminates the cell with monochromatic light and gives high precision. All cells were of Pyrex glass with fused plane glass windows mounted in Dewars.

The experimental results from the study of fluorenone indicate that it gives rise to a ketyl which obeys Beer's law within the accuracy of our experimental measurements. A series of measurements at room temperature gave ratios for the optical densities which agreed very closely with the values for the dilution ratio. In order to find evidence for association if possible at lower temperatures a series of dilutions were carried out, measurements being made at −112°, using solid carbon disulfide as the cooling agent. These measurements also showed close agreement with Beer's law. Since one would expect a temperature coefficient for the process of dissociation which would greatly increase the frac-

(1) Submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy at the University of Missouri. This paper was presented at the spring meeting of the American Chemical Society at Detroit in 1943.

(1a) Schlenk, *et al.*, *Ber.*, **44**, 1183 (1911); **46**, 2840 (1913); **47**, 473 (1914).

(2) Bachmann, THIS JOURNAL, **55**, 1179 (1933).

(3) Ziegler and Ewald, *Ann.*, **473**, 163 (1929).

(4) Conant and Wheland, THIS JOURNAL, **54**, 1212 (1932).

(5) McEwen, *ibid.*, **58**, 1124 (1936).

(6) Conant, *J. Chem. Phys.*, **1**, 427 (1933).

(7) Bent and Keevil, THIS JOURNAL, **58**, 1367 (1936).

(8) Jacobsohn, Bent and Harrison, *Rev. Sci. Inst.*, **11**, 220 (1940).

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tion dissociated at room temperature as compared with −112°, we may conclude that this compound exists essentially 100% in the form of a free radical at room temperature.

On lowering the temperature of a solution of this ketyl there is an increase in the molecular extinction coefficient which by itself might be taken as evidence for dissociation! The series of dilutions at the lower temperature, however, give no such evidence. Examination of the absorption curve indicates that the percentage change in the molecular extinction coefficient is not constant on lowering the temperature but depends upon the wave length, there being an increase in the maximum and a narrowing of the band. Hence one is not justified in taking the value of the molecular extinction coefficient at infinite dilution at one temperature and using this with values at other temperatures to calculate the fraction dissociated.

The results with benzophenone are perhaps more interesting but unfortunately somewhat less trustworthy. On dilution, the solution does not obey Beer's law and as one would predict from this observation, there is a large temperature coefficient for the optical density. Contrary to the observations on fluorenone there is no change which is larger than our experimental error in the shape of the absorption curve, over the more limited range of 20°. In this case we would be justified in using a value of the molecular extinction coefficient of the pure ketyl as calculated from data at one temperature to determine the fraction dissociated at another temperature. The temperature coefficient is so large that the range of measurement did not need to exceed that from 0 to 20°.

Many dilution series gave deviations from Beer's law which could not be explained by the simple assumptions made at the beginning of this paper. In practically every case the dilute solution was darker than could be accounted for by any experimental error or by the dissociation of the pinacolate into the free radical. We are inclined to believe that in these series some excess ketone was present, produced by hydrolysis, the ketyl reacting with minute traces of water firmly held on the glass apparatus even after evacuating and washing with ketyl solution. We have observed that the addition of ketone to the ketyl does destroy the blue color. If one assumes that an unstable compound is formed containing one molecule of ketone and two of ketyl, possibly forming a chelate ring, it is possible to account for our experimental data quantitatively. The possible presence of the disodium derivative of the ketone has been considered but can be ruled out by a consideration of the difference between the absorption curves for the mono- and the di-sodium derivatives. The strong maximum for the latter at a wave length of 510 is sufficiently far from the wave length used of 630 to permit one to say from a study of the latter curve that only an extremely small amount of the disodium derivative could have been present.

In some series of dilutions, especially those carried out with fresh solutions which had been in contact with the glass for too short a time to react with much water, the deviations from Beer's law could be quantitatively accounted for by a simple equilibrium between pinacolate and free radical. Using these runs alone values have been calculated for the equilibrium constant.

The results on the two ketyls mentioned above are not what one would predict from a consideration of the behavior of similar hydrocarbon free radicals. The relatively small association of triphenylmethyl as compared with phenylfluoryl indicates that the removal of two hydrogen atoms and the connection of two benzene rings by a carbon–carbon bond favors association. In the study of the ketyls described in this paper the effect is just the opposite.

The explanation of this apparent inconsistency is probably to be found in the assumption that phenylfluoryl has more resonance than triphenylmethyl. The converse has usually been assumed in accounting for phenylfluoryl being less stable as a free radical than triphenylmethyl.[9] If one considers the symmetry of the free radical alone one would be led to this conclusion. If on the other hand we assume that phenylfluoryl has more resonance, then we must also assume that the greater tendency to associate is due to a smaller amount of steric hindrance. This is in accord with the observation of Cline[10] that diphenyldifluoryl can be hydrogenated with much less ease than hexaphenylethane, indicating a smaller amount of steric hindrance in the undissociated molecule. The hydrogenation experiment gives an answer to the question of steric hindrance without the complication of resonance which appears in the process of dissociation to give a free radical.

The details of the way in which this extra resonance appears in the free radical phenylfluoryl have been suggested to one of the writers by R. W. Stoughton. It is evident from the illustration below that whereas the odd electron can appear on only alternate carbon atoms in triphenylmethyl, in phenylfluoryl the odd electron can appear on every carbon of the fluoryl group and hence we have a much larger number

(9) Pauling and Wheland, *J. Chem. Phys.*, **1**, 373 (1933), have concluded that one can give a reasonable explanation for a smaller amount of resonance in the fluoryl radical and thus explain the smaller amount of dissociation without recourse to steric hindrance. Muller and Janke, *Z. Elektrochem.*, **45**, 386 (1939), come to similar conclusions. No experimental data were available in 1933 to suggest the need of any other explanation. The data of Muller and Janke do not agree with ours on the two ketyls under consideration. Although it is true that Muller and Janke were working in more concentrated solutions it seems hardly likely that this would reverse the relative ease of dissociation of the two compounds.

(10) H. E. Bent and J. E. Cline, THIS JOURNAL, **58**, 1626 (1936).

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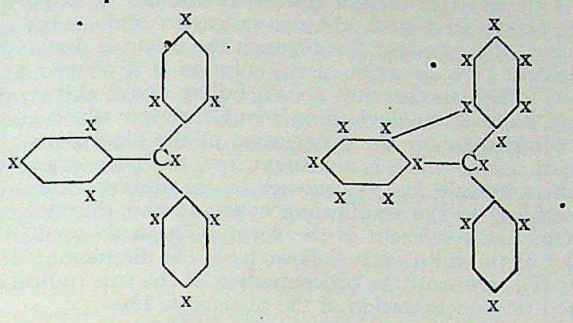
of resonating structures. A double bond appears between two rings in some cases.



We will now summarize the above discussion and then proceed to indicate the way in which our conclusions aid in understanding the peculiarities of five-membered rings referred to in the third paragraph of this paper. Our conclusions based upon evidence given above is that two phenyl groups attached to a single carbon differ in two important respects from the fluoryl group. In the first place the removal of two hydrogen atoms and the connection of the rings by a single bond produces a more compact group and reduces the probability of steric hindrance. In the second place the formation of a five-membered ring makes possible an increase in the stability of the group on account of the resonance resulting from an odd electron (or resulting from a free pair of electrons) taking up every position in each ring.[11]

As we will see, sometimes one and sometimes both factors are important in a given chemical reaction.

Taking up first a case where only steric hindrance is involved we consider the oxygenation of hexaphenylethane and diphenyldifluoryl. Resonance does not concern us in this reaction since the initial and final products are hydrocarbons involving no special resonance of the type found in free radicals. We would expect steric hindrance to weaken the carbon–carbon bond in the former compound more than in the latter and thus to cause more heat to be liberated in the former case than in the latter. The difference of 15 kcal. experimentally measured by Cline is in accord with this explanation.

An illustration involving chiefly resonance and little steric hindrance is that of the ketyls discussed in this paper. One cannot say with certainty that steric hindrance is of no importance but one would hardly expect it to be of great importance on account of the relatively small size of the O–Na group as compared with a benzene ring. If then resonance is of primary importance in determining the behavior of ketyls we would expect that the ketyl from benzophenone would dissociate slightly as compared with the ketyl derived from fluorenone. Experimentally, we have shown in this paper that this is the case, sodium fluorenone being entirely dissociated under conditions which give rise to only partial dissociation of sodium benzophenone.

Turning now to a case in which both factors are of significance we find an excellent illustration in the dissociation of hexaphenylethane and diphenyldifluoryl. We might expect that the greater steric hindrance in hexaphenylethane promoting dissociation would be offset by the greater resonance in phenylfluoryl. Actually we find that these two factors nearly compensate each other so that experimentally the difference is only about 8 kcal. as estimated by Conant,[6] leading to greater dissociation of hexaphenylethane. Subtracting this from the 15 kcal. difference for the heat of oxygenation gives 7 kcal. for the excess resonance of two phenylfluoryl radicals as compared with two triphenylmethyl radicals, or 3.5 kcal. for the difference between phenylfluoryl and triphenylmethyl.

A similar situation is to be found in the addition of sodium to hexaphenylethane and to diphenyldifluoryl. Here we might expect steric hindrance to favor the addition to the former compound and resonance to favor addition to the latter. Since steric hindrance is found to be more important than resonance in the case of simple dissociation, we might expect the same to be the case with the addition of sodium. Experimentally, Keevil[7] has shown that sodium adds more readily to the diphenyldifluoryl than to hexaphenylethane. This fact may be accounted for by bringing in the additional fact that in diethyl ether solution the sodium compounds are not dissociated into ions but exist as ion pairs. This indicates that the smaller ion will give rise to the more stable ion pair and hence sodium will react more readily with diphenyldifluoryl than with hexaphenylethane.[12]

Another way of expressing the same idea is to say that we are dealing here with a situation analogous to that described under hydrogenation. In the case of hydrogenation only steric hindrance was involved as no free radical was produced as a final product. Here, in the addition of sodium, we may be justified in saying that steric hindrance is of little if any significance compared with resonance which occurs in the negative ion. The reason for saying that steric hindrance may be of little or no importance here is that, although present in one molecule of the reactant it is also present in both molecules of the product and hence tends to cancel out.

Finally, a very striking example from the work of Conant and Wheland is to be found in the relative acid strengths of triphenylmethane and phenylfluorene. The essential reaction involved in those experiments is the substitution of a

(11) Resonance in an ion is to be treated in the same way as in the corresponding free radical as pointed out by Wheland, *J. Chem. Phys.*, 2, 479 (1934).

(12) One might expect to find a sodium to carbon distance which would determine the stability of the ion pair, but Kraus and Hawes have shown, THIS JOURNAL, 55, 2784 (1933), that this is not the case. Rather, it is the total size of the ion which determines the value of "a" of closest approach and hence the stability of the ion pair.

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proton by an alkali metal ion. The inference based upon the foregoing discussion would be that steric hindrance would not be a factor in the acid where the hydrogen atom is localized on a single carbon but that it would be a factor in the ion pair formed as the product of the reaction and that it would operate in the same direction as resonance rather than against it as in one of the earlier examples. Thus we would expect from both of these factors that phenylfluoryl would behave as though it were a stronger acid than triphenylmethane. Experimentally, Conant and Wheland[4] have shown that it behaves as though it were stronger by a factor of 10^7. A revision of this value by McEwen[5] in extending the work of Conant and Wheland increases the value from 10^7 to 10^{12}. This would correspond to a free energy value of about 15 kcal. This is in the direction one would expect from resonance but larger than would be predicted by resonance alone. At least part of this difference is doubtless due to smaller steric hindrance in the ion pair.

Experimental

Experimental precautions have been discussed in previous papers of this series dealing with similar procedures. A high vacuum technique was employed to avoid contamination with air or water vapor. The ketones were purified, the ethyl ether distilled from a solution of sodium fluorenone and decomposition of ether avoided during sealing off from the vacuum line by condensing the ether vapor. The solution of the ketyl is found to be quite stable, a sample having been kept for more than a year without appreciable decomposition or change in color; sunlight and temperatures of 40° produce no appreciable decomposition. Nevertheless we sometimes observed a decrease in the optical density of solutions during rather short intervals of time. We attribute this to small amounts of water liberated from the rather large surface of glass exposed to the solution during the dilution experiments.

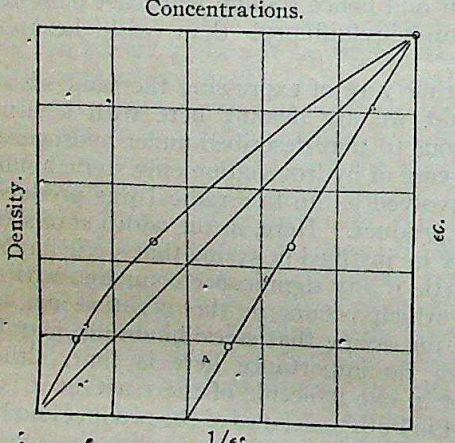

Fig. 2.—Deviations from Beer's law as shown by sodium benzophenone. Top curve is calculated from the equilibrium constant and the value of ϵ_∞. The points are experimental, only two of the three being required to evaluate K and ϵ_∞. Middle curve is what one would expect from Beer's law. Bottom curve is drawn through the experimental points, illustrating the way in which deviations from Beer's law can be expressed by a straight line. The triangles are for another series of measurements made on an older solution.

Typical experimental results on sodium benzophenone are shown in Fig. 2, the concentration scale being arbitrary. The straight line through the origin is drawn in to illustrate the behavior of the solution if it obeyed Beer's law. The experimental points, falling above this straight line, indicate the deviations from Beer's law which may be accounted for by the dissociation of the pinacolate. The third curve, which is a straight line, has been drawn to a different scale for convenience in calculating values proportional to the equilibrium constant and the molecular extinction coefficient of the ketyl. The scale used in the plot of the third curve follows from the discussion: If we let (R) represent the concentration of the free radical and (R_2) the concentration of the pinacolate then

$$K = (R)^2/(R_2) = \frac{2(\epsilon/\epsilon_\infty)^2 C}{1 - (\epsilon/\epsilon_\infty)}$$

in which C is the mole fraction of solute expressed as ketyl, ϵ_∞ is the molecular extinction coefficient of the pure free radical and ϵ is the apparent molecular extinction coefficient defined by the expression $\log I_0/I = \epsilon Cl$. I_0/I is the ratio of light intensities and l is the length of the cell expressed in centimeters. The ratio ϵ/ϵ_∞ gives the fraction of the material dissociated. The above expression for the equilibrium constant may be transformed into the more convenient expression

$$\frac{1}{\epsilon} = \frac{2\epsilon C}{\epsilon_\infty 2K} + \frac{1}{\epsilon_\infty}$$

which is the equation of a straight line if we plot the reciprocal of the apparent molecular extinction coefficient against the product of the molecular extinction coefficient and the concentration. The intercept gives the molecular extinction coefficient at infinite dilution and the slope gives, in combination with the intercept, the equilibrium constant. Actually, before we analyzed the solutions to determine the concentration we plotted the concentration, in arbitrary units, divided by the optical density against the optical density. The final analysis, giving the concentration, gives the appropriate factor for converting the equilibrium constant and the molecular extinction coefficient into absolute values.

The analysis of the solution was accomplished by extracting the ether solution with small portions of 0.5 N hydrochloric acid. This hydrolyzes the ketyl and gives an aqueous solution of sodium chloride. The method of McCance and Shipp[13] permits the determination of quantities of sodium of the order of 0.05 mg. Since we are dealing with very dilute solutions it seemed best to use a method capable of handling quantities of this order of magnitude. Subsequent experiments have shown our solutions to contain considerably larger quantities of sodium which would have made possible a more precise determination of the concentration. The optical density changes with time, but by standardizing the procedure and taking a measurement with the spectrophotometer one hour after the formation of the red color, results were obtained which indicate a possible accuracy of perhaps one or two per cent.

The results obtained with benzophenone, using only those series which give evidence by the straightness of the $1/\epsilon$ against ϵC plot that hydrolysis was unimportant, give values of K of $4 \pm 1 \times 10^{-5}$ and for ϵ_∞ of $7 \pm 2 \times 10^3$ when concentrations are converted into moles per liter. The calculation of the heat of the reaction may be carried out in a variety of ways, the most obvious of which is to calculate from dilutions at two temperatures two values of the equilibrium constant. This method gives results not too far out of line with the value reported below but probably is not as good a procedure as to take a solution of a given concentration quickly from the higher to the lower temperature. The possibility of reaction with water on the glass is minimized by this method and probably the results are more reliable. If one takes the change in

(13) McCance and Shipp, *Biochem. J.*, **25**, 449 (1931).

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optical density and calculates a value for the heat of the reaction assuming the associated material to be constant one obtains as a minimum value for the heat the quantity 3.3 ± 0.5 kcal. A still better method is to correct for the change in the concentration of the undissociated material using values for the equilibrium constant obtained from dilution experiments. This does not raise the value very much but leads us to report 4 ± 1 kcal. as the heat of the reaction. This value may be compared with 10 kcal. found by Ziegler and Ewald for the dissociation of hexaphenylethane.

Preliminary measurements on the sodium derivative of di-biphenyl ketone at 24 and 0° give no evidence of association at the lower temperature.

TABLE I

SODIUM FLUORENONE

Run	Temp., ° C.	Optical density	Relative concentration	Ratio of optical densities
1	20	0.4076	1[a]	
		.1716	0.429 ± 0.002	0.421
2	20	.1716	1	
		.0711	0.429	.414
3	20	.3148	1	
		.1354	0.429	.430
4	20	.3006	1	
		.1345	0.429	.447
	−112	.3751	1	
		(.3131 cor.)[b]		
		.1653	0.429	.441
		(.1379 cor.)		
5	20	.2832	1	
		.1224	0.429	.432
	−112	.3511	1	
		(.2940 cor.)		
		.1496	0.429	.426
		(.1250 cor.)		
		20° average	.429 ± 0.009	
		−112° average	.434 ± 0.008	

[a] Actual concentration 1.21 × 10^{-4} expressed as the mole fraction of the ketyl. Wave length 640 mμ. Cell length 1.4668 cm. [b] Values given in parentheses under runs 4 and 5 at −112 as "corrected" take into account the contraction of the ether on cooling from 20 to −112°. The increase in the corrected value over that found at 20° would suggest dissociation but this is not borne out by the dilution experiments. The difference is discussed in the text.

The data of Bent and Keevil[14] have been recalculated in order to obtain the value for the free energy of addition of sodium to benzophenone. As pointed out by them the existence of an appreciable amount of the ketyl in the form of the pinacolate will reduce the calculated value for the addition of sodium to the free radical. The change which we have found is scarcely of importance, the value being changed from −22.4 to −22.1 kcal., which is little more than the experimental error in the determination of Bent and Keevil.

Summary

The ketyl formed by treatment of fluorenone with sodium amalgam gives no evidence of associating to a pinacolate at either room temperature or −112°.

The shape of the absorption curve for sodium fluorenone is a function of temperature which rules out as a general procedure the using of a molecular extinction coefficient at one temperature in calculating with precision the fraction dissociated at another temperature.

Benzophenone forms a ketyl with sodium in ether solution which is associated at room temperature to a large extent to form a pinacolate. The dissociation constant for this reaction is found to be 4 ± 1 × 10^{-5} at 20°, concentrations being expressed as mole fractions.

Sodium benzophenone in ether solution has an apparent molecular extinction coefficient which decreases rapidly as the temperature is lowered. Combining such data with dilution experiments at 0° enables one to calculate a temperature coefficient for the dissociation constant and a corresponding heat of dissociation of 4 ± 1 kcal.

TABLE II

SODIUM BENZOPHENONE

Run	Temp., ° C.	Mole fraction expressed as ketyl[b] × 10^4	Optical density[a]	Fraction dissociated	Equilibrium constant × 10^5
1	20	0.540	0.9980	0.41	
		.168	.4553	.60	
		.052	.1896	.79	3
2	20	.320	.7498	.61	
		.0895	.2795	.83	
		.0254	.0943	.93	6
3	20	.400	1.694	.41	
		.1732	0.9679		3
		.154	.9017	.71	
		.067	.4567		5
	0	.396	1.326	.23	
		.1715	0.805		1
		.153	.754	.58	
		.066	.400		2

[a] The optical density was measured at a wave length of 630 mμ. The equilibrium constant is expressed as a mole fraction. The cell length in runs 1 and 2 was 0.6689 cm. and in run 3 was 1.4669 cm. [b] The concentration of the ketyl at the beginning of a run is based upon an analysis of the solution for sodium. The accuracy of the determination of sodium involves an error of probably not more than 5%. However, decomposition of ketyl before the first measurement of optical density and calculations of concentrations for some of the later runs from the optical density may involve an error in concentration of as much as 30%. Inasmuch as the value for the equilibrium constant is directly proportional to the value assumed for the concentration a corresponding error is present in the equilibrium constant. The relative values of the concentration, however, are known with an error of probably not more than 1%.

COLUMBIA, MISSOURI RECEIVED JANUARY 17, 1944

(14) H. E. Bent and N. B. Keevil, THIS JOURNAL, 58, 1368 (1936).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF ROCHESTER]

Photochemical Studies. XXXVII. Some Tests of Mechanism for the Photochemical Decomposition of Acetone

BY J. J. HOWLAND, JR.,[1] AND W. ALBERT NOYES, JR.

A study of the photochemical decomposition of acetone vapor was published several years ago.[2] Two important questions remain to be answered: (1) the importance of the decomposition of acetyl radical into methyl radical and carbon monoxide; (2) the homogeneity of this decomposition. Anderson and Rollefson[3] and Feldman, Ricci and Burton[4] as well as work in this Laboratory[5] have thrown much light on these important questions.

Spence and Wild[6] have published a discussion of earlier work[7] and have presented some new data. Comparisons were made between results obtained under different conditions, and some deductions made which may not have been justified.

It was claimed that the Herr and Noyes mechanism[2] explained the results only over a very narrow range of low intensities. The work herein presented was performed in an endeavor to answer some of the questions raised in the article of Spence and Wild.[6]

Herr and Noyes assumed a primary dissociation at all wave lengths whereas Spence and Wild assumed a primary dissociation only in the "continuum" below 2900 Å. The following steps have been proposed for the mechanism

(1)	$CH_3COCH_3 + h\nu = CH_3CO + CH_3$	ϕI_a
(2)	$CH_3CO = CH_3 + CO$	$b\phi I_a$
(3)	$CH_3CO = CH_3 + CO$	$k_2\ (CH_3CO)$
(4)	$2CH_3 + M = C_2H_6 + M$	$k_a\ (CH_3)^2\ (M)$
	walls	
(5)	$CH_3CO = 1/2(CH_3CO)_2$	$k_3\ (CH_3CO)/P$
(6)	$2CH_3CO + M = (CH_3CO)_2 + M$	$k_b\ (CH_3CO)^2\ (M)$
(7)	$2CH_3CO = (CH_3CO)_2$	$k_4\ (CH_3CO)^2$
(8)	$CH_3 + CH_3CO + M = CH_3COCH_3 + M$	$k_c\ (CH_3)(CH_3CO)\ (M)$
(9)	$CH_3CO + CH_3 = CH_3COCH_3$	$k_5\ (CH_3CO)(CH_3)$
(10)	$CH_3 + CH_3CO = C_2H_6 + CO$	$k_d\ (CH_3)(CH_3CO)$
(11)	$CH_3CO + M = CH_3 + CO + M$	$k_e\ (CH_3CO)\ (M)$
	walls	
(12)	$CH_3 = 1/2\ C_2H_6$	$k_6\ (CH_3)/P$

The Spence and Wild mechanism is based on equations 1, 4, 6, 8, 10 and 11 whereas the mechanism proposed by Herr and Noyes is based on 1, 2, 3, 5, 7, 9, and 12, although reaction 7 was not considered in deriving the rate equations.

Spence and Wild emphasize the following points: (1) At low intensities the ratio ethane/carbon monoxide in the reaction products approaches unity with increasing acetone pressure whereas in their experiments at very high intensities they found the ratio to rise with pressure. These effects are predicted if the exponents y and z are less than 0.5. (2) The Herr and Noyes mechanism does not account for the rise in the above ratio with increasing intensity. This can be explained by the introduction of reaction 6 or reaction 7, a suggestion made by Herr and Noyes.[2]

There is no evidence that reaction 10 is important under any conditions. In any case it is unnecessary since 3 has been clearly demonstrated.[3,4] Acetone was photolyzed in a flow system in which methyl radicals were removed by a lead mirror, and the remaining acetyl radicals passed through a section warmed to 45°.[4] New methyl radicals were produced as shown by the formation of $Pb(CH_3)_4$ at a second lead deposit.[4]

For wave lengths above 3000 Å. (the so-called "banded" region) Spence and Wild have proposed an elaborate scheme involving two kinds of excited acetone molecules

(13)	$CH_3COCH_3 + h\nu = CH_3COCH_3^*$	
(14)	$CH_3COCH_3^* = CH_3CO + CH_3$	$\tau = 10^{-8}$ sec.
(15)	$CH_3COCH_3^* + M = CH_3COCH_3^{**} + M$	
(16)	$CH_3COCH_3^{**} = CH_3COCH_3$	
(17)	$CH_3COCH_3^{**} = C_2H_6 + CO$	$\tau = 10^{-2}$ sec.
	walls	
(18)	$CH_3COCH_3^{**} = C_2H_6 + CO$	

This mechanism was based on the fact that apparent reduction in the mean distance from the positions of the absorbed quanta to the walls of the vessel causes a decrease in the ethane/carbon monoxide ratio. The authors also felt that results of the full mercury arc lamp could not be explained by adding the effects of the separate spectral regions. Thus the observed ratio rose to a maximum of 2 and then fell to 1.5 with increasing intensity whereas in the "continuum" alone it rose steadily toward a value of 2.5.

Spence and Wild also point out that the data of Herr and Noyes for 3130 Å. show no decrease in quantum yield of acetone disappearance with increasing intensity as was found to be true at 2537 Å. They conclude that a mechanism not involving free radicals was indicated for the "banded" region.

Spence and Wild believe that reaction 14 and the free radical reactions which follow are important only at low pressures whereas at higher pressures 15 predominates and ethane and carbon

(1) Fellow under the Sherman Clarke Fund for 1942–1943.
(2) D. S. Herr and W. Albert Noyes, Jr., THIS JOURNAL, 62, 2052 (1940).
(3) H. W. Anderson and G. K. Rollefson, *ibid.*, 63, 816 (1941).
(4) M. H. Feldman, J. E. Ricci and M. Burton, *J. Chem. Phys.*, 10, 618 (1942).
(5) J. J. Howland, Jr., and W. Albert Noyes, Jr., THIS JOURNAL, 63, 3401 (1941).
(6) R. Spence and W. Wild, *J. Chem. Soc.*, 590 (1941).
(7) R. Spence and W. Wild, *ibid.*, 352 (1937).

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monoxide would be formed by 17 or 18. These last two reactions are theoretically improbable.[8]

There is no sound basis for believing that there is a difference in primary process as the wave length is changed. The so-called "continuum" below 3000 Å. and the diffuseness of the bands above 3000 Å. may be explained in the first case as a great deal of overlapping of structure[9] and in the second case possibly by predissociation.[10]

A major objection to the mechanism embodied in reactions 13 to 18 is its inability to explain the rise of the quantum yields to unity as the temperature is raised to 100°.[2] Only a small rise of absorption coefficient is observed experimentally up to this temperature and hence pronounced absorption from higher levels in the ground state can scarcely be the correct explanation.

The present paper presents results designed to test the various mechanisms more thoroughly since the quantum yields as well as the ratio of the gaseous products have been determined. At short wave lengths and high intensities the mechanism of Spence and Wild predicts a rise in biacetyl yield and a fall of carbon monoxide yield. For long wave lengths their mechanism predicts a decrease in biacetyl with decrease in cell size at constant intensity. Also a smaller cell should cause the yield of acetone decomposed to rise. The mechanism of Herr and Noyes leads to the opposite conclusion in the first two instances and to a rise in acetone yield for a smaller cell at all wave lengths. Also the mechanism of Herr and Noyes leads to little change with wave length except that b in equation 2 should increase with decrease in wave length, leading to higher yields of everything except biacetyl.

Experimental Procedure

The apparatus used was nearly identical with that of previous work in this Laboratory[2,5] using the Manning[10] gas analysis technique. Merck reagent acetone was redistilled three times, dried with anhydrous calcium sulfate and then distilled at room temperature into a blackened trap which was kept at −78°. A Hanovia Uviarc mercury lamp was the source of radiation. Filters of cobalt and nickel sulfates and of potassium biphthalate gave very pure 3130 Å. light. With this light the absorption by acetone obeyed Beer's law within the experimental error of 1–2%. For the shorter wave lengths, the biphthalate filter was replaced by one of chlorine gas. The latter combination transmitted all the lines from 2320 to 2804 Å. in significant intensities.

A series of photographs of the spectrum of the mercury arc were made with and without the filters to determine their transmission for the various lines. Lines on the plates were matched at densities where the reciprocity law is approximately valid. Then from the known distribution of the intensity throughout the lines of the arc[11] and the absorption coefficients of acetone,[12] the percentage absorption was calculated at both 57 and 160 mm. pressure. The calculated percentages agreed with those measured by the photoelectric cell within 1%. The calculations also showed that the 2537 and 2654 Å. lines account for 68% of the incident light, and 83% of it is between 2480 and 2700 Å. It will be referred to as 25–2700 Å.

The polychromatic nature of this light discredits any conclusion drawn from the apparent variations in the quantum yields with pressure or cell size. Beer's law failed even for small percentages of absorption. This filter system was also used by Spence and Wild and was the only combination which made possible the high intensities at which they found the pressure effect reversal. Light intensity was measured by a plane quartz window photoelectric cell which was calibrated both by means of a uranyl oxalate actinometer[13] and by runs on acetone at 100° where the quantum yields are believed to be unity.[2] The observed light absorption was corrected for reflections back into the reaction vessel from its rear window and from the window of the photoelectric cell. Since for light of 3130 Å. each window reflects 7.3% of the light incident upon it, and the transmission of the 1.5-mm. rear window is about 0.88,[14] the true absorption is

$$I_a = I_a' + 0.129 I_t I_a'/I_0$$

where I_0 is the intensity at the rear of the front window, I_t is the intensity at the front of the rear window, and $I_a' = I_0 - I_t$. At 25–2700 Å.

$$I_a = I_a' + 0.138 I_t I_a'/I_0$$

The correction for loss at the rear window was incorporated into the photoelectric cell calibration.

One of the cylindrical quartz vessels was 2.35 cm. inside diameter × 20 cm. long; the second was 2.2 cm. × 1.00 cm. Their respective volumes were 87 cc. and 3.80 cc.

Assuming that carbon monoxide, ethane, and biacetyl are the only products, the yields of acetone decomposed were calculated by the relation

$$N_{CH_3COCH_3} = 2N_{C_2H_6} - N_{CO}$$

and those of biacetyl formed by

$$N_{(CH_3CO)_2} = N_{C_2H_6} - N_{CO}$$

TABLE I

EFFECT OF PRESSURE ON QUANTUM YIELDS

T = 27°; wave length, 3130 Å.; I_a, 3 × 10^{12} quanta/cc./sec.

P	$N_{C_2H_6}/N_{CO}$	Quantum yields: CO formation	C_2H_6 formation	Biacetyl formation	Acetone decomposition
54	2.02	0.089	0.180	0.091	0.271
82	1.61	.099	.159	.060	.219
121	1.34	.106	.142	.036	.178
203	1.12	.125	.140	.015	.155

T = 27°; wave length, 25–2700 Å.; I_a = 1.2 × 10^{12} quanta/cc./sec.

52	1.46	.268	.391	.123	.514
82	1.44	.261	.376	.115	.491
118	1.40	.250	.350	.100	.450
158	1.40	.244	.342	.098	.440

T = 27°; wave length, 25–2700 Å.; I_a = 1.2 × 10^{12} quanta/cc./sec.

57	1.76	.240	.423	.183	.606
82	1.52	.240	.363	.125	.490
116	1.42	.228	.324	.096	.420
160	1.39	.211	.293	.082	.375

(8) I. P. Howe and W. Albert Noyes, Jr., THIS JOURNAL, **58**, 1404 (1936).

(9) E. J. Bowen and H. W. Thompson, *Nature*, **133**, 571 (1934).

(10) W. M. Manning, THIS JOURNAL, **56**, 2589 (1934).

(11) Bulletin No. 112, General Electric Vapor Lamp Company, Hoboken, N. J., p. 2.

(12) C. W. Porter and C. Iddings, THIS JOURNAL, **48**, 40 (1926).

(13) P. A. Leighton and G. S. Forbes, *ibid.*, **52**, 3139 (1930).

(14) W. Albert Noyes, Jr., and P. A. Leighton, "Photochemistry of Gases," Reinhold Publishing Corporation, New York, N. Y., 1941, pp. 80, 84.

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TABLE II

EXPERIMENTS IN SMALL REACTION VESSEL, T = 27°; WAVE LENGTH, 3130 Å.

			Quantum yields			
I_a	P	$N_{C_2H_6}/N_{CO}$	CO formation	C_2H_6 formation	Biacetyl formation	Acetone decomposition
2.76	53	1.95	0.100	0.195	0.095	0.290
3.19	215	1.38	.098	.136	.038	.174
		T = 27°; wave length, 25-2700 Å.				
4.03	53	1.60	.236	.378	.142	.520
4.42	214	1.39	.220	.306	.086	.392
24.7	53	1.99	.222	.442	.220	.662
23.9	214	1.58	.206	.326	.120	.446

Results and Discussion

In order to make comparisons of the two reaction cells, some data are given in the form of tables. Other results are shown graphically only. Since the variation of quantum yields and of C_2H_6/CO ratio with pressure at 3130 Å. are nearly identical with those of the earlier work at about a five-fold lower intensity, they are not plotted here.

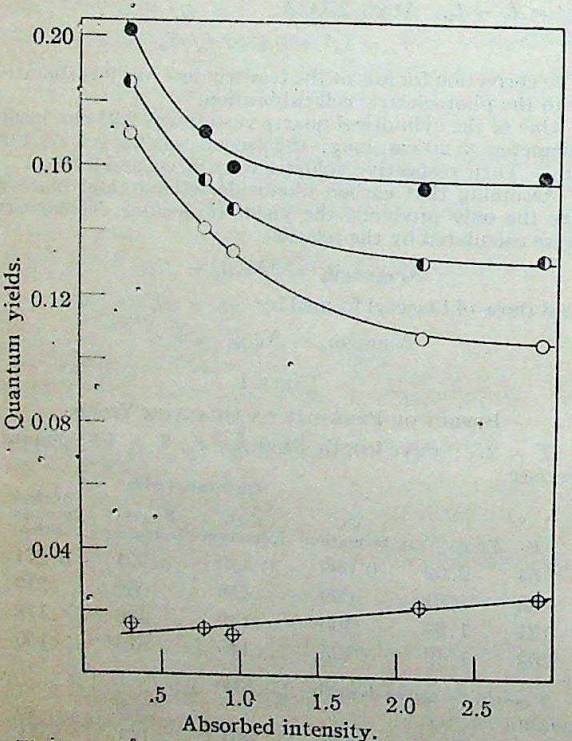

Fig. 1.—Effect of intensity on quantum yields: pressure, 120 mm.; wave length, 3130 Å.; O, carbon monoxide; ◐, ethane; -⊕-, biacetyl; ●, acetone.

It is apparent that the quantum yield of acetone decomposition does fall off with increasing intensity even at 3130 Å. A higher pressure was selected than in the earlier[2] runs in order that the reactions of excited acetone molecules should have predominated if the Spence and Wild mechanism were correct.

The experiments using the smaller reaction cell and 3130 Å. show the reverse of the effect previously reported.[6] In that comparison, however, use was made of three different sets of data, two by the authors, four years apart, and with different analytical methods, and the third by Herr and Noyes.[2] Unfortunately, the mean distance from points of absorption of quanta to the walls in the work of Herr and Noyes was taken as 1 cm., the estimate given by the authors.[2] To be consistent with the mean distances used for the other two vessels, the mean shortest distance of 0.4 cm. ($^1/_3$ of the radius) should lie between the 0.6 and the 0.25 cm. used for the other cells. In the data of Spence and Wild the rise in ethane/carbon monoxide ratio with this mean distance at constant intensity is only from 1.05 to 1.2. The results in the larger cells scatter badly, one value being 0.89.

Although the light intensity in the "continuum" was well into the range where the rise in C_2H_6/CO ratio was reported, the opposite effect was found. The older results for about the same light intensity are given in Table III. Their units of I_a are cc. × 10^5 of acetone decomposed/hr./cc. 100 of these units equals 12 × 10^{12} quanta/cc./sec. Their effect is not great except for the run at 32 mm.

TABLE III

RESULTS OF SPENCE AND WILD[5,6]

P, mm.	I_a	$N_{C_2H_6}/N_{CO}$
70	83.9	1.94
70	100.8	1.92
160	95.4	2.18
32	51.5	1.62
160	43.5	2.23

The drop in the yield of carbon monoxide with increasing pressure in the "continuum" favors the use of reaction (5). However, the apparent variation in quantum yields when using such polychromatic light should be viewed with suspicion. The combination of weaker absorption of acetone and greater sensitivity of the photoelectric cell at shorter wave lengths would be expected to cause an apparent drop in quantum yields with increased pressure (greater percentage absorption), since the increased absorption is actually less than measured and less than calculated by Beer's law.

The use of the smaller cell at 3130 Å. showed a slight increase in the yield of acetone decomposed as predicted by both mechanisms.

To attempt to explain satisfactorily results for an unfiltered arc is a nearly impossible and perhaps useless undertaking. Spence and Wild suggest that the fall in the C_2H_6/CO ratio with intensity increase at very high intensities is due to a reaction between excited acetone molecules resulting from absorption in the "banded" region and acetyl radicals produced by light of the shorter wave lengths.

(19) $CH_3COCH_3^* + CH_3CO = CH_3COCH_3 + CH_3 + CO$

They felt this to be necessary also because the

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ratio C_2H_6/CO was too much lower than for the case of "continuum" light only.

It should be pointed out that most of the drop in C_2H_6/CO ratio with increasing intensity occurs at intensities not attainable with filtered light. It is possible that the same effect would take place with "continuum" light of sufficiently high intensity.

The general conclusion from the present study is that there is no evidence which definitely indicates that the decomposition by light of 3130 Å. is anything but a free radical reaction, just as for shorter wave lengths. In the "continuum" region, either of the two mechanisms is satisfactory as far as its ability to explain the known facts is concerned. The scheme of Spence and Wild is more cumbersome in that it requires an additional step which can also be objected to on theoretical grounds. One test which might have decided between the two free radical mechanisms, the variation of the yield of CO with pressure at high intensity, was inconclusive because of the polychromatic nature of the light. The generally higher C_2H_6/CO ratios as a result of decreasing the reaction cell size, while not very pronounced, favor the use of a wall process for biacetyl formation as opposed to the supposition of pressure dependence for the decomposition of acetyl radical. One of those alternatives is sufficient to explain the general pressure effects.

Summary

1. The quantum yield of acetone decomposition falls off with increasing intensity at 3130 Å. just as it does around 2500 Å.

2. With all other conditions and techniques held constant, a decrease in the reaction cell size causes a rise in the C_2H_6/CO ratio regardless of the choice of intensity, pressure, and wave length.

3. The reported increase in the C_2H_6/CO ratio with increasing pressure at high intensity was not confirmed. The reverse effect resulted for all intensities.

4. Our previously modified mechanism is found to be adequate for correlation of the definitely established facts. Particularly, the use of reactions of excited acetone molecules at 3130 Å. seems unnecessary.

ROCHESTER, NEW YORK RECEIVED NOVEMBER 16, 1943

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

The Ionization Constants of Very Weak Acids. Acetoxime, Methyl Ethyl and Diethyl Ketoximes

BY CECIL V. KING AND ALEXANDER P. MARION

Difficulty has always been encountered in determining the ionization constants of very weak acids or bases. The conductance method fails when ionization is so small that conductance of water and its normal impurities become comparatively large, and the interpretation of conductivity in buffered solutions is uncertain. Hydrogen or other electrode measurements are useful in special cases, but usually only with very careful planning and interpretation. Rate measurements in which hydrogen or hydroxyl ion concentrations are determined from their catalytic effect on a suitable reaction have been often used. This method is capable of considerable refinement, and while not as accurate in general as other methods for the ordinary weak electrolytes, may be the best available for exceedingly weak ones. In the past salt effects have generally been ignored or inadequately treated. The purpose of the present work was to develop a method for determining acid dissociation constants of the order of 10^{-12} to 10^{-13} as a function of ionic strength with a reasonable degree of precision.

The Method.—A solution of acetoxime, unless in exceptionally pure water, would have an indefinite hydrogen ion concentration because the ionization is so small. A reaction sufficiently sensitive to hydrogen ion to be used in buffered solutions would probably be sensitive to general acid catalysis. The best procedure in such a case is to add the weak acid to a solution of strong base, and measure the extent of neutralization by means of a reaction only moderately sensitive to hydroxyl ion. From the rates the "hydrolysis constant" of the salt may be calculated.

For this purpose the catalyzed decomposition of nitrosotriacetonamine was chosen. The reaction has been studied in some detail by Francis and his co-workers,[1] by Brönsted and King[2] and by Kilpatrick.[3] The hydroxyl ion determination was first standardized by using solutions of sodium hydroxide, with sodium chloride to make up the ionic strengths desired. The previous work indicates that anions of even exceedingly weak acids do not catalyze the reaction, and the present work confirms this. The assumption is also made that in the specific salt effect, differences due to chloride, hydroxyl and weak acid anions are negligible.

(1) Francis, *et al.*, *J. Chem. Soc.*, **101**, 2358 (1912); **103**, 1722 (1913); **107**, 1651 (1915).

(2) Brönsted and King, THIS JOURNAL, **47**, 2523 (1925).

(3) Kilpatrick, *ibid.*, **48**, 2091 (1926).

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Experimental

Eastman Kodak nitrosotriacetonamine, acetoxime and methyl ethyl ketoxime were used without further treatment (samples of the oximes redistilled before use gave no appreciable difference in rate). Diethyl ketoxime was prepared from diethyl ketone and hydroxylamine as described by Scholl.[4] The product was distilled under reduced pressure several times and finally the portion boiling at 75° at 15 mm. was retained. Various samples prepared in this way gave good agreement.

Fresh stock solutions of the oximes were prepared frequently by direct weighing into a volumetric flask, followed by addition of carbon dioxide-free water. Carbonate-free sodium hydroxide, kept in paraffin-lined bottles, was used throughout. Reagent grade sodium chloride was used and either weighed directly for experiments or made into stock solutions.

The rates were measured in an apparatus similar to that previously described.[2] In each experiment 60 cc. of solution was used, with 66 mg. of nitrosotriacetonamine (0.006 *M*). The thermostat was maintained at 24.9°. The first order rate constants were mostly evaluated as described by Guggenheim,[5] either graphically or by the least squares method.

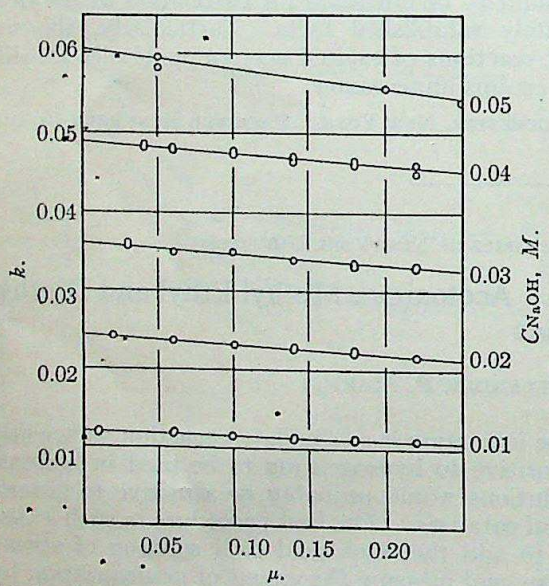

Fig. 1.—Salt effect (NaCl) in the catalytic decomposition of nitrosotriacetonamine.

The rate constants obtained in the standardization (*i. e.*, in solutions of sodium hydroxide and sodium chloride alone, $kt = 2.3 \log C_0/C$) are shown graphically in Fig. 1. The salt effect in this type of reaction is small and linear with ionic strength, and the straight lines represent the least square equations calculated from the experimental points

$$0.01\ M\ \text{NaOH}\quad k = 0.0120 - 0.0049\,\mu$$
$$.02\ M\ \text{NaOH}\quad k = .0243 - .0118\,\mu$$
$$.03\ M\ \text{NaOH}\quad k = .0360 - .0137\,\mu$$
$$.04\ M\ \text{NaOH}\quad k = .0488 - .0152\,\mu$$

The greatest deviation from these equations shown by any one experiment was 1.4%. Averaging the coefficients (divided by sodium hydroxide concentration) the general equation is obtained

$$k = (1.209 - 0.479\,\mu)C_{OH^-} \qquad (1)$$

which represents the rate satisfactorily in any solution used. The maximum deviation from the proceeding equations is 3% with 0.02 and 0.04 *M* sodium hydroxide at 0.22 ionic strength. In other solutions the divergence is 1% or less.

In Fig. 1 the straight line for 0.05 *M* sodium hydroxide represents equation (1) for this concentration, the circles a few check experiments made at a later date. In all succeeding work, equation (1) was used to calculate the hydroxyl ion concentration in any experiment.

The neutralization of a very weak acid by a strong base may be represented by the equation

$$HA + OH^- \rightleftarrows H_2O + A^-$$

The amount of hydroxyl ion which disappears may be taken as a measure of the amount of anion formed, and the unneutralized acid remaining can be found by difference. The "hydrolysis constant" of the salt (or its reciprocal) can then be calculated

$$1/K_h = K_{HA}/K_w = C_{A^-}/C_{OH^-}C_{HA} \qquad (2)$$

and if the water constant is known the dissociation constant K_{HA} follows. If K_{HA} is determined at various ionic strengths, suitable extrapolation will give K^0_{HA}, the true thermodynamic dissociation constant.

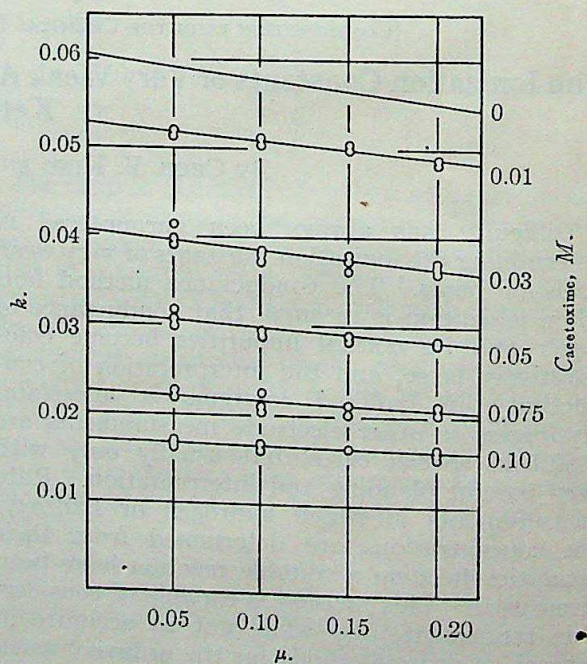

Fig. 2.—The effect of acetoxime and sodium chloride on the rate in 0.05 *M* sodium hydroxide.

The rate constants obtained for 0.05 *M* sodium hydroxide with various acetoxime concentrations are shown in Fig. 2. If dissociation constants are calculated from individual rate constants, the values vary widely—differences of 2% in rate constants lead to differences of approximately 20% in dissociation constants. In order to analyze the hundreds of experimental values obtained, each series was first plotted as in Fig. 2

(4) Scholl, *Ber.*, **21**, 509 (1888).
(5) Guggenheim, *Phil. Mag.* [7] **2**, 538 (1926).

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and since the salt effect is, within experimental error, linear, what seemed to be the best straight line was drawn through the points. A few values falling 3% or more from these lines were discarded and a linear equation was calculated, by the method of least squares, for each concentration. Later all results with 0.01 *M* oxime were discarded, since the small degree of neutralization leads to large errors in K_{HA}.

All the least square equations retained are given in Table I. From these values and equation (1), hydroxyl ion concentrations were calculated for ionic strengths 0, 0.05, 0.10, 0.15 and 0.20 (the first being, of course, a hypothetical value); and K_{HA}/K_w calculated from equation (2). The complete set of values for acetoxime and average values for the other oximes are given in Table II.

TABLE I

SALT EFFECT ON THE DECOMPOSITION OF NITROSOTRIACETONAMINE IN SODIUM HYDROXIDE–OXIME SOLUTIONS AT 24.9°

C_{NaOH}	C_{oxime}	k
	Acetoxime	
0.01	0.03	0.00604 − 0.00358 μ
	.05	.00444 − .00231 μ
	.075	.00331 − .00150 μ
	.10	.00270 − .00227 μ
.03	.03	.0215 − .00848 μ
	.05	.0164 − .00791 μ
	.075	.0118 − .00562 μ
	.10	.00900 − .00355 μ
.05	.03	.0402 − .0184 μ
	.05	.0315 − .0172 μ
	.075	.0228 − .0121 μ
	.10	.0169 − .00320 μ
	Methyl Ethyl Ketoxime	
.01	.03	.00538 − .00045 μ
	.05	.00455 − .00158 μ
	.075	.00347 − .00474 μ
.03	.03	.0219 − .0102 μ
	.05	.0169 − .00644 μ
	.075	.0121 − .00328 μ
	.10	.01055 − .00729 μ
.05	.03	.0414 − .0230 μ
	.05	.0327 − .0173 μ
	.075	.0246 − .0141 μ
	.10	.0199 − .0127 μ
	Diethyl Ketoxime	
.01	.03	.00685 − .00409 μ
.03	.03	.0234 − .0100 μ
	.05	.0195 − .0106 μ
	.075	.0143 − .00596 μ
	.10	.0130 − .0147 μ
.05	.03	.0430 − .0212 μ
	.05	.0359 − .0215 μ
	.075	.0281 − .00600 μ

Although both K_{HA} and K_w vary exponentially with ionic strength, the ratio of the two shows only a small linear variation as is to be expected for weak electrolytes of the same valence type. Least square equations for average values of the ratio, valid at least to $\mu = 0.22$, are given in Table II.

TABLE II

THE RATIO K_{HA}/K_w FOR ACETOXIME AT VARIOUS IONIC STRENGTHS

C_{NaOH}	C_{oxime}	K_{HA}/K_w 0	0.05	0.10	0.15	0.20
0.05	0.03	38.3	38.7	39.4	40.2	40.9
	.05	35.6	35.6	37.2	38.1	39.1
	.075	37.7	38.0	38.6	39.1	39.7
	.10	40.5	39.5	38.9	38.1	37.4
0.03	.03	38.5	38.2	38.3	38.2	38.1
	.05	36.3	36.3	36.8	37.1	37.5
	.075	38.3	38.2	38.7	38.9	39.2
	.10	39.4	39.1	39.2	39.1	39.1
0.01	.03	40.3	40.9	41.9	42.9	44.0
	.05	39.7	39.8	40.3	40.7	41.2
	.075	39.4	39.3	39.5	39.6	39.8
	.10	38.0	38.8	40.2	41.4	42.9
Average, acetoxime		38.5	38.5	39.1	39.5	39.9
	$K_{HA} = K_w (38.3 + 7.6\,\mu)$					
Methyl ethyl		35.6	35.7	36.4	37.0	37.7
	$K_{HA} = K_w (35.4 + 11.0\,\mu)$					
Diethyl		25.4	25.9	26.5	27.0	27.7
	$K_{HA} = K_w (25.4 + 11.4\,\mu)$					

Rather than express K_{HA} as a semi-empirical function of ionic strength it seems more useful to calculate values of K_w from the data of Harned and Mannweiler[6] for sodium chloride solutions and tabulate corresponding values of K_{HA}. This is done in Table III. Although the values of K_w are given in terms of molalities ($m_H m_{OH}$) the deviation from molarities is very small up to 0.22 ionic strength.

TABLE III

IONIZATION CONSTANTS OF THE THREE KETOXIMES AS A FUNCTION OF IONIC STRENGTH AT 24.9°

μ	$K_w \times 10^{14}$	$K_{HA} \times 10^{13}$ Acetoxime	Methyl ethyl ketoxime	Diethyl ketoxime
0	1.00	3.83	3.54	2.54
0.01	1.22	4.68	4.33	3.11
.05	1.48	5.72	5.32	3.84
.10	1.63	6.37	5.95	4.33
.15	1.73	6.82	6.41	4.69
.20	1.80	7.17	6.77	4.98

No previous determinations of the ionization constants of methyl ethyl or diethyl ketoximes or of the "hydrolysis constants" of their salts were found in the literature. For acetoxime the value 6.0×10^{-13} at 25° has been cited by Scudder[7] based on the measurements by Lundén[8] of the

(6) Harned and Mannweiler, THIS JOURNAL, **57**, 1873 (1935).

(7) Scudder, "Conductivity and Ionization Constants of Organic Compounds," D. Van Nostrand Co., New York, N. Y., 1914.

(8) Lundén, *Z. physik. Chem.*, **54**, 532 (1906).

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rate of hydrolysis of ethyl acetate in solutions of barium hydroxide partially neutralized by the oxime. This agrees with our value at $\mu \sim 0.075$ but is based on $K_w = 1 \times 10^{-14}$ which is correct only at $\mu = 0$.

Summary

The rate of decomposition of nitrosotriacetonamine, catalyzed by hydroxyl ion, has been measured as a function of ionic strength at 24.9°, up to $C_{OH^-} = 0.05$ and $\mu = 0.22$ and may be expressed in the equation

$$k = (1.209 + 0.479\ \mu)\ C_{OH^-}$$

Using this catalytic reaction to measure hydroxyl ion concentration in solutions of sodium hydroxide partially neutralized by acetoxime, methyl ethyl and diethyl ketoximes, the acid dissociation constants of these oximes have been determined as a function of ionic strength.

WASHINGTON SQUARE COLLEGE
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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK UNIVERSITY]

The Ternary System Silver Bromate–Sodium Bromate–Water

BY JOHN E. RICCI AND JACK J. ALESHNICK*

Introduction.—The formation of a compound or of a solid solution of silver bromate and sodium bromate from aqueous solutions of the salts came to be suspected from certain difficulties encountered in attempts to determine bromate ion in the presence of sodium ion, using silver nitrate as precipitant. Estimated gravimetrically the precipitate was always too light. Volumetric determination of the excess of silver ion in the filtrate by the Volhard method revealed the same error, in that too much silver ion was found unprecipitated. These analytical errors appeared regularly and despite care in the original precipitation of the bromate ion with silver nitrate.

The equilibrium relations at room temperature in the ternary system consisting of silver bromate, sodium bromate and water were therefore investigated. The isotherm at 25° shows the formation of a 1:1 double salt capable of forming continuous solid solutions with silver bromate. The salts actually form two solid solutions: sodium bromate containing up to about 3% of silver bromate, and silver bromate containing up to 39.0%, a limit corresponding to the compound $AgBrO_3 \cdot NaBrO_3$.

The consequent contamination (which is of an equilibrium nature and therefore unavoidable) of silver bromate with sodium bromate whenever the silver salt is precipitated from solution containing sodium ion, and especially in the presence also of excess of bromate ion, not only explains the above-mentioned analytical difficulties in the attempted determination of bromate by precipitation as silver bromate, but also accounts, presumably, for the difficulty experienced in the preparation of pure silver bromate.[1-4] This difficulty is obvious from the great variation in the values of the aqueous solubility of the salt reported in the literature. In fact, even the C. P. grade of silver bromate used in the present experiments was found to contain about 1.8% of sodium bromate.

Such behavior on the part of silver bromate appears important not only in connection with possible applications of silver bromate in analytical procedures, but also because of its frequent use in experimental tests of theoretical principles involving solutions of electrolytes.[1-7]

Experimental Procedure

The solubility measurements were made by methods already described for similar determinations. The ternary complexes were made up by weight, using distilled water, C. P. sodium bromate and C. P. silver bromate. The sodium bromate was found to be of satisfactory purity (100.0 ± 0.1%) by iodometric titration using standard thiosulfate. The silver bromate was analyzed in several ways: (1) after reduction with sodium nitrite in the presence of nitric acid and of a small excess of sodium bromide, the precipitate of silver bromide was weighed and was found to correspond to 98.4% silver bromate. (2) After reduction with sulfur dioxide in the presence of nitric and hydrochloric acids, thus precipitating all the silver as silver bromide and chloride, the filtrate was evaporated, finally with sulfuric acid, and weighed, after recrystallization, as sodium sulfate; the sodium was evident in this residue, from ordinary flame tests. The result showed about 1.8% sodium bromate. (3) After reduction with sodium nitrite in the presence of nitric acid and of a small excess of silver nitrate, the precipitate of silver bromide was weighed, and, on the assumption that the original sample consisted of silver and sodium bromates, a purity of 98.0% silver bromate was calculated. These analyses were all done in duplicate and with blank corrections for reagents and apparatus. A value of 98.2% silver bromate and 1.8% sodium bromate was therefore assumed in calculating the compositions of ternary complexes prepared from the C. P. silver bromate.

It must be pointed out that these quantitative analyses of the silver bromate, with consequent correction of the compositions of the synthetic ternary complexes, were performed after a preliminary study of the ternary isotherm had indicated first of all the extensive formation of solid solution between the two salts, and, second, from certain consistent deviations of the tie-lines from the stoichiometric composition of the 1:1 compound, the probability of the presence of a definite amount of sodium bromate in the supposedly C. P. silver bromate.

* Present address: U. S. Army.

(1) Hill, THIS JOURNAL, **39**, 230 (1917).
(2) Reedy, *ibid.*, **43**, 1443 (1921).
(3) Dalton, Pomeroy and Weymouth, *ibid.*, **46**, 61 (1924).
(4) Vosburgh and McClure, *ibid.*, **65**, 1062 (1943).
(5) Noyes, *Z. physik. Chem.*, **6**, 246 (1890).
(6) Owen, THIS JOURNAL, **55**, 1922 (1933).
(7) Neuman, *ibid.*, **56**, 28 (1934).

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TABLE I

SYSTEM $AgBrO_3$–$NaBrO_3$–H_2O

Temp., °C.	No.	Original complex: Wt., % $NaBrO_3$	Original complex: Wt., % $AgBrO_3$	Liquid Solution: Wt., % $NaBrO_3$	Liquid Solution: Density	% $AgBrO_3$ in solid phase, by extrapolation	Solid phase
25	1	..	0.0	28.26 (±0.02)	1.264 (±0.002)		$NaBrO_3$
	2	30.0	.0027	28.26	1.264	0.11	S.S.I.[a]
	3	29.98	.0105	28.24	1.261	.43	S.S.I.
	4	30.0	.0244	28.21	1.262	.97	S.S.I.
	5	29.80	.0401	28.16	1.261	1.7	S.S.I.
	6	29.94	.0590	28.14	1.260	2.3	S.S.I.
	7	30.17	.0779	28.08	1.260	2.6	S.S.I.
	8	30.0	.0941	28.00	1.261	3.2	S.S.I. + $AgBrO_3$·$NaBrO_3$
	9	29.8	.490	27.96	1.259	15.3	S.S.I. + $AgBrO_3$·$NaBrO_3$
	10	29.7	.970	27.96	1.262	25.9	S.S.I. + $AgBrO_3$·$NaBrO_3$
	11–21						S.S.I. + $AgBrO_3$·$NaBrO_3$
	22	31.18	14.71	27.94	1.258	59.1	S.S.I. + $AgBrO_3$·$NaBrO_3$
	23	30.99	14.71	28.00	1.260	59.8	S.S.I. + $AgBrO_3$·$NaBrO_3$
	24	30.76	14.71	27.99	1.261	60.8	S.S.I. + $AgBrO_3$·$NaBrO_3$
	Average	(8–24)		27.97 (±0.02)	1.260 (±0.001)		S.S.I. + $AgBrO_3$·$NaBrO_3$
	25	28.48	3.426	27.84	1.257	60.74	$AgBrO_3$·$NaBrO_3$
	26	28.27	2.747	27.78	1.257	61.23	$AgBrO_3$·$NaBrO_3$
	27	28.29	3.424	27.66	1.256	61.16	$AgBrO_3$·$NaBrO_3$
	28	27.99	3.00	27.41	1.252	60.83	$AgBrO_3$·$NaBrO_3$
	29	28.01	3.431	27.35	1.251	60.95	$AgBrO_3$·$NaBrO_3$
	30	27.72	3.430	27.05	1.248	61.03	$AgBrO_3$·$NaBrO_3$
	31	27.07	2.939	26.42	1.241	60.24	$AgBrO_3$·$NaBrO_3$
	32	26.02	2.98	25.36	1.232	61.11	$AgBrO_3$·$NaBrO_3$
	33	25.07	3.140	24.32	1.220	61.09	$AgBrO_3$·$NaBrO_3$
	34	23.62	3.45	22.71	1.203	61.16	$AgBrO_3$·$NaBrO_3$
		Average	(25–34)			60.95	(Theoretical: 60.98)
	35	22.20	3.441	21.28	1.185	62.13	S.S. II
	36	18.07	3.443	16.99	1.143	63.23	S.S. II
	37	14.09	3.439	13.04	1.108	66.60	S.S. II
	38	11.07	3.427	10.28	1.079	72.86	S.S. II
	39	9.14	4.41	8.39	1.062	78.3	S.S. II
	40	7.582	3.932	7.17 (0.01% $AgBrO_3$)	1.051	84.0	S.S. II
	41	3.968	3.854	3.92 (0.03% $AgBrO_3$)	1.025	94.8	S.S. II
	42	0.0	...	(0.204 ±0.004, % $AgBrO_3$)	0.9985 (±0.0003)		$AgBrO_3$
50	1	..	0.0	35.64	1.341		$NaBrO_3$
	2	36.60	14.71	35.25	1.333	59.3	S.S.I. + $AgBrO_3$·$NaBrO_3$
	3	36.36	14.71	35.21	1.335	60.1	S.S.I. + $AgBrO_3$·$NaBrO_3$
	4	36.18	14.71	35.25	1.335	60.9	S.S.I. + $AgBrO_3$·$NaBrO_3$
		Average	(2–4)	35.24	1.334		S.S.I. + $AgBrO_3$·$NaBrO_3$
	5	35.98	14.71	35.05	1.334	61.09	$AgBrO_3$·$NaBrO_3$
	6	35.79	14.71	34.73	1.331	60.88	$AgBrO_3$·$NaBrO_3$
	7	35.59	14.71	34.57		61.19	$AgBrO_3$·$NaBrO_3$
	8	30.00	9.80	28.77	1.258	63.29	S.S. II
	9	25.18	10.81	23.32	1.196	65.42	S.S. II
	10	0.0	...	(0.430% $AgBrO_3$)	0.9934		$AgBrO_3$
5		..	0.0	21.41	1.192		$NaBrO_3$
		Average of 4 detns.		21.32	1.190	57–60.3	S.S.I + $AgBrO_3$·$NaBrO_3$
		0.0	...	(0.0905% $AgBrO_3$)	0.9998		$AgBrO_3$

[a] S.S.I.: $NaBrO_3$ containing up to 2.5–3.0% $AgBrO_3$.

The solubilities of "pure" silver bromate reported below were determined on samples of this C. P. salt which were repeatedly washed with considerable quantities of water. As may be seen from the ternary diagram, however, such a process of purification would be slow and incomplete. A purity of about 99.7% was finally thus attained, but it is evident that great accuracy cannot be claimed for these solubilities. The ternary diagram, however, and the reported relations of the two salts involved, are independent of the exact solubility of pure silver bromate, the ternary measurements possessing actually a very high degree of accuracy. They involve simply the weighing operations of

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preparing the original complexes, and the sampling and analysis of the filtered liquid solutions at equilibrium. Because of the high concentration of bromate ion in these solutions, the silver ion concentration was so small as to be not even detectable in all but the last one or two complexes in Table I (at 25°). In these the silver bromate content was determined gravimetrically as silver bromide after reduction with sodium nitrite. In all other cases, it was sufficient simply to evaporate the solution to dryness and to assume the residue to be sodium bromate.

The composition of the solid phase was calculated by algebraic extrapolation of the tie-lines joining the composition of the saturated liquid solution with that of the total original complex.[8] Attainment of equilibrium was proved in almost all cases by repeated analysis of the solution after further stirring. The complexes were stirred for periods of two to eight weeks. The densities were determined by using calibrated pipets for the withdrawal of samples to be weighed for analysis.

Results

The results are presented in Table I, which includes the complete 25° isotherm and some data at 50 and 5°, and in Fig. 1, the usual graphical representation of the 25° isotherm. The compositions in Table I are given in terms of weight per cent.

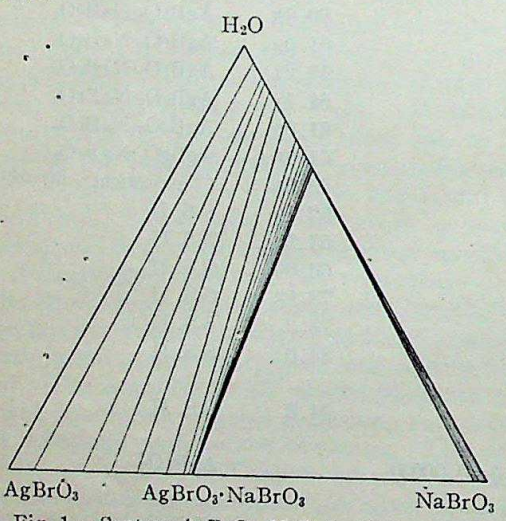

Fig. 1.—System $AgBrO_3$–$NaBrO_3$–H_2O at 25°.

The determinations at 25° show first of all a variable solid phase based on sodium bromate and containing up to 2.5–3.0% of silver bromate. This is seen in the first seven points, in which the liquid and solid compositions (the latter as determined by algebraic extrapolation) vary simultaneously and concomitantly. When this first solid solution (S.S.I.) reaches its limiting composition, a second solid phase evidently appears, and the liquid solution becomes isothermally invariant; the composition of this liquid solution, averaged from a great number of determinations, is 27.97 (±0.02) % sodium bromate, the percentage of silver bromate being analytically zero; its density is 1.260 (±0.001). The second solid is a saturated solid solution of the two salts containing, by extrapolation, 60.95 (±0.17)% silver bromate. This at any rate is the evidently constant composition of the solid in equilibrium with liquids ranging from 27.97 to about 22% sodium bromate, where, without the appearance of any break in the solubility curve, the solid composition begins to vary, gradually and continuously, increasing in silver bromate content until the composition of the pure salt is reached.

The second branch of the solubility curve therefore represents liquid solutions saturated with a second solid solution (S.S. II) starting at pure silver bromate, and whose limiting binary composition can be fixed very precisely because of the sharp convergence of the tie-lines at the binary limit. This sharp convergence indicates the existence of a definite compound, and the observed composition (by extrapolation of tie-lines) agrees very well with that theoretically required for the 1:1 compound, $AgBrO_3 \cdot NaBrO_3$, namely, 60.98% silver bromate.

Only a few determinations were made at 50°, so chosen as to verify the same general behavior. The isothermally invariant solution contains 35.24% sodium bromate as compared with 35.64%, the solubility of pure sodium bromate at this temperature. Since the relationship of these two points is the same as that of the corresponding points at 25°, it may be inferred that here too one of the solid phases is a solid solution of some small amount of silver bromate in sodium bromate. The second solid phase, as shown by the extrapolations, is again the compound, $AgBrO_3 \cdot NaBrO_3$, representing the limit of a solid solution presumably extending to pure silver bromate.

The nature of the limit of this second solid solution as a definite chemical compound, $AgBrO_3 \cdot NaBrO_3$, is of course corroborated by the constancy of the limiting composition at the two temperatures, 25 and 50°.

At 5° only the points of the isotherm have been determined; but the relation of the invariant point to the solubility of sodium bromate is still the same, indicating the probability of the same reaction and relationship between the salts at this as at the higher temperatures studied.

Discussion

The conclusion from this equilibrium study is that silver bromate precipitated in the presence of sodium ion and particularly in the presence also of excess of bromate ion, must be contaminated with sodium bromate. Mere recrystallization or digestion in water cannot be expected to purify it "completely" or analytically except through repeated and prolonged treatments. It may be suggested that this effect of sodium bromate is probably the reason for the disagreement in the published values for the solubility of this salt, and for the difficulties experienced by careful workers in attempting to obtain samples of constant and reproducible solubility. Thus, in a recent article on the silver–ammine ions, Vosburgh and McClure[4] state that their two different samples of the salt "gave appreciably different solubilities

(8) Hill and Ricci, THIS JOURNAL, 53, 4305 (1931).

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in water," and they do not consider these solubilities worth reporting.

The solubility here reported, of 0.204% at 25°, is not claimed to be final and accurate, and is to be compared with the following literature values (recalculated into units of weight per cent.)

Longi (1883)[9]	0.166 at 25°
Noyes (1890)[5]	.192 at 24.5°
Böttger (1903)[10]	.159 at 25°
Whitby (1910)[11]	.171 at 27°
Hill (1917)[1]	.195 at 25°
Reedy (1921)[2]	.196 at 25°
Dalton, Pomeroy and Weymouth (1924)[3]	.189–0.191 at 25°
Owen (1933)[6]	.192 at 25°
Neuman (1934)[7]	.192 at 25°

The highest values reported are those of Hill and of Reedy. The latter apparently took the greatest pains in purifying the salt by recrystallization. The present investigation shows that the presence of even small amounts of sodium bromate reduces considerably the solubility of silver bromate.

Reedy found that the purity of his silver bromate tended to be low, 99.6 to 99.8%, and he attributed this deviation from purity to the presence of air occluded in the crystals during precipitation. He even recommended the salt as a standard in iodimetry. But in view of the formation of a solid solution with sodium bromate, such use of silver bromate should obviously be undertaken only with serious precautions. The only other analysis of the silver bromate used for solubility work is given by Hill, who reported, without comment, that his salt gave 44.97 and 45.00% of silver (determined as silver chloride) as compared to the theoretical 45.75%. His sample was made by precipitation from potassium bromate and silver nitrate; the same reaction was used for the preparation of the material used in References 9, 10, 11, in which no analysis is given.

(9) Longi, *Gazz. chim. ital.*, **13**, 87 (1883).
(10) Böttger, *ibid.*, **46**, 603 (1903).
(11) Whitby, *Z. anorg. Chem.*, **67**, 108 (1910).

Summary

1. The system silver bromate–sodium bromate–water has been studied in detail at 25°, and, partially, at 50° and 5°.

2. The salts form a definite compound, $AgBrO_3 \cdot NaBrO_3$, which forms a continuous solid solution with silver bromate. Sodium bromate also forms a solid solution containing up to 2.5–3.0% of silver bromate.

3. Some implications of these results on analytical procedures involving silver bromate are discussed. Precipitation of silver bromate from solutions containing sodium ion must result in an impure salt which can be purified by recrystallization only with difficulty.

4. The results may explain the great variation in the values of the solubility of silver bromate reported in the literature, and suggest that the samples of the salt used in various theoretical studies may have been contaminated with sodium bromate.

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[CONTRIBUTION FROM THE AMERICAN CYANAMID COMPANY AND POLYTECHNIC INSTITUTE OF BROOKLYN]

Mechanism of Peroxide Initiated Styrene Polymerization

BY HARRY F. PFANN[1] D. J. SALLEY[1a] AND H. MARK

Recent publications of Price and his co-workers[2] and of Kern and Kammerer[3] have succeeded in clarifying the mechanism of the peroxide initiated polymerization of styrene. Their results confirm and extend proposals advanced by Norrish,[4] Schulz[5] and others that the active centers for chain propagation are free radicals resulting from the decomposition of the peroxide as such or an addition compound between peroxide and styrene. As there appears to be continued interest[6,7,8] in this problem, the writers wish to present the following data obtained from experiments[9] in progress from 1940 to 1942, which were not published at that time due to the outbreak of the war.

In this work, halogen-containing polymer was prepared from styrene and *m*-bromobenzoyl peroxide. Non-combined initiator was removed by repeated extraction, and the presence of bromine in the polymer was demonstrated by combustion of the sample followed by determination of the halogen, as well as by measurement of the radioactivity of the polymer samples after neutron bombardment.

Experimental Procedure

Polymer samples were prepared by heating commercially pure styrene (Dow Chemical Company, 1941, $n^{25}D$ 1.5432, d^{24} 0.9025) with *m*-bromobenzoyl peroxide (m. p. 127–128°, 99% of theoretical active oxygen) in sealed glass tubes 33 mm. × 180 mm. immersed in an oil-bath at

(1) (a) American Cyanamid Company, Stamford, Connecticut.
(1) (b) Present address: Koppers United Company, Butadiene Division, Kobuta (Monaca), Pennsylvania.
(2) Charles C. Price, *et al.*, THIS JOURNAL, **63**, 2798 (1941); **64**, 1103, 2508 (1942); **65**, 517 (1943).
(3) W. Kern and H. Kammerer, *J. prakt. Chem.*, **161**, 81–112 (1942); *C. A.*, **37**, 5381 (1943).
(4) Norrish and Brockman, *Proc. Roy. Soc.*, **A171**, 147–71 (1939); Norrish, *Trans. Faraday Soc.*, **35**, 1082 (1939).
(5) G. V. Schulz, *Naturwissenschaften*, **27**, 387, 456, 659 (1939).
(6) (a) Abere, Goldfinger, Mark and Naidus, *J. Chem. Phys.*, **11**, 379 (1943); (b) *Ann. N. Y. Acad. Sci.*, **44**, 267 (1943).
(7) Compare also Mayo, THIS JOURNAL, **65**, 2324 (1943).
(8) Bartlett and Cohen, *ibid.*, **65**, 543 (1943).

(9) Taken in part from the Thesis for the Degree of Master of Science by Harry F. Pfann, Polytechnic Institute of Brooklyn, June, 1942.

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140 ± 2°. Each tube was sealed off under vacuum (except Sample No. 100). The temperature of reactants was followed by use of a thermocouple placed in a well extending into the center of the reaction mixture. Heating was continued until *ca.* 50% of the styrene was polymerized, after which the reaction was quenched by sudden cooling.

Polymer was isolated by precipitation from benzene solution with methanol. A 5% solution of polymer in benzene was extracted three times by agitation with 15% aqueous sodium hydroxide at *ca.* 50° during one hour. The extracted polymer, precipitated with methanol, was digested in methanol on the steam-bath, and dried in a vacuum oven.

Chemical determination of the bromine content of the polymer was carried out by combustion in a macro combustion tube over a platinum gauze catalyst, absorption of the halogen in an alkaline sodium bisulfite solution, and gravimetric determination of silver bromide by a modification of the Pregl micro technique.[10] Combustion of the non-volatile polymer was attended by considerable difficulty, but the results tabulated represent fairly successful determinations.

Physical determination of the bromine content was carried out by measuring the intensity of the radioactive isotopes of bromine produced by irradiation with neutrons. Cast films of the polymer 1.0 sq. cm. by 1 mm. were subjected to neutron bombardment in the Columbia University cyclotron. Measurements of the resulting intensities were carried out with a mica-window type of Geiger counter tube. All counts were corrected for decay and for slight variation in the thickness of the specimens. The ratio of the corrected intensities gave the relative amounts of bromine present, and the absolute amount was obtained using one of the samples as the basis.

TABLE I

PREPARATION OF POLYSTYRENE SAMPLES

Initiator: *m*-bromobenzoyl peroxide; bath temperature, 140 ± 2°.

Sample	Initiator concentration, mg./g./styrene	Heating period, minutes	Reaction temp. maximum, °C.	Polymerized, %
100	Oxygen[a]	41	191	50.8
101	Evacuated	41	...	53.5
104	1.54	31	164	51.8
111	7.68	14	187	50.2
115	12.84	7	220	59.0
116	12.84	4	217	48.0

[a] Tube evacuated and filled with oxygen at 760 mm. before sealing.

indicated by the thermocouple, showing that there was a marked deviation from the isothermal condition of the heating bath. Comparison of samples 100 and 101 suggests that oxygen may act initially as an inhibitor, as it does, *e. g.*, in certain emulsion polymerizations.

In Table II are given the properties observed for the several polymer preparations. Sample 116-E-3 differed from 116-E-1 in that it was given three standard extractions and precipitations after polymerization. The essential constancy of the bromine content indicates that the halogen determined represents chemically bound, not associated or adsorbed, catalyst fragments. The agreement between the chemical and radioactive determinations appears quite satisfactory.

The analytically determined bromine content does not agree well with the value calculated from the viscosity average molecular weight, which calculation is based on the assumption of two initiator fragments per polymer molecule. This would be the case if chain termination is only effected through mutual saturation of two growing chains.[11,12]

Perhaps of more significance is the variation shown under "Comparison of Values." Polymer sample 104 was prepared with the smallest peroxide concentration at the lowest temperature, and it was found to have only 58% of the halogen calculated from viscosity measurements. Sample 116, prepared with greatest peroxide concentration and highest temperature, was found to have 166% of the calculated halogen content. Sample 104-E-1, of highest molecular weight, would be expected to have been subject to the greatest degree of chain transfer. A high incidence of chain transfer would result in a low concentration of initiator per polymer molecule.[13]

It must also be borne in mind that the viscosity average as contained in column three of Table II places less emphasis on the short chains than the counting of the bromine end-atoms does. If the

TABLE II

PROPERTIES OF EXTRACTED POLYMER SAMPLES

Sample	Relative viscosity[a]	Viscosity average molecular weight[b]	Bromine content of sample (mg. Br per 1 g. polymer) Original reaction mixture	Determined Gravimetric	Determined Radioactive	Calculated:[c] 2 Br atoms per polymer molecule
104-E-1	1.77	155,000	0.61	0.8 ± 0.1 (3)[d]	0.6	1.04
111-E-1	1.43	86,500	3.05	3.5 ± .4 (5)	3.4	1.86
116-E-1	1.24	48,800	5.12	5.4 ± .5 (3)	5.4	3.28
116-E-3	..	..	5.12	5.2 ± .5 (3)	..	..

[a] Relative viscosity of 1% solution of dried polymer in toluene at 20°. [b] Viscosimetric molecular weight calculated from equation $M = \eta sp/K_m \times$ Concn., using $K_m = 0.50 \times 10^{-4}$ given for thermal polymerization at 135°. Compare H. Staudinger and G. V. Schulz, *Ber.*, **68**, 2332 (1935). [c] Based on viscosimetric molecular weight. [d] Number of determinations averaged.

Experimental Results

Table I gives the conditions for preparation of the polymer samples. "Reaction Temperature Maximum" indicates the highest temperature

low molecular fractions of the polymer are initiated by the brominated peroxide while the high molecular weight fractions are produced after the consumption of the initiator by thermal activa-

(10) F. Pregl, "Quantitative Organic Microanalysis," Blakiston Co., Philadelphia, Pa., 1930.

(11) See reference 6a, p. 383; 6b, p. 296.

(12) Compare also Price, *Ann. N. Y. Acad. Sci.*, **44**, 365 (1943).

(13) Reference 12, p. 366.

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tion, the viscosity average is bound to give distinctly larger molecular weights than the counting of the end-groups. This may explain the high bromine content of the polymer prepared at 217° (sample 116-E) where the decomposition of the catalyst should be expected to be very fast and at the same time thermal activation would be most efficient.

Acknowledgment

The authors are anxious to express appreciation to the directors of the Stamford Research Laboratories of the American Cyanamid Company for extending to the junior author the use of the laboratories' facilities. Thanks are also extended to the staff of the Columbia University cyclotron for bombardment of the samples.

Summary

1. Styrene has been polymerized in the pure liquid phase at various temperatures and with various amounts of *p*-bromobenzoyl peroxide.

2. The bromine content of the polymer was determined gravimetrically and with the aid of a radioactive bromine isotope. The values obtained by the two methods agreed reasonably well with each other.

3. The polymers contain on the average between one and three bromine atoms per chain, if the viscosity average chain length is compared with the analytical bromine content.

4. It is shown that the radioactive tracer method can be fairly easily applied to this problem of polymer chemistry.

KOBUTA (MONACA), PA.
BROOKLYN, N. Y. RECEIVED MARCH 23, 1944

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

Rearrangement of Alkyl Halides[1]

BY FRANK R. MAYO[2a] AND ARTHUR A. DOLNICK[2b]

The addition of hydrogen bromide to a 1-alkene may yield either of two products, depending on the mechanism of addition.[3] The normal addition, giving a secondary or tertiary bromide, proceeds by an ionic or molecular mechanism. The abnormal addition, which is accelerated by oxygen and peroxides and is inhibited by certain antioxidants, proceeds by an atom-chain mechanism, giving a primary bromide. On the assumption that the rearrangement of an alkyl bromide proceeds by loss and readdition of hydrogen bromide, it was concluded that the rate of rearrangement should be affected by the same catalysts which influence the addition of hydrogen bromide. This paper describes the effects of such catalysts on the rearrangement of normal and isopropyl bromides to an equilibrium mixture. These readily available bromides were chosen because the carbon skeleton cannot rearrange and because a mixture of the halides is easily analyzed. For comparison with a representative pair of alkyl chlorides, experiments were made with *i*- and *t*-butyl chlorides. Data were also obtained on the two dibromoethanes.

Previous Work

When an alkyl bromide is strongly heated, it rearranges to give an equilibrium mixture of all the isomeric bromides which can be formed without rearrangement of the carbon skeleton. In spite of considerable work in the field, there is marked disagreement on the composition of some equilibrium mixtures, on the factors which influence the rate of approach to equilibrium, and on the mechanism of rearrangement.

In the liquid phase at 250°, normal and isopropyl bromides rearrange to give a mixture containing 30 and 70%, respectively, of these bromides.[4a] The proportion of primary bromide increases with the temperature[4a] and is smaller in the vapor phase.[4b] Equilibria between tertiary and isobutyl bromides have been more extensively investigated[5] in both the liquid and the vapor phase, but although the tertiary bromide always predominates, wide discrepancies in the composition of the equilibrium mixture have been reported; secondary butyl bromide (with rearrangement of the carbon skeleton) has also been detected.[5g] Equilibria between the four bromoisopentanes and between some isomeric dibromoalkanes have received less attention.[5a,6]

The rearrangement of the bromoisobutanes is retarded by the corresponding alcohols and by di-isobutylene.[5b] Michael has recently suggested[7]

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(2) Present addresses: (a) General Laboratories, United States Rubber Company, Passaic, N. J.; (b) Publicker Commercial Alcohol Company, Philadelphia, Pa.

(3) Mayo and Walling, *Chem. Rev.*, **27**, 351 (1940).

(4) (a) Brouwer and Wibaut, *Rec. trav. chim.*, **53**, 1001 (1934); (b) Brunel and Rafsky, *Science*, **60**, 23 (1924).

(5) (a) Michael and Leupold, *Ann.*, **379**, 263 (1911); (b) Michael, Scharf, and Voigt, THIS JOURNAL, **38**, 653 (1916); (c) Brunel, *Ber.*, **44**, 1000 (1911); (d) Brunel, *Ann.*, **384**, 245 (1911); (e) Brunel, THIS JOURNAL, **39**, 1978 (1917); (f) Dienger, *Z. physik. Chem.*, **136**, 93 (1928); (g) Hückel and Ackermann, *J. prakt. Chem.*, [2] **136**, 15 (1933).

(6) (a) Gustavson, *J. prakt. Chem.*, [2] **36**, 303 (1887); (b) Favorsky, *et al.*, *Ann.*, **354**, 325 (1907); (c) Michael and Zeidler, *ibid.*, **385**, 227 (1911).

(7) Michael, *J. Org. Chem.*, **4**, 521 (1939), footnote 9.

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that his earlier work[5a,b] shows an acceleration by oxygen. Aluminum,[5a,8b,d] zinc and mercuric[5b] bromides accelerate the rearrangement of several bromides. There is disagreement as to whether rearrangement is faster in the vapor than in the liquid phase[5a,b,e,8a] and as to the effect of various surfaces on the rate of rearrangement.[5a-c,6c] Difficulty in reproducing results has been mentioned frequently; catalytic effects have seldom been demonstrated by duplicate experiments, and frequent discrepancies between workers suggest that many conclusions are open to question. Typical of the state of the subject are the repeated claims,[5a,c,f,6c,8c] often refuted,[5e,6b,8f] that equilibrium is approached much faster from one side than from the other, that it can be approached only from one side, and that impurities[5b] determine the composition of the equilibrium mixture.

Rearrangement through loss and readdition of hydrogen bromide has been postulated,[4a,5d,6b,8a-c,9a] while those who favor an intramolecular rearrangement base their contentions upon failure to observe dissociation sufficient to account for rearrangement.[5a,b,f,g,8e,9b]

Alkyl chlorides, which rearrange with difficulty, have received comparatively little attention.[10]

Experimental

Conditions for Isomerization.—Generally, the propyl bromide[11] (3 cc. measured at room temperature) was heated for six hours at 250° in a sealed, heavy-walled, Pyrex tube (5.7 mm. inside diameter, 35 cm. long, 8–9 cc. capacity), enclosed in a close-fitting iron pipe. In runs where air was excluded, measured quantities of the dried bromide were distilled *in vacuo* into the cooled reaction tube containing the catalyst (if any), and sealed off (final pressure 10^{-4} mm. or less). When hydrogen bromide or propene was added, it was measured out in the vapor phase and condensed in the reaction vessel. For runs in the presence of air, the halides were pipetted into cooled (−80°) tubes and sealed off.

In the first third of the experiments, the reaction tubes were heated in a horizontal electric furnace, but when it was found that the temperature varied from 250° at the center to 210° at the ends of the tubes, the remaining experiments were carried out in boiling diphenyl ether (temperature 248–252°).[12] Tubes were introduced into the preheated furnace or bath; they attained the maximum temperature within fifteen minutes in the diphenyl ether-bath, more slowly in the furnace. In most of the experiments, the two methods of heating gave nearly identical results, but the runs without added catalysts or air tend to fall into two groups (Fig. 1). Less rearrangement was found in the electrically heated runs, ten out of eleven products having indices of refraction between 1.4328 and 1.4332. The halide presumably rearranged faster in the diphenyl ether-bath experiments because the temperature was higher and more rapidly attained.

Analysis of Reaction Products.—The heated tubes were cooled to −80° and opened. The products (usually colorless but containing hydrogen bromide) were washed several times with water, with concentrated sulfuric acid, and again with water. The percentage composition of the halide mixture (dried over potassium carbonate) was then estimated by determination of the index of refraction.[13] The analytical procedure was proved applicable by tests with known mixtures. It was found unnecessary to distil the rearrangement products of *n*-propyl bromide[14] except that those formed in the presence of aluminum bromide, catechol, or diphenylamine were vacuum-distilled before washing. In the experiments with bromobenzene, the bromopropanes were separated before washing by fractionation through a short Vigreux column. This procedure was found adequate with a known mixture. The chloroisobutanes were merely distilled before their refractive indices were determined. Because the dibromoethanes partially decomposed to hydrogen bromide and a black solid (amounting to about 15% of the product), the volatile products were distilled *in vacuo*, dried with anhydrous potassium carbonate, and fractionated through a small Vigreux column. Material boiling below 105° (mostly at 40–51°, probably ethyl and vinyl bromides) was rejected; the composition of the fraction boiling at 105–132° was determined by index of refraction.[15] Residue and hold-up were negligible.

Reagents.—One preparation of *n*-propyl bromide (made from *n*-propanol[16]), having the usual physical properties, rearranged unusually rapidly and was found to contain peroxides. This sample was washed with 2% aqueous potassium permanganate until no more reduction occurred; it was then washed until colorless with concentrated sulfuric acid. After treatment with aqueous potassium carbonate and then with water, the dried and distilled propyl bromide rearranged at the usual rate. Thereafter, all the propyl bromide (b. p. 749 mm. 70–71°, $n^{20}D$ 1.4341), from which about 75% of the runs were made, was treated in this manner. Isopropyl bromide (Eastman Kodak Co.) was washed with concentrated sulfuric acid and water, dried and fractionally distilled; b. p. 747 mm. 58.5–59.0°, $n^{20}D$ 1.4251. *t*-Butyl chloride,[17a] b. p. (739 mm.) 49.5°, $n^{20}D$ 1.3853, and isobutyl chloride,[10a,17b] $n^{20}D$ 1.3974, were prepared from the corresponding alcohols.

Catechol and diphenylamine were sublimed at reduced pressure; *n*-propanol, di-isopropyl ether, and bromobenzene were fractionally distilled. Anhydrous aluminum bromide was prepared from aluminum and reagent grade bromine[18] and stored and transferred in a dry atmosphere. The colorless salt dissolved rapidly and completely in alkyl halides with discoloration and development of heat.

Results

Rate Studies.—Since the equilibrium between the bromopropanes at 250° lies on the side of the secondary halide, isomerization of *n*-propyl bromide to the equilibrium mixture results in a greater change in composition and refractive index than would occur with its isomer. Conse-

(8) (a) Eltekoff, *Ber.*, **8**, 1244 (1875); (b) Kekulé and Schrötter, *ibid.*, **12**, 2279 (1879); (c) Aronstein, *Rec. trav. chim.*, **1**, 134 (1882); (d) Gustavson, *Ber.*, **16**, 958 (1883); (e) Ramart-Lucas and Salmon-Legagneur, *Compt. rend.*, **186**, 39 (1928); (f) Bethoud and Porret, *J. chim. phys.*, **30**, 396 (1933).

(9) (a) Meerwein and van Emster, *Ber.*, **55**, 2520 (1922), footnote; (b) Eltekoff, quoted in reference 6b.

(10) (a) Michael and Zeidler, *Ann.*, **393**, 81 (1912); (b) Nagai, *C. A.*, **34**, 7844 (1940).

(11) Ethylene and ethylidene bromides were heated in tubes which were about three-quarters filled.

(12) A temperature of 300° for the chloroisobutane experiments was obtained by the use of boiling benzophenone.

(13) Kharasch, McNab and Mayo, THIS JOURNAL, **55**, 2531 (1933); Kharasch and McNab, *ibid.*, **56**, 1425 (1934).

(14) Distillation caused an inconsistent change in refractive index of 0.0002 or less. The absence of significant amounts of by-products was shown by distillation of the accumulated rearrangement products (700 g.), which yielded about 1 g. of material boiling below 58° and about 3 g. boiling above 70°.

(15) Kharasch, McNab and Mayo, THIS JOURNAL, **55**, 2521 (1933).

(16) Carothers, "Organic Syntheses," Vol. 13, John Wiley and Sons, Inc., New York, N. Y., 1933, p. 21.

(17) (a) Gilman, "Organic Syntheses," Coll. Vol. 1, John Wiley and Sons, Inc., New York, N. Y., 1932, p. 138; (b) Gerrard, *J. Chem. Soc.*, 99 (1939).

(18) Winter and Cramer, *Ind. Eng. Chem.*, **32**, 856 (1940).

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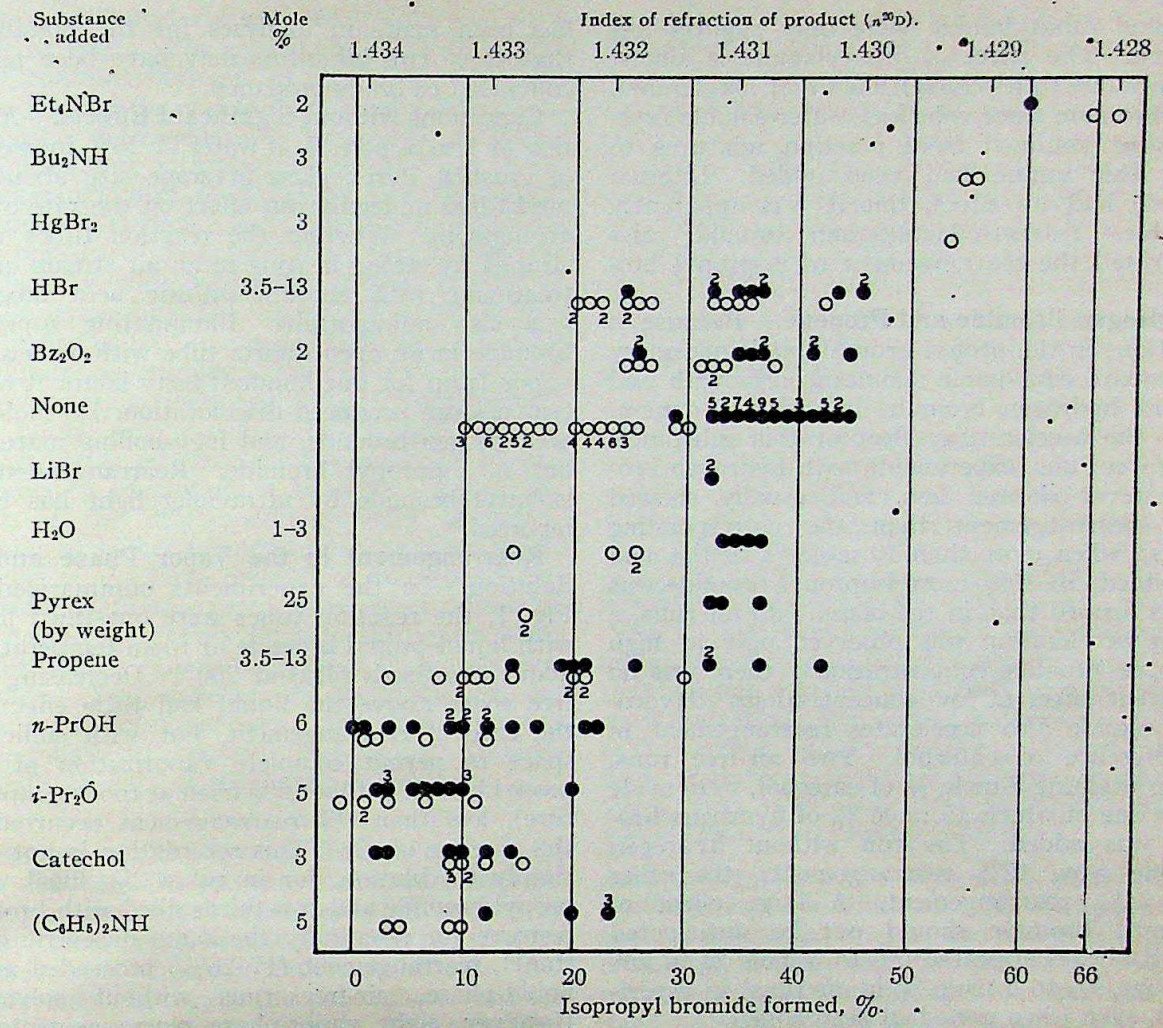

Fig. 1.—Extent of rearrangement of *n*-propyl bromide after six hours at 250°. Hollow circles represent experiments made in the absence of air; solid circles indicate presence of air. A number above or below a point shows the total number of duplicate experiments which gave the indicated result. The equilibrium mixture contains 66–67% isopropyl bromide.

quently, rate studies were carried out by heating the liquid primary bromide for six hours at 250°. Results are summarized in Fig. 1.

Oxygen and Peroxides; Precision of Results.—In the absence of air at 250°, 9–30% of *n*-propyl bromide rearranges during six hours to the secondary halide (Fig. 1), whereas 67% represents equilibrium. Using the same *n*-propyl bromide for each set, eight pairs of duplicate experiments gave products having a maximum difference in index of refraction of 0.0002 (2.2%) within each pair; hence catalytic impurities in the halides and the method of heating are probably responsible for the wide differences in the results obtained.

While the values actually overlap slightly, the rearrangement of *n*-propyl bromide (29–43%) is unmistakably faster in the presence of air than in its absence. Whenever air and air-free experiments were made simultaneously from the same sample of *n*-propyl bromide, 11–25% (average 17%) more rearrangement was always obtained in the presence of air. Hence the overlapping of air and air-free runs shown in Fig. 1 is due to variations in the *n*-propyl bromide or in heating. Oxygen is responsible for the accelerating effect of air: in simultaneous experiments, 9% rearrangement was found in a vaccum run, 18% and 42% were found after bubbling commercial nitrogen and oxygen, respectively, through the bromide samples before the reaction tubes were sealed. Air was also found to accelerate the rearrangement of isopropyl bromide.

Experiments with benzoyl peroxide yielded some charred material and erratic results. In view of the short life of the peroxide above 100°, the results are not considered to be significant.

Bromide Salts.—The powerful catalytic effect of aluminum bromide, which caused extensive side-reactions at elevated temperatures, was demonstrated by equilibrium studies at low temperatures. Addition of 2 mole % of tetraethylammonium bromide to reaction mixtures resulted in close approach to equilibrium (67% rearrangement) in six-hour runs at 250°;[19] mercuric bro-

(19) Only 17% rearrangement was found in the same time at 200°.

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mide and dibutylamine were only slightly less effective. The effect of dibutylamine is almost certainly due to its conversion to an alkylammonium bromide since colorless, water-soluble crystals were obtained from reaction mixtures to which this amine had been added. Lithium bromide had no effect, but it was apparently insoluble. Tetraethylammonium bromide also accelerated the rearrangement of isopropyl bromide.

Hydrogen Bromide and Propene.—Because of variations in the propyl bromide, it is necessary to compare runs made simultaneously with and without hydrogen bromide, in order to demonstrate the accelerating effect of this substance. In air-free runs, experiments with hydrogen bromide never showed less, and usually showed more, rearrangement than the corresponding blanks; when more than 10 mole % of the acid was added, 10–15% more isopropyl bromide was always formed than in the blank. In air runs, a similar acceleration was observed only at high hydrogen bromide concentrations; there was no consistent effect at low concentrations. Hydrogen bromide also accelerates rearrangement in the presence of catechol. Two air-free runs, each containing 3 mole % of catechol, were made up, to one of which 15 mole % of hydrogen bromide was added. The run without hydrogen bromide gave 10% rearrangement; the other gave 34% rearrangement. A large effect of hydrogen bromide should not be anticipated since it always appeared (1/3 to 5 mole % in air-free runs, 1/3 to 2 mole % in air runs) in experiments, even when none had been added.

A small retarding effect of added propene can be shown in both the presence and absence of air. In ten experiments with added propene accompanied by simultaneous blank runs, nine rearranged 2–18% less (average 11%) than the blank, but a definite relation between the amount of alkene and the extent of rearrangement is not discernible.

Inhibitors.—Experiments with added catechol show that this antioxidant completely overcomes the accelerating effect of air on the rearrangement and reduces the effects of accidental catalysts in the *n*-propyl bromide. When simultaneous experiments were made with catechol, the air and air-free runs were identical (four pairs of experiments). In four pairs of experiments in the absence of air, the inhibitor had a marked retarding effect (12–16% rearrangement) only when the blanks rearranged rather rapidly (23% rearrangement), a slight effect when the blanks rearranged slowly (9–10% rearrangement). Diphenylamine proved to be a less effective inhibitor.

Figure 1 shows that *n*-propanol is also a fairly effective inhibitor. Di-isopropyl ether is the most effective; in the absence of air, it sometimes stops rearrangement completely. No allowance has been made in analyses for the possibility that these two inhibitors may have been partly converted to bromopropanes.

Conditions without Significant Effects.—Addition of 1 to 3 mole % of water or 25% by weight of crushed Pyrex glass (average size about 30 mesh) had no significant effect on the rate of rearrangment. Whether the reaction tubes were cleaned by strong heating in an air stream or by treatment with chromic–sulfuric acid mixture was also unimportant. Illuminating *n*-propyl bromide in an open quartz tube with a mercury vapor lamp for one hundred forty hours at room temperature produced discoloration, 1.5 mole % of hydrogen bromide, and high-boiling material, but no isopropyl bromide. Rearrangement of isobutyl bromide by ultraviolet light has been reported.[8c]

Rearrangement in the Vapor Phase and in Solution.—In the experiments summarized in Fig. 1, the reaction tubes were one-third filled with liquid propyl bromide at room temperature, about two-thirds filled at 250°. Decreasing the free space above the liquid had little effect on the rate of rearrangement, but with sufficient space to permit complete vaporization of the propyl bromide (tubes 2% filled at room temperature), less than 1% rearrangement occurred in the absence of air. This retardation is not due simply to dilution, for in tubes 2% filled with propyl bromide and two-thirds filled with bromobenzene (of essentially the same dielectric constant), rearrangement (17–26%) proceeded as in liquid-phase, air-free runs without solvents. However, eight vapor-phase rearrangements in the presence of air gave 12–31% (mean, 20%) rearrangement, just half the average of simultaneous liquid-phase blanks with air in small tubes. In six bromobenzene experiments with air present, 12–42% (mean, 25%) rearrangement was found.

Equilibrium between *n*- and Isopropyl Bromides.—As shown in Fig. 2, the same equilibrium mixture (containing 67% isopropyl bromide as compared with 70% reported by Brouwer and Wibaut[4a]) was obtained at 250° from both *n*- and isopropyl bromides, regardless of the presence or absence of tetraethylammonium bromide or air. With these catalysts, equilibrium could not be obtained within a reasonable time at or below 200°. Aluminum bromide could not be used at 250°, but gave equilibrium mixtures containing 85% isopropyl bromide at 70°, 91% at 26°.

Rearrangement of *i*- and *t*-Butyl Chlorides.—Isobutyl and *t*-butyl chlorides were unchanged after six hours at 250°, but each gave about 10% rearrangement in seven hours at 300°. Neither catechol nor air affects the rearrangement of isobutyl chloride. About 26% of this chloride rearranged in fifteen hours at 300°, in the presence or absence of air and/or 3 mole % of catechol. On the other hand, addition of 3 mole % of triethylammonium chloride increased rearrange-

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ment of isobutyl chloride to 78 during seven hours at 300°. The equilibrium mixture apparently contains between 78 and 92% of tertiary chloride, but the value is uncertain due to the formation of considerable high-boiling material in runs starting with *t*-butyl chloride.

Rearrangement of Ethylene and Ethylidene Halides.—Ethylene and ethylidene chlorides were boiled with 2 mole % of aluminum chloride; ethylene bromide was refluxed with 1 mole % of aluminum bromide, and ethylidene bromide was heated to 100° in a sealed tube with 4 mole % of aluminum bromide. No rearrangement was observed over periods of six and one-half to ninety-four hours, but considerable halogen exchange occurred when ethylene chloride was refluxed with 23 mole % of aluminum bromide. Rearrangement of the dibromoethanes with aluminum bromide at higher temperatures was unsuccessful because of the large amount of tar formed, but less side reaction occurred when either dibromide was heated for twenty-eight to thirty-two hours at 250° with 4–5 mole % of tetraethylammonium bromide. Two experiments were carried out with each dibromoethane; the four products were found to contain 76–82% of ethylene bromide, 18–24% of ethylidene bromide.

Discussion

Correlation with Previous Work.—The present work supports the previous statements that rearrangement of alkyl bromides is accelerated by air and some metal bromides, and is retarded by alcohols and alkenes. With reference to previously disputed points, this paper shows that the rearrangement is much slower in the vapor than in the liquid phase, that there is no surface effect from glass, that reproducibility of results is highly dependent on catalysts and inhibitors present as impurities in the alkyl bromide, and that equilibrium can be approached from both sides. The analogies discussed below, as well as the formation of free hydrogen bromide in all experiments, point to rearrangement by loss and readdition of hydrogen bromide rather than by an intramolecular mechanism.

The Mechanisms of Rearrangement of Alkyl Halides.—Addition of hydrogen bromide to propene may occur by either of two mechanisms, each associated with different catalysts and each leading to a different propyl bromide.[3] Loss of hydrogen bromide from an alkyl bromide presumably occurs by the reverse processes. The present observations on the rate of rearrangement of the bromopropanes are entirely consistent with the view that rearrangement consists of loss and readdition of hydrogen bromide by the same two mechanisms, but here the two mechanisms can be distinguished not by the products formed, but only by analogy with the addition reaction. On this basis, the accelerating effect of oxygen on the rearrangement of the bromopropanes, and the counteracting effect of antioxidants,

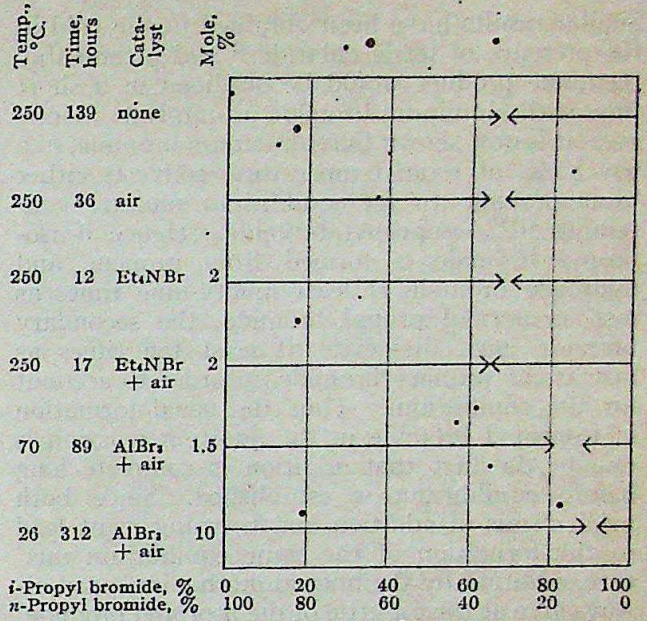

Fig. 2.—Liquid-phase equilibrium between *n*- and isopropyl bromides. Each line indicates the change undergone by a propyl bromide sample when heated under the stated conditions. The starting materials are indicated at the margins; the arrow heads show the final compositions. Experiments at 250 and 70° were carried out in sealed tubes; at 26°, open reflux condensers were used, with protection from moisture in the air.

are associated with the atom-chain mechanism of hydrogen bromide addition. The slight acceleration by hydrogen bromide and the greater effect of soluble bromide salts are associated with the normal, molecular mechanism of hydrogen bromide addition according to Markownikoff's rule. Substances which reduce the concentration of hydrogen bromide, such as propene, propanol and di-isopropyl ether, retard the rearrangement; the alcohol and ether may also retard the chain reaction. Since hydrogen chloride does not add to alkenes by the chain mechanism, both the absence of an oxygen effect and the presence of a catalytic effect of triethylammonium chloride are observed and expected.

As in many hydrogen bromide additions, the rearrangement of the bromopropanes seems to proceed by both mechanisms in the absence of air, as shown by the variable rates observed and their tendency to approach a lower limit in the presence of the antioxidant, catechol. The differences in the effectiveness of inhibitors, and the retardation or elimination of the molecular mechanism by diluting or operating in the vapor phase also have nearly identical counterparts in the addition reactions.[3]

Rates and Equilibria in the Formation and Rearrangement of Alkyl Bromides.—Hydrogen bromide adds rapidly to propene under ordinary conditions to give isopropyl bromide.[13] This isomer must be formed at least ninety-nine times as fast as *n*-propyl bromide since probably no more than 1% of the primary halide is present.

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Similar results have been obtained in the cold in the presence of ferric chloride,[20] and presumably the same product would be obtained in a short time with aluminum bromide as catalyst. However, it is now shown that aluminum bromide, in a few hours at room temperature, converts either bromopropane to an equilibrium mixture containing 91% isopropyl bromide. Hence if isopropyl bromide is formed from propene and hydrogen bromide at least ninety-nine times as fast as normal propyl bromide, the secondary bromide must dissociate at least ten times as fast as the primary bromide, in order to account for the equilibrium. Thus the usual formation of isopropyl bromide in the addition reaction is due to the fact that addition is complete long before equilibrium is established. Since both mechanisms of addition and rearrangement lead to the formation of the same equilibrium mixture, addition by the normal mechanism must always give at least a little of the *n*-propyl bromide; addition by the chain mechanism must always give some isopropyl bromide; and any catalyst which preferentially accelerates formation of one bromopropane must also preferentially favor the dissociation of the same bromopropane.

From the liquid-phase equilibrium data for normal and isopropyl bromides (the equilibrium mixture containing 91% of isopropyl bromide at 26°, 67% at 250°), calculation shows that the isomerization of primary to secondary halide evolves 2.2 kcal./mole.[21] Conn, Kistiakowsky and Smith[22] have justified the Markownikoff rule for the addition of halogen acids to alkenes because it predicts the formation of the thermodynamically more stable alkyl halides. While this generalization may well be correct for unsaturated hydrocarbons, it does not apply to vinyl bromide. Although in this case the normal addition of hydrogen bromide yields almost exclusively ethylidene bromide in the liquid phase at room temperature[15] or 100°,[23] or in the vapor phase at 200°,[23] the equilibrium mixture at 250° contains about 80% of ethylene bromide. Thus, here the abnormal addition yields the more stable of the two possible products.

The Redistribution Reaction.—Ethyl chloride and ethylene bromide react at room temperature in the presence of aluminum chloride to give a mixture containing ethyl bromide, ethylene chloride, ethylene chlorobromide, and the original halides.[24] Since it has now been shown that aluminum chloride does not rearrange the dichloro- and dibromoethanes below their boiling points, while replacement of one halogen by another occurs easily, the redistribution reaction of Calingaert, *et al.*, must involve a displacement reaction,[25] not loss and readdition of hydrogen halides.

Summary

The liquid-phase rearrangement of the bromopropanes to an equilibrium mixture has been studied. Many analogies between this reaction and the addition of hydrogen bromide to alkenes suggest that rearrangement of an alkyl bromide occurs by loss and readdition of hydrogen bromide and that the reactions proceed by two mechanisms. The first of these is a non-chain mechanism accelerated by soluble bromide salts or hydrogen bromide and retarded by substances which remove hydrogen bromide. The second is an atom-chain mechanism accelerated by oxygen and inhibited by antioxidants. Alkyl chlorides rearrange by the non-chain mechanism.

Since rearrangement of either propyl bromide is accelerated by catalysts for both mechanisms, the commonly observed formation of a single addition product from a halogen acid and an alkene is due to the fact that the first-formed addition product rearranges very slowly. Although the non-chain addition (in accord with Markownikoff's rule) usually yields the thermodynamically more stable isomer, the addition of hydrogen bromide to vinyl bromide is exceptional.

With the dihaloethanes, the replacement of one halogen by another in the presence of aluminum chloride or bromide proceeds much more easily than rearrangement.

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(20) Kharasch, Kleiger and Mayo, *J. Org. Chem.*, **4**, 428 (1939).

(21) Errors of 2% in the composition of the equilibrium mixtures would lead to a maximum error of 0.4–0.5 kcal./mole in the heat of isomerization. The heat effect for the vapor-phase isomerization can be calculated as 2.9 kcal./mole from the heats of hydrogenation and bromination of alkenes, Kistiakowsky, Ruhoff, Smith and Vaughan, THIS JOURNAL, **57**, 876 (1935).

(22) Conn, Kistiakowsky and Smith, *ibid.*, **60**, 2764 (1938).

(23) Wibaut, *et al.*, *Rec. trav. chim.*, **50**, 313 (1931). The maximum recorded yield of ethylidene bromide is assumed to approach most closely the composition of the normal addition product, for the most probable side-reactions (abnormal addition and rearrangement) tend only to increase the proportion of ethylene bromide.

(24) Calingaert, Soroos, Hnizda and Shapiro, THIS JOURNAL, **62**, 1545 (1940).

(25) Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 131.

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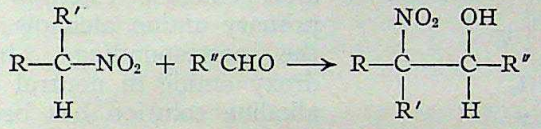
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, POLYTECHNIC INSTITUTE OF BROOKLYN]

Preparation and Catalytic Reduction of 3-Nitrobutyl-2 *p*-Nitrobenzoate[1]

BY JULIAN R. REASENBERG AND G. B. L. SMITH

The commercial production of the nitroparaffins has greatly stimulated interest in the derivatives of these compounds.[2] Of these derivatives, the nitroalcohols and the corresponding amino alcohols are of prime importance because of their similarity in structure to compounds exhibiting physiological activity.

The reaction between nitroparaffins and aliphatic aldehydes to produce nitroalcohols was first described by Henry,[3] and since then has been studied extensively. A glance at the structure



of a nitroalcohol formed from a nitroparaffin higher than nitromethane and an aldehyde higher than formaldehyde, will indicate that the compound contains two asymmetric carbon atoms and should exist in diastereoisomeric forms. To date, only one case of the separation of the *erythro* and *threo* forms of an aliphatic nitroalcohol has been reported.[4]

The compound prepared from nitroethane and acetaldehyde, 3-nitrobutanol-2, fulfills these conditions and should exist as two chemical entities. However, careful fractionation of this compound by the authors as well as by Vanderbilt and Hass[4] has failed to show the presence of the diastereoisomerides.

Some of the fatty acid esters of the nitroalcohols have been described. Vanderbilt and Hass[4] have prepared the acetates of a wide variety of nitroalcohols by allowing them to react with acetic anhydride. Tyndall[5] has prepared the propionates, butyrates, and isobutyrates of these compounds. The nitroalcohols and corresponding esters in which the nitro group is linked to a secondary carbon atom are relatively unstable. Boiling water or 0.1 *N* sodium bicarbonate decomposed the esters of 3-nitrobutanol-2 into the acid and 3-nitrobutene-2.[4,5]

3-Nitrobutanol-2 was prepared by a method similar to that described by Vanderbilt and Hass[4] although the method was developed independently before the publication of the method of Vanderbilt and Hass. The product could be purified by vacuum distillation without decomposition although it has been reported to decompose explosively at times upon low pressure distillation.[6] On standing for several months in a sealed container it decomposed somewhat with the formation of nitrobutene. Attempts to prepare the nitrobenzoate by the usual chemical methods resulted in failure until a low temperature acylation in the presence of pyridine was performed. The product so obtained was a white solid with a wide melting point range, 80–85°. After eight to ten recrystallizations from alcohol the product melted sharply at 107–108°. This purification could also be effected with greater ease by a partial and stepwise treatment of the alcoholic solution with sodium hydroxide. Two successive treatments with 10% of the theoretical amount of alkali each time usually sufficed to give a product which, after one recrystallization from alcohol, melted at 107–108°.

The "crude" ester and the purified ester gave the same saponification equivalent 134, and both products contained essentially the same percentage of carbon, hydrogen, and nitrogen. This would indicate that the "crude" ester is a mixture of the diastereoisomerides previously postulated. The lachrymator 3-nitrobutene-2 was always present in the mother liquors from the recrystallization of the impure product but was not present in the liquor from the recrystallization of the pure product. Also the nitro-olefin was present in large quantities in the liquor resulting from the alkali treatment.

All of these facts seem to indicate that the 3-nitrobutanol-2 is a mixture of the two isomers and on esterification, the ester formed is "crude" because of the presence of both isomers. Also, one of the isomers is preferentially hydrolyzed and(or) is decomposed in the presence of alkali to 3-nitrobutene-2. Dilute solutions of ammonium hydroxide and sodium bicarbonate were also effective in this process. Several attempts were made to isolate the unstable isomer by fractional crystallization of the mother liquors but these were unsuccessful because of the thermal instability of the compound,[4,5] and only the decomposition products, *p*-nitrobenzoic acid and 3-nitrobutene-2, were isolated.

A study was made of the reduction and reduction products of 3-nitrobutyl-2 *p*-nitrobenzoate. Figure 1 illustrates the products formed under varying conditions of reduction with both Raney nickel and Adams platinum oxide catalysts. In all of the reductions employing Raney nickel the catalyst was promoted with platinic chloride

(1) This paper is abstracted from part of the thesis submitted by Julian R. Reasenberg (Novocol Chemical Co. Research Fellow 1938–1940, present address G. M. Chemical Co., Inc., New York, N. Y.) to the Graduate Faculty of Polytechnic Institute of Brooklyn in partial fulfillment of the requirements for the degree of Doctor of Philosophy in June, 1941.

(2) Hass, *et al.*, *Ind. Eng. Chem.*, **28**, 339 (1936); **30**, 67 (1938); **31**, 118, 648 (1939); **32**, 427 (1940); *Chem. Rev.*, **32**, 373 (1943).

(3) Henry, *Compt. rend.*, **120**, 1265 (1895).

(4) Vanderbilt and Hass, *Ind. Eng. Chem.*, **32**, 34 (1940).

(5) Tyndall, *ibid.*, **33**, 65 (1941).

(6) Private communication, The Commercial Solvents Corp.

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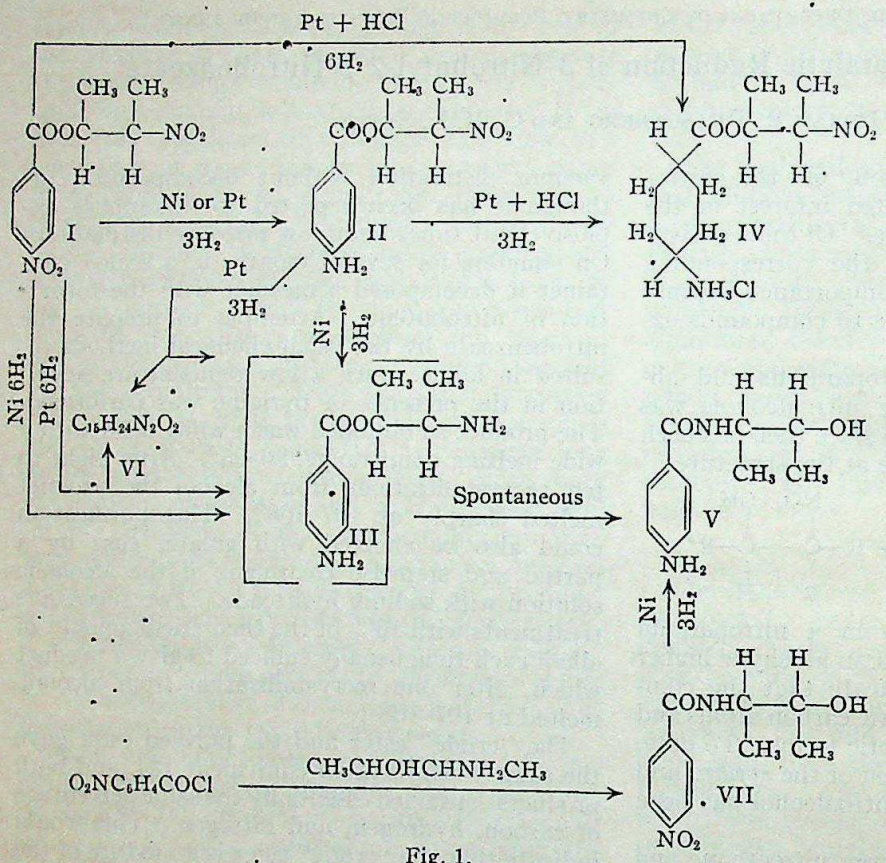

Fig. 1.

as previously described.[7] The qualitative and quantitative results did not vary when similar experiments were performed with the promoted and unpromoted nickel but the reduction proceeded at a much more rapid rate when the platinic chloride was added to the nickel. Also the results did not vary whether the hydrogenation was performed at atmospheric pressure or at 3–4 atmospheres. The apparatus has been described previously.[7]

3-Nitrobutyl-2 *p*-nitrobenzoate I, contains two nitro groups and the reduction could be effected either stepwise or completely by allowing either 3 or 6 moles of hydrogen to be absorbed. With either catalyst the only product formed when 3 moles of hydrogen was absorbed was the corresponding amino compound II. This compound was then reduced under varying conditions to give a number of products. The hydrochloride of II was quite acidic and Raney nickel could not be used to effect its reduction. With Adams catalyst however, the hydrogenation proceeded slowly but smoothly with the formation of the cyclohexane derivative 3-nitrobutyl-2 *p*-aminohexahydrobenzoate hydrochloride IV. The formation of this product is probably due to the fact that acid inhibits the reduction of an aliphatic nitro group by means of platinum and promotes the reduction of the benzene ring by means of platinum.[8] On acid hydrolysis, 3-nitrobutene-2 and *p*-aminohexahydrobenzoic acid, m. p. 285°,[9] were formed.

In neutral solution with Raney nickel, II is reduced slowly to give V, N-(*p*-amino benzoyl)-2,3-butanolamine. The formation of this amide alcohol presumably occurs through the rearrangement of compound III, 3-aminobutyl-2 *p*-aminobenzoate. This rearrangement of esters of β-primary amino alcohols to the corresponding β-hydroxy amide in neutral or alkaline solution has been described for a wide variety of compounds.[10,11,12,13] The structure of compound V was proved by its synthesis from N-(*p*-nitrobenzoyl)-2,3-butanolamine by catalytic reduction.

With Adams platinum oxide in neutral solution, 3-nitrobutyl-2 *p*-aminobenzoate II is reduced to give two products, V and VI. Compound VI is an oily base which is insoluble in water but is soluble in most organic solvents and in dilute acid. The numbing effect of a local anesthetic is produced when a drop of the oil is placed on the tongue and mucous membranes of the mouth. All attempts to produce a solid salt with the common inorganic and organic acids failed. On hydrolysis, *p*-aminobenzoic acid was isolated. A diacetyl derivative was formed which could be obtained in pure crystalline form. The empirical formula of the oil is tentatively set at $C_{15}H_{24}N_2O_2$ and that of the diacetyl derivative at $C_{19}H_{28}N_2O_4$. The picrate was also prepared and analyzed. Its formula is postulated as $C_{21}H_{27}N_5O_9$.

In addition to compounds V and VI there was also isolated from the reduction of II, *p*-amino benzoic acid and ammonia. The difference between the postulated formula of VI and the formula of III is C_4H_8, and this together with the fact that ammonia was one of the products of reduction would indicate that VI might be formed by the reaction of III with butanolamine with the elimination of ammonia and water.

The complete reduction of 3-nitrobutyl-2 *p*-nitrobenzoate I with the absorption of 6 moles of

(7) Lieber and Smith, THIS JOURNAL, **58**, 1417 (1936); Reasenberg, Lieber and Smith, *ibid.*, **61**, 384 (1939); Scholnik, Reasenberg, Lieber and Smith, *ibid.*, **63**, 1192 (1941).

(8) Hiers and Adams, *Ber.*, **59**, 162 (1926).

(9) Greenstein and Wyman, THIS JOURNAL, **60**, 2341 (1938).

(10) Gabriel and Heymann, *Ber.*, **23**, 2492 (1890).

(11) Gabriel, *Ann.*, **409**, 326 (1915).

(12) Jacobs and Heidelberger, *J. Biol. Chem.*, **21**, 421 (1915).

(13) Bergmann and Brand, *Ber.*, **56B**, 1280 (1923).

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hydrogen produces the same results and products as the sum of the two stepwise hydrogenations involved. Thus I with Pt and HCl forms IV; I with Pt in neutral solution gives V and VI; and I with Raney nickel forms V.

Experimental

3-Nitrobutanol-2.[14]—A solution of 40 g. of acetaldehyde (0.91 mole) and 71 g. of nitroethane (0.90 mole) dissolved in 60 ml. of 95% ethanol was treated with 0.8 g. sodium hydroxide dissolved in 2 ml. of water. The solution was allowed to stand for five days at room temperature at which time the color had deepened to yellow. The alkali was neutralized with concd. hydrochloric acid, the color changing to blue-green, and the precipitated sodium chloride was allowed to settle and was separated by decantation. The solvent was removed by distillation under diminished pressure and the residue was vacuum distilled. After a small fore-run of 3-nitrobutene-2 (strong lachrymator) the main fraction of 3-nitrobutanol-2 came over as a light yellow liquid with a slight acrid odor weighing 99 g. The product had the following characteristics: b. p. 90° (11 mm.), b. p. 99° (17 mm.), d^{20}_4 1.1260, $n^{22}D$ 1.4425, mol. ref. calcd. 28.0, found 28.0.[15]

2,3-Butanolamine.[16,17,18,19]—A solution of 47.6 g. of 3-nitrobutanol-2 dissolved in 120 ml. of ethanol was reduced at 3–4 atm. with 3–4 g. of Raney nickel. The reduction was complete in two hours. The catalyst was removed by filtration and the filtrate was distilled at atmospheric pressure. The aminoalcohol, 7.8 g., boiled at 159°; d^{20}_{20} 0.9414, d^{20}_4 0.9396, $n^{24}D$ 1.4520, mol. ref. calcd. 25.5, found 25.6. Primary oxalate $C_4H_{11}ON \cdot H_2C_2O_4$ from ethanol m. p. 164° dec., secondary oxalate $(C_4H_{11}ON)_2 \cdot H_2C_2O_4$ from ethanol m. p. 206° dec.[20]

3-Nitrobutyl-2 *p*-Nitrobenzoate (I).—Freshly distilled *p*-nitrobenzoyl chloride (53 g. 0.29 mole) was dissolved in 350 ml. of benzene and 34 g. of 3-nitrobutanol-2 (0.29 mole) was added. The beaker and contents were cooled with an ice-bath and, to the well-stirred, yellow solution, was slowly added 26 g. of pyridine (excess), the temperature being kept below 25°. During the addition the color changed to blue-green. The pyridine hydrochloride was removed by filtration and was washed with 50 ml. of benzene. The filtrates were combined and washed with cold dilute solution of sodium bicarbonate which changed the blue-green solution to yellow. The liquid was then washed with water, dried over anhyd. sodium sulfate, and evaporated under diminished pressure to a volume of 100 ml. The temperature was adjusted to 50° and the solution was diluted with 100 ml. of petroleum ether and a precipitate formed. When cold the solution was filtered and the product washed with a little petroleum ether and dried; 70 g. of crude ester m. p. 80–85° was obtained. This was recrystallized once from hot ethanol to give a product melting at 85–90°.

Anal. Calcd. for $C_{11}H_{12}N_2O_6$: C, 49.27; H, 4.51; N, 10.45; sap. eq., 134.1. Found: C, 49.76; H, 4.68; N, 10.17; sap. eq., 134.0.

Separation of Isomers.—The "crude" nitro nitro ester described just above was purified as follows: a hot solution of 450 g. of "crude" ester dissolved in 2500 ml. of ethanol and 500 ml. of water was treated with a solution of 8 g. of sodium hydroxide in 50 ml. of water. The solution darkened to an orange-yellow color and the strong odor of the lachrymous nitrobutene was evolved. The solution was allowed to cool and a white crystalline product started to form. When the temperature reached 40° another 8 g. of sodium hydroxide was added slowly with stirring over a period of one hour. The solution was allowed to stand overnight and the precipitate was then removed by filtration and washed with two 50-ml. portions of cold ethanol and gave on drying 190 g. of ester m. p. 100–104°. This was recrystallized from 2 liters of hot ethanol to give 166 g. of product m. p. 106–108°. One subsequent recrystallization raised the m. p. to 107–108°. The product was a white crystalline compound with a very slight yellowish cast.

Anal. Calcd. for $C_{11}H_{12}N_2O_6$: C, 49.27; H, 4.51; N, 10.45; sap. eq., 134.1. Found: C, 49.17; H, 4.55; N, 10.39; sap. eq., 134.5.

***p*-Nitrobenzoic Anhydride.**—The pyridonium chloride obtained in the acylation described above was dissolved in water and the insoluble fraction was filtered, washed with water and dried; 8 g. of product m. p. 180–185° was obtained. This was recrystallized from ethyl acetate and benzene; soft, slightly yellow, nacreous plates m. p. 191–192° were formed. This product is *p*-nitrobenzoic anhydride[21] and was also synthesized by the method of Holleman,[22] m. p. 191–192°, and a mixed m. p. gave the same value.

Anal. Calcd. for $C_{14}H_8N_2O_7$: N, 8.86; eq. wt., 158. Found: N, 8.98; eq. wt., 158.

3-Nitrobutyl-2 *p*-Aminobenzoate (II).—A solution of 26.8 g. of nitro ester (I) (0.10 mole) dissolved in 100 ml. of dioxane was treated with 4.5 g. of Raney nickel and 0.30 ml. of 10% platinum tetrachloride solution as promoter. The hydrogenation was performed at atmospheric pressure and the hydrogen was absorbed at the rate of 100 ml. per min. When 7200 ml. of hydrogen (0.3 mole) had been absorbed, the rate of hydrogenation diminished considerably and the reduction stopped. The reductate was separated from the catalyst by filtration and the yellow filtrate was treated with 16.7 ml. of 6 *N* hydrochloric acid dissolved in isopropanol (0.10 mole). The copious white precipitate which formed was filtered, washed twice with 30 ml. of dioxane and twice with 50 ml. of ether and dried; 21 g. of white product resulted. This was recrystallized from isopropanol and white platelets of 3-nitrobutyl-2 *p*-aminobenzoate hydrochloride (II HCl) m. p. (rapid heating) 182–183° (dec.) resulted. This compound could be diazotized and coupled with beta-naphthol and gave a red dye. Acid hydrolysis of the amino nitro ester hydrochloride yielded *p*-aminobenzoic acid and 3-nitrobutene-2.

Anal. Calcd. for $C_{11}H_{15}N_2O_4Cl$: C, 48.09; H, 5.50; N, 10.20; Cl, 12.91; sap. eq., 91.5. Found: C, 47.90; H, 5.62; N, 10.23; Cl, 12.99; sap. eq., 91.8.

The free base was prepared by dissolving 65 g. of (II HCl) in 600 ml. of hot ethanol and pouring the resulting solution with stirring into 1 liter of ice and water, containing an excess of ammonium hydroxide. The precipitate was allowed to stand for one hour and was filtered, washed with water and dried; 54 g. of product m. p. 100–102° was obtained. This was recrystallized from 350 ml. of isopropanol after treatment with Darco and 48 g. of white crystalline 3-nitrobutyl-2 *p*-aminobenzoate (II) resulted, m. p. 103°, acetyl derivative m. p. 110°, nitrate m. p. (fast heating) 167–169° (dec.).

Anal. Calcd. for $C_{11}H_{14}N_2O_4$: N, 11.76; sap. eq., 119.0. Found: N, 11.52; sap. eq., 119.0.

3-Nitrobutyl-2 *p*-Aminohexahydrobenzoate Hydrochloride (IV).—A solution of 9.15 g. of 3-nitrobutyl-2 *p*-aminobenzoate hydrochloride (II HCl) (0.033 mole) dissolved in 100 ml. of ethanol was treated with 0.40 g. of platinum oxide. The reduction was performed at atmospheric pressure and room temperature. The hydrogenation proceeded very slowly, 200 ml. of hydrogen being absorbed in seventy-five minutes. After about 800 ml. of hydrogen had been absorbed another 0.20 g. of platinum oxide was added until a total of 2670 ml. of hydrogen had been added and a total of 1.0 g. of platinum oxide had been used.

(14) Henry, *Compt. rend.*, **121**, 210 (1895).
(15) Ref. 6, b. p. 92° (10 mm.), d^{25}_4 1.1296, $n^{20}D$ 1.4420.
(16) Henry, *Ber.*, **33**, 3169 (1900).
(17) Batalin and Ugryumov, *C. A.*, **30**, 6701 (1936).
(18) Wieland and Bossert, *Ann.*, **509**, 1 (1934).
(19) Leffler and Adams, THIS JOURNAL, **59**, 2252 (1937).
(20) Ref. 18, acid oxalate, m. p. 164–165° dec., normal oxalate, m. p. 208° dec.
(21) Thiele, *Ann.*, **314**, 305 (1901).
(22) Holleman, *Rec. trav. chim.*, **15**, 362 (1896).

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This corresponds to 3 equivalents of hydrogen plus that required for the reduction of the platinum oxide. The reductate was filtered and the filtrate was evaporated under diminished pressure until all of the solvent had been removed and 30 ml. of benzene and 50 ml. of *n*-butanol were added. A white precipitate formed which was filtered, washed with butanol and ether and dried; 2.50 g. of 3-nitrobutyl-2 *p*-aminohexahydrobenzoate hydrochloride (IV) was obtained. This was recrystallized from isopropanol and a fine white crystalline product resulted which decomposed at 177° with slow heating and at 184° with rapid heating. The compound formed a neutral aqueous solution which could not be diazotized and coupled with β-naphthol. Upon alkaline hydrolysis the lachrymous nitrobutene was evolved. The chloroplatinate was formed in water solution from which it crystallized as orange cubes with 2 moles of water of crystallization which could be removed by heating at 110° leaving a hygroscopic product.

Anal. Calcd. for $C_{11}H_{21}N_2O_4Cl$: C, 47.06; H, 7.54; Cl, 12.63. Found: C, 46.86; H, 7.70; Cl, 12.71. Calcd. for $(C_{11}H_{21}N_2O_4Cl)_2 \cdot PtCl_4 \cdot 2H_2O$: C, 28.27; H, 4.96; Pt, 20.89. Found: C, 28.47; H, 4.73; Pt, 20.78.

p-Aminohexahydrobenzoic Acid.—One hundred ml. of 10% sulfuric acid was added to 1.92 g. of IV and the solution was refluxed for twenty-four hours. 3-Nitrobutene-2 was evolved during the initial stages of the hydrolysis. The resulting clear colorless solution was treated with an excess of silver sulfate and the silver chloride removed by filtration. The solution was treated with hydrogen sulfide, the precipitate, silver sulfide, was separated by filtration, and the excess hydrogen sulfide was expelled by boiling. The solution was then treated with barium hydroxide until alkaline to phenolphthalein and the slight excess of barium hydroxide was carefully neutralized with 0.1 *N* sulfuric acid. The barium sulfate was removed and the clear colorless solution was evaporated to a volume of 20 ml. On dilution with isopropanol a precipitate formed which was separated by filtration, washed with alcohol and ether and dried; 0.6 g. of white product was obtained. This was recrystallized from aqueous acetone and *p*-aminohexahydrobenzoic acid, m. p. 285°,[9] resulted.

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.63; H, 9.14. Found: C, 58.45; H, 9.04.

N-(*p*-Aminobenzoyl)-2,3-butanolamine V.—A solution of 7.63 g. of II in 100 ml. of alcohol was treated with 4.5 g. of promoted Raney nickel and reduced at 3–4 atm. The equivalent of 3 moles of hydrogen was absorbed in two and one-half hours and on further shaking for two hours no more was absorbed. The solution was filtered and the filtrate was evaporated *in vacuo*. The oily residue was dissolved in 75 ml. of dioxane and saturated with hydrogen chloride. The insoluble oil which formed was separated from the dioxane and dissolved in 50 ml. of isopropanol, 35 ml. of benzene was added and the solution was evaporated to a volume of 35 ml. when, on cooling, a precipitate formed. This was filtered, washed with a few ml. of isopropanol and dried: 3.56 g. of N-(*p*-aminobenzoyl)-2,3-butanolamine hydrochloride was obtained.

The free base was prepared from the hydrochloride, which decomposes without melting, by dissolving it in water and making the solution ammoniacal. On standing this solution deposited crystals which were recrystallized from water to give V as white crystals which can be diazotized and coupled with β-naphthol, m. p. 145–146°. The acetyl derivative, formed from acetic anhydride and water solution of V, crystallized from water as white needles, m. p. 194–195.

Anal. Calcd. for $C_{13}H_{18}N_2O_3$: C, 32.38; H, 7.25; N, 11.19. Found: C, 62.31; H, 7.44; N, 11.40.

V was also synthesized directly. The corresponding *p*-nitrobenzamide was prepared by allowing 1 mole of *p*-nitrobenzoyl chloride to react with 2 moles of 2,3-butanolamine in chloroform solution. The resulting solid was recrystallized from water and gave N-(*p*-nitrobenzoyl)-2,3-butanolamine, VIII, m. p. 158°. This was reduced in alcohol with Raney nickel and 3 moles of hydrogen was absorbed. The reductate was filtered, evaporated, and a solid resulted which by recrystallization from water yielded V, m. p. 145–146° (mixed m. p. 145–146°); acetyl derivative, m. p. 194–195° (mixed m. p. 194–195°).

$C_{15}H_{24}N_2O_2$, VI.—A solution of 12.0 g. of amino nitro ester II, 0.7 g. of platinum oxide and 80 ml. of methanol was treated with hydrogen at atmospheric pressure. A total of 3750 ml. of hydrogen (3 mol.) was absorbed in six hours. The reductate was filtered free of catalyst and the filtrate was evaporated on the water-bath under vacuum after the addition of 20 ml. of benzene. The gummy residue was dissolved in dilute hydrochloric acid and treated with Darco. The filtrate was made neutral to litmus with sodium bicarbonate and the small amount of oil which had formed was removed by filtration. The clear solution was made ammoniacal and the oil which formed was extracted with ether. This was dried over anhydrous sodium sulfate and evaporated; 2.50 g. of oil was obtained which was anesthetic to the tongue.

The water solution which remained after the ether extraction was treated with an excess of acetic anhydride; 3.55 g. of *p*-acetaminobenzoic acid m. p. 255 was formed. The filtrate was made ammoniacal once again and on standing deposited 1.74 g. of N-(*p*-acetaminobenzoyl)-butanolamine m. p. 190–193° (acetyl derivative of V).

The anesthetic oil is a yellow viscous liquid insoluble in water but soluble in all the common organic solvents and dilute acids. Attempts to form a solid salt of this base with the common acids failed. On alkaline hydrolysis, *p*-aminobenzoic acid is formed. The acetyl derivative prepared from acetic anhydride and recrystallized from benzene-ligroin solution melts at 151°.

Anal. Calcd. for $C_{19}H_{28}N_2O_4$: C, 65.49; H, 8.10; N, 8.04. Found: C, 65.58; H, 8.35; N, 8.20.

The picrate, a bright yellow solid, was formed in benzene, m. p. 171.5–172.0°.

Anal. Calcd. for $C_{21}H_{27}N_5O_9$: C, 51.11; H, 5.51; N, 14.20. Found: C, 50.99; H, 5.51; N, 15.09.

Summary

1. The existence of diastereoisomers in 3-nitrobutanol-2 has been demonstrated. One of these had been isolated in the form of the *p*-nitrobenzoate.

2. The catalytic reduction of 3-nitrobutyl-2 *p*-aminobenzoate has been studied under a variety of conditions.

3. Reduction of 3-nitrobutyl-2 *p*-aminobenzoate with Raney nickel results in the formation of N-(*p*-aminobenzoyl)-2,3-butanolamine by rearrangement of the expected product O-(*p*-aminobenzoyl)-2,3-butanolamine.

4. Reduction of 3-nitrobutyl-2 *p*-aminobenzoate with platinum in acid solution causes the ring to be reduced without affecting the aliphatic nitro group.

5. Reduction in neutral solution with platinum results in the formation of an anesthetic oil whose structure has not been completely elucidated.

BROOKLYN, N. Y.

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Carbanilates of α- and β-Methyl-*d*-glucosides

BY W. M. HEARON, GORDON D. HIATT AND CHARLES R. FORDYCE

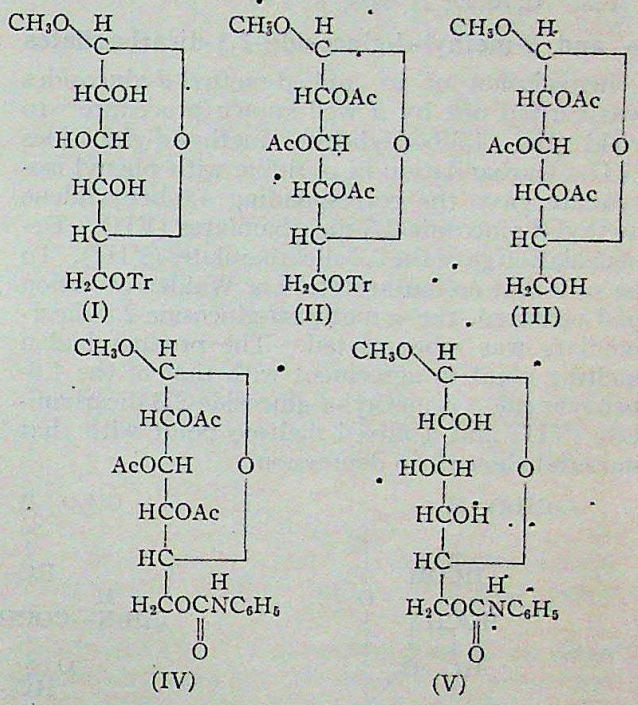
The carbanilate group imparts to its derivatives certain properties which are of considerable value for investigations in the sugar field. These include tendency toward high melting point, water insolubility, tendency to crystallize, ease of preparation under mild conditions, and stability toward mild acid and alkaline reagents.

Tessmer[1] in 1885 prepared carbanilate derivatives of certain sugar alcohols. In 1904, carbanilates of five common sugars were prepared.[2] Jolles and Botrini[3] in 1935 used the carbanilate group to prepare derivatives of four naturally occurring glucosides, and recently Wolfrom and Pletcher[4] have extended this reaction to include several of the simple methyl glucosides. The tendency for glucoside carbanilates to crystallize was utilized by Salmon and Powell.[5]

This report covers the preparation of representative mono, di, and tri carbanilates of α- and β-methyl-*d*-glucosides, and comparison of their physical properties.[5a]

α- and β-Methyl-*d*-glucoside-6-carbanilates. The tritylation[6] of α- or β-methyl-*d*-glucoside[7] gives the corresponding 6-monotrityl derivative (I). Acetylation of this gives 6-trityl methyl-*d*-glucoside 2,3,4-triacetate (II). However, both tritylation and acetylation may be carried out without isolating the intermediate.[8,9] Removal of the trityl group with complete retention of acetyl has been found by Helferich to proceed in acetic acid under the influence of dry hydrogen bromide.[10]

Methyl *d*-glucoside-2,3-4-triacetate (III) prepared by this procedure was carbanilated with phenyl isocyanate in pyridine to produce methyl *d*-glucoside-2,3,4-triacetate-6-carbanilate (IV), which upon deacetylation yielded methyl-*d*-glucoside-6-carbanilate (V). That neither mutarotation nor migration of groups had occurred during deacetylation was shown by reacetylation of the α-methyl-*d*-glucoside-6-carbanilate in good yields to a product whose melting point and



mixed melting point showed no depression with that of α-methyl-*d*-glucoside-2,3,4-triacetate-6-carbanilate.

α- and β-Methyl-*d*-glucoside-2,3,4-triacetate-6-carbanilates.—After drying at 90° for two hours, 50 g. of α-methyl-glucoside-2,3,4-triacetate was dissolved in 40 cc. of dry pyridine and treated with 24 g. (1.5 theory) of phenyl isocyanate. After the initial liberation of heat, the mixture was heated under reflux at 100° for one hour, cooled, diluted with 30 cc. of methanol to remove excess isocyanate, and heated another ten minutes. After cooling, the mixture was poured into cold water, stirred until semi-solid, and the water decanted. Recrystallized twice from hot methanol, 46 g. of α-methyl-*d*-glucoside-2,3,4-triacetate-6-carbanilate (84%) was obtained melting at 147–148°; $[\alpha]^{25}D$ +145°, ($CHCl_3$, $C = 1$).

Anal. C, 54.62; H, 5.80; N, 3.26. Calcd. for $C_{20}H_{25}O_{10}N$: C, 54.7; H, 5.68; N, 3.19.

The crude product from 10 g. of the β-isomer was isolated by warm ligroin, then recrystallized from hot methanol–water; yield, 12 g. (87.5%); m. p. 147–148°; $[\alpha]^{25}D$ +15, ($CHCl_3$, $C = 1$).

Anal. C, 54.95; H, 5.84; N, 3.29.

α- and β-Methyl-*d*-glucoside-6-carbanilates.—Five grams of α-methyl-*d*-glucoside-2,3,4-triacetate-6-carbanilate was refluxed for two hours at 100° with 100 cc. of 0.5% hydrogen chloride in methanol. After cooling, 5 g. of barium carbonate was added, the mixture shaken and filtered. The neutral solution was evaporated by means of an air stream to a sirup containing a white precipitate. The sirup was dissolved in warm ethyl acetate, and filtered from the barium chloride. The solution deposited a gelatinous precipitate which was filtered off, washed with ethyl acetate, and dried. Recrystallization from ethyl acetate yielded 2.5 g. (70%), m. p. 131–133°; $[\alpha]^{25}D$ +115° (pyridine, $C = 1$).

Anal. Calcd. for $C_{14}H_{19}O_7N$: methoxyl, 9.9; C, 53.7; H, 6.07; N, 4.47. Found: methoxyl, 10.2; C, 53.38; H, 6.07; N, 4.46.

(1) H. Tessmer, *Ber.*, **18**, 968 (1885).

(2) L. Maquenne and W. Goodwin, *Bull. soc. chim.*, [3] **31**, 430 (1904).

(3) E. Jolles and M. Botrini, *Gazz. chim. ital.*, **65**, 1217–1221 (1395).

(4) M. L. Wolfrom and D. E. Pletcher, THIS JOURNAL, **62**, 1151 (1940).

(5) M. R. Salmon and G. Powell, *ibid.*, **61**, 3507 (1939).

(5a) For table giving solubilities of the Compounds, order Document 1808 from the American Documentation Institute, 1719 N Street, N.W., Washington 6, D. C., remitting 50¢ for microfilm or 50¢ for photoprints.

(6) B. Helferich, *Ann.*, **440**, 8 (1924).

(7) β-Methyl-*d*-glucoside was prepared by the method of M. L. Maquenne, *Bull. soc. chim.*, [3] **33**, 469–470 (1905).

(8) Helferich, Klein and Schafer, *Ber.*, **59**, 81 (1926).

(9) Helferich and Schneidmuller, *ibid.*, **60**, 2002 (1927).

(10) Helferich, Broderich and Schneidmuller, *Ann.*, **458**, 111 (1927).

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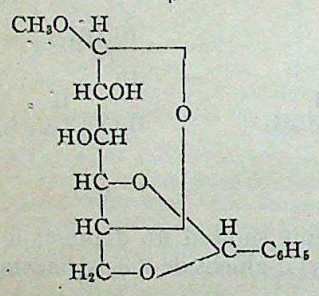
Prepared as the α-isomer, 5 g. of β-methyl-*d*-glucoside-2,3,4-triacetate-6-carbanilate with 100 cc. of 0.5% HCl in methanol gave after recrystallization from ethyl acetate, 2.7 g. (75%) melting at 144–145°. A mixed melting point with the triacetate precursor gave a 10° depression. $[\alpha]^{25}D$ −9°, (pyridine, $C = 1$).

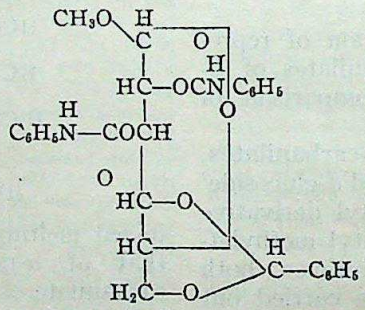
Anal. C, 53.29; H, 6.08; N, 4.44.

α- and β-methyl-*d*-glucoside-2,3-dicarbanilates

Benzalation of α- and β-methyl-*d*-glucosides was carried out by a well-known procedure[11] to yield the 4,6-benzylidene methyl-*d*-glucosides (VI). Carbanilation in pyridine with phenyl isocyanate gave the corresponding 4,6-benzylidene methyl-*d*-glucoside-2,3-dicarbanilates (VII). Debenzalation gave the 2,3-dicarbanilates (VIII). To be sure that no mutarotation or Walden inversion had occurred, the α-methyl-*d*-glucoside-2,3-dicarbanilate was rebenzalated. The product had a melting point in agreement with that of the 4,6-benzylidene α-methyl-*d*-glucoside-2,3-dicarbanilate (VII) and a mixed melting point with that material showed no depression.



(VI)



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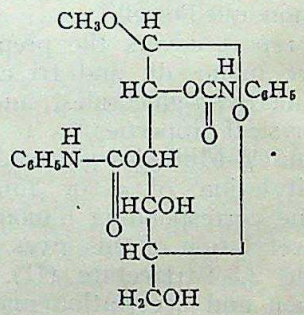

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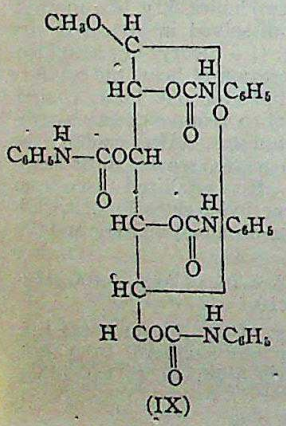

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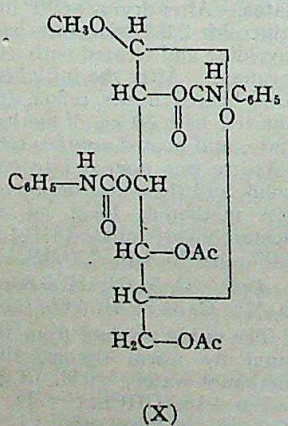

(X)

α-Methyl-*d*-glucoside-2,3-dicarbanilate (VIII) further reacted completely with phenyl isocyanate in pyridine to give the tetracarbanilate (IX) previously prepared.[4] Both α- and β-methyl-*d*-glucoside-2,3-dicarbanilates (VIII) were acetylated in pyridine with acetic anhydride to give the corresponding 4,6-diacetates (X). These materials have somewhat better crystallizing properties than their precursors, as might be expected.

4,6-Benzylidene α- and β-Methyl-*d*-glucoside-2,3-dicarbanilates.—To 20 g. of 4,6-benzylidene α-methyl-*d*-glucoside (dried at 100° for four hours) dissolved in 40 cc. of dry pyridine was added 25 g. of phenyl isocyanate (1.5 × theoretical). After the initial evolution of heat, the mixture was heated for one hour at 100° under reflux. To the cold solution was added 10 cc. of methanol to remove excess isocyanate. After ten minutes, 700 cc. of ligroin was added and the mixture stirred on a steam-bath. The oil changed to a white solid and was removed by filtration while hot. The filtrate containing methyl carbanilate was discarded. The precipitate when dried was ground to a powder, digested with hot methanol, cooled, and filtered; yield, 30 g. (92%); m. p. 216–217°; $[\alpha]^{25}D$ +40°, ($CHCl_3$, $C = 1$).

Anal. Calcd. for $C_{28}H_{28}O_8N_2$: C, 64.6; H, 5.43; N, 5.38; CH_3O, 5.96. Found: C, 64.64; H, 5.36; N, 5.39; CH_3O, 5.91.

Nine grams of 4,6-benzylidene β-methyl-*d*-glucoside in 30 cc. of dry pyridine treated with 11.4 g. of phenyl isocyanate gave 14 g. of product from hot alcohol (85%), m. p. 247–248°; $[\alpha]^{25}D$ −50°, ($CHCl_3$, $C = 1$).

Anal. C, 64.94; H, 5.40.

α- and β-Methyl-*d*-glucoside-2,3-dicarbanilates.—Thirty grams of 4,6-benzylidene-α-methyl-*d*-glucoside-2,3-dicarbanilate was refluxed for two hours with 300 cc. of 0.75% hydrogen chloride in methanol. The hydrogen chloride was removed with 36 g. of barium carbonate, the filtrate concentrated to a sirup, and after dilution with chloroform was filtered from barium chloride and concentrated to a small volume. Seeding the solution yielded a white precipitate, which was recrystallized from a mixture of ligroin and ethyl acetate (3:1); yield 23 g. (92%); m. p. 151–153°; $[\alpha]^{25}D$ +55°, (pyridine, $C = 1$).

Anal. Calcd. for $C_{21}H_{24}O_8N_2$: C, 58.3; H, 5.60; N, 6.48. Found: C, 58.51; H, 5.53; N, 6.49.

4,6-Benzylidene β-methyl-*d*-glucoside-2,3-dicarbanilate (13.5 g.) in 135 cc. of 0.75% hydrogen chloride in methanol gave 6 g. of product from hot methanol (53%); m. p. 219–220°; $[\alpha]^{25}D$ −103°, (pyridine, $C = 1$).

Anal. C, 58.2; H, 5.54; N, 6.35.

α- and β-Methyl-*d*-glucoside-2,3-dicarbanilate-4,6-diacetates.—Acetylation of α-methyl-*d*-glucoside-2,3-dicarbanilate (6.5 g.) in 50 cc. of pyridine by 30 cc. of acetic anhydride for three hours at 100° gave, after recrystallization from methanol, 5.2 g. (67%), m. p. 189–190°; $[\alpha]^{25}D$ +124° (pyridine, $C = 1$).

Anal. Calcd. for $C_{25}H_{28}O_{10}N_2$: C, 58.2; H, 5.47; N, 5.43. Found: C, 58.31; H, 5.44.

β-Methyl-*d*-glucoside-2,3-dicarbanilate (0.44 g.) in 3 cc. of pyridine, treated with 2 cc. of acetic anhydride gave 0.4 g. from hot methanol (64%), m. p. 217–218°; $[\alpha]^{25}D$ −22° (pyridine, $C = 1$).

Anal. C, 58.2; H, 5.28; N, 5.48.

α- and β-Methyl-*d*-glucoside-2,3,4-tricarbanilates

6-Trityl methyl-*d*-glucoside (I) treated with phenyl isocyanate in pyridine gave the tricarbanilate (XI) which on detritylation produced the desired 2,3,4-tricarbanilate (XII).

(11) Freudenberg, Toepffer and Anderson, *Ber.*, 61, 1753 (1928).

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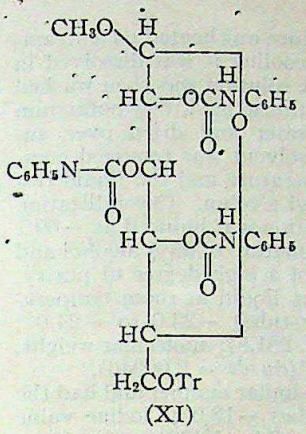
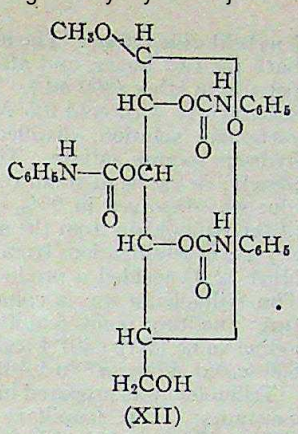


(XI)



(XII)

6-Trityl α- and β-Methyl-*d*-glucoside-2,3,4-tricarbanilates.—To 10 g. of 6-trityl-α-methyl-*d*-glucoside, dried at 100°, in 25 cc. of dry pyridine was added 15.9 g. of phenyl isocyanate. After one hour at 100°, the mixture was washed with water, then with hot ligroin, after which it solidified. Recrystallization from benzene gave 12.8 g. (83%), m. p. 229–231°, $[\alpha]^{25}D$ +52° ($CHCl_3$, $C = 1$).

Anal. Calcd. for $C_{47}H_{43}O_9N_3$: C, 71.2; H, 5.42; N, 5.29; trityl, 30.6. Found: C, 70.89; H, 5.35; N, 5.53; trityl, 30.1.

Prepared as the α-isomer, 10 g. of 6-trityl-β-methyl-*d*-glucoside in 15 cc. of pyridine and 15 cc. of phenyl isocyanate gave from hot benzene 7.45 g. (82%), m. p. 232–234°; $[\alpha]^{25}D$ −5° ($CHCl_3$, $C = 1$).

Anal. C, 71.13; H, 5.45; N, 5.35.

α- and β-Methyl-*d*-glucoside-2,3,4-tricarbanilates.—6-Trityl α-methyl-*d*-glucoside-2,3,4-tricarbanilate (4 g.) was refluxed for two hours with 20 cc. of methanol containing 1% hydrogen chloride. After cooling, the solution was seeded with trityl methyl ether. The precipitate was filtered off and the filtrate evaporated on a steam-bath to a small volume then to dryness by means of air. The residue was dissolved in acetone diluted with benzene and the solution heated until most of the acetone had boiled off. On cooling, the product was precipitated and was filtered off. This purification was repeated twice, giving 1.5 g. (54%), m. p. 192–193°; $[\alpha]^{25}D$ +84° ($CHCl_3$, $C = 1$). The product, when dissolved in concentrated sulfuric acid, gave no yellow color and on dilution with water produced no precipitate.

Anal. Calcd. for $C_{23}H_{29}O_9N_3$: C, 60.96; H, 5.27; N, 7.62. Found: C, 60.71; H, 5.20; N, 7.56.

Following the procedure for the α-isomer, 5 g. of 6-trityl-β-methyl-*d*-glucoside-2,3,4-tricarbanilate was refluxed for three hours in 40 cc. of methanol containing 1% hydrogen chloride. During this period of heating β-methyl-*d*-glucoside-2,3,4-tricarbanilate precipitated. After cooling the precipitate was filtered, washed with methanol and dried; yield, 2.4 g. (68%), m. p. 230–232°. By repeated crystallization from ethyl acetate and acetone, the melting point could be raised to 234.5°; $[\alpha]^{25}D$ +6° (pyridine, $C = 1$).

Anal. C, 60.83; H, 5.18; N, 7.59.

Acknowledgment.—The authors wish to express their appreciation for the assistance of John T. Clarke in connection with the experimental part of this paper.

Summary

Certain mono-, di- and tricarbanilates of both α- and β-methyl-*d*-glucosides have been prepared and identified.

For preparation of glucoside derivatives these carbanilates have the advantages of being high melting, stable, readily prepared, and, in general, easily crystallized.

ROCHESTER, N. Y. RECEIVED DECEMBER 6, 1943

[CONTRIBUTION NO. 522 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Unsaturated Synthetic Glycerides. VII. Preparation and Properties of Synthetic 1-Monoglycerides and Simple Triglycerides of Linoleic and Linolenic Acids[1]

BY B. F. DAUBERT AND A. R. BALDWIN[2]

During the investigation in this Laboratory on the preparation of synthetic glycerides containing unsaturated acids, it was determined experimentally that both linoleyl and linolenyl chlorides could be prepared, in good yields, from the respective debromination acids and oxalyl chloride.[3] The total diene conjugation in each acid chloride, when examined spectrophotometrically, was less than 1%. As a result of this work these acid chlorides were considered satisfactory for the synthesis of highly purified synthetic glycerides.

Since both 1-monolinolein and trilinolein have been reportedly prepared by other methods, a comparison of the properties of the compounds prepared by independent methods would serve to establish whether the glycerides synthesized, using acid chlorides as intermediates, exhibit any significant differences in properties.

The preparation of 1-monolinolein by heating dry potassium linoleate with 1-monochlorhydrin at 160° for one hour in an atmosphere of carbon dioxide was reported by Izar.[4] This same investigator also reported the synthesis of trilinolein from trichlorhydrin and potassium linoleate. In both instances, the compounds were reported as oily liquids but were not further characterized. More recently Black and Overley[5] reported the synthesis of 1-monolinolein and trilinolein by debromination of the respective 1-(9,10,12,13-tetrabromo)-stearin and tri-(9,10,12,13-tetrabromo)-stearin; the latter compounds were synthesized using tetrabromostearyl chloride. These investigators indicated that possible configurational changes could be avoided when de-

(1) The authors are indebted to the Buhl Foundation and to Swift and Company for grants in support of this investigation.

(2) Nutrition Foundation, Inc., Fellow.

(3) Wood, Jackson, Baldwin and Longenecker, THIS JOURNAL, 66, 287 (1944).

(4) Izar, *Biochem. Z.*, 60, 320 (1914).

(5) Black and Overley, THIS JOURNAL, 61, 3051 (1939).

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bromination of the glycerides was delayed until the final step of the synthesis. Later, Wheeler, Riemenschneider and Sando[6] reported the preparation of trilinolein by direct esterification of glycerol with linoleic acid. While iodine values and saponification equivalents of the latter two independently prepared trilinoleins agreed well with theoretical values, the melting points and refractive indices were significantly different. To clarify the obvious discrepancies in these two physical constants we have prepared trilinolein, by an accepted method of synthesis, using linoleyl chloride and glycerol. Analytical constants of the resulting product indicated a high degree of purity. The refractive index and capillary melting point were essentially the same as those reported by Wheeler, *et al.*[6] Thermometric measurements, by a method described previously,[7] verified the existence of the two polymorphic forms reported by the latter investigators.

Experimental

Preparation of Intermediates.—Linoleic and linolenic acids were prepared from tetrabromostearic acid (m. p. 115°) and hexabromostearic acid (m. p. 186°), respectively, by debromination in ether solution according to the method of Frankel and Brown.[8]

Linoleyl and linolenyl chlorides were prepared from the respective acids by the method described previously.[3] In each case, the resulting chlorides had the same constants as those reported.

Preparation of 1-Monolinolenin.—To a cooled solution of acetone-glycerol (36 g.) in quinoline (23 g.) and dry chloroform (40 ml.) there was added slowly linolenyl chloride (43 g.). The mixture was allowed to stand at room temperature for four hours. After the addition of dry peroxide-free ether, the solution was washed carefully and successively with cold 0.5 *N* sulfuric acid, 5% potassium carbonate solution and distilled water. The ether solution was then dried over anhydrous sodium sulfate and after filtration it was then reduced in volume to *ca.* 100 ml., *in vacuo*, at room temperature. The solution was transferred to a liter beaker and cooled to approximately 0° in an ice-bath. Hydrochloric acid (100 ml.) was poured into the solution slowly with constant stirring. After allowing the solution to stand for thirty minutes, ice water (500 ml.) was added, the separated product dissolved in peroxide-free ether, and the solution was washed with distilled water until free of mineral acid. The ether solution was dried over anhydrous sodium sulfate and after filtration it was reduced to a volume of *ca.* 75 ml. After the addition of an equal volume of petroleum ether, it was cooled to −20° for twenty-four hours. The 1-monolinolenin, which separated as a white crystalline mass, was recrystallized several times from the same mixture of solvents: melting point (capillary tube)[9] 16.0–17.0°; iodine value (Wijs) 214.8 (calcd. 216.2); molecular weight, 351.6 (calcd. 352.5); $n^{50.0}D$ 1.47589 (dn/dt = 0.00039).

1-Monolinolein was prepared in a similar manner and had the constants: m. p. (capillary tube) 14.0–15.0°; iodine value (Wijs) 142.7 (calcd. 143.3); $n^{20.0}D$ 1.47682 (dn/dt = 0.00038).

Preparation of Trilinolenin.—Glycerol (1 g.) was dissolved in a mixture of quinoline (6 g.) and dry chloroform (30 ml.) and to the solution there was added slowly linolenyl chloride (10 g.). The mixture was heated on a steam-bath for two hours, and after cooling it was dissolved in petroleum ether (300 ml.). The solution was then washed successively with cold 0.5 *N* sulfuric acid, 5% potassium carbonate solution, distilled water and dried over anhydrous sodium sulfate. The solvent was removed completely, *in vacuo*, at room temperature and the liquid residue was dissolved in 95% ethyl alcohol. Crystallization of the trilinolenin from the solution was induced at −60°. Several crystallizations from a mixture of 95% alcohol and ether (2:1) yielded a product of a high degree of purity. The trilinolenin was a colorless liquid at room temperature: melting point (capillary tube) −23.0 to −24.0°; iodine value (Wijs) 261.4 (calcd. 261.6); molecular weight, 866 (calcd. 873); $n^{40.0}D$ 1.48190 (dn/dt = 0.00040).

Trilinolein was prepared in a similar manner and had the constants: m. p. (capillary tube) −13.0°; iodine value (Wijs) 172.8 (calcd. 173.3); $n^{50.0}D$ 1.46815 (dn/dt = 0.00039).

Bromination of Monoglycerides and Triglycerides.—The bromination procedure, given in detail for trilinolenin, was essentially the same for 1-monolinolein, 1-monolinolenin and trilinolein.

Trilinolenin (2 g.) was dissolved in cold petroleum ether (50 ml.). Bromine was added dropwise to the solution, with constant stirring, until the liquid assumed a definite orange color. During the addition of the bromine a gummy mass separated. After decantation of the supernatant liquid, the gummy mass was washed repeatedly with cold petroleum ether. During this treatment practically all of the color was removed. The bromides were then dissolved in a small volume of warm dioxane and on the addition of an equal volume of petroleum ether, crystalline bromides separated. After repeated crystallizations from the same mixture of solvents, the product was dried in a vacuum desiccator; melting point 150–151°.

Anal. Calcd. for $C_{57}H_{92}O_6Br_{18}$; Br, 62.22. Found: Br, 62.18, 62.15.

Bromination of 1-monolinolenin produced a crystalline bromide melting at 172°.

Anal. Calcd. for $C_{21}H_{36}O_4Br_6$: Br, 57.63. Found: Br, 57.60, 57.55.

Melting points of the crystalline bromides obtained from 1-monolinolein and trilinolein were 101.5° and 81.0°, respectively, and were in agreement with those previously reported.[5,6]

Spectrophotometric Analyses.—Each synthetic glyceride was examined for total diene and triene conjugation using a Beckmann Quartz Spectrophotometer, Model DU. In each product, the total diene conjugation was less than 1% and the triene conjugation was negligible. The glyceride exhibiting the least conjugation, oddly enough, was trilinolenin. The absence of a greater amount of conjugation seems to indicate that the synthesis of glycerides containing linoleic and linolenic acids through the acid chlorides does not materially affect the position of the double bonds. It should be borne in mind, however, that the acids present in the synthetic glycerides, while not significantly different from the original debromination acids, may not be identical with the naturally occurring acids.[8]

Discussion

In the warming curves for trilinolein (Fig. 1) it may be observed that Form II melts at −45.6° and Form I at −12.9°. In the thermometric measurements[10] on a bulk sample (1.0 to 1.5 g.), cooling at −75° for twenty to thirty minutes was necessary for its solidification into Form II. Since the temperature of melting was so low, visual observation of the transition of Form II to Form I was possible during warming of the

(6) Wheeler, Riemenschneider and Sando, *J. Biol. Chem.*, **132**, 687 (1940).

(7) Daubert and Clarke, THIS JOURNAL, **66**, 690 (1944).

(8) Frankel and Brown, *ibid.*, **65**, 415 (1943).

(9) Liquid samples placed in capillary tubes were held at −20° for twenty-four hours prior to determination of the melting point.

(10) The assistance of Dr. T. H. Clarke in the thermometric measurements is gratefully acknowledged.

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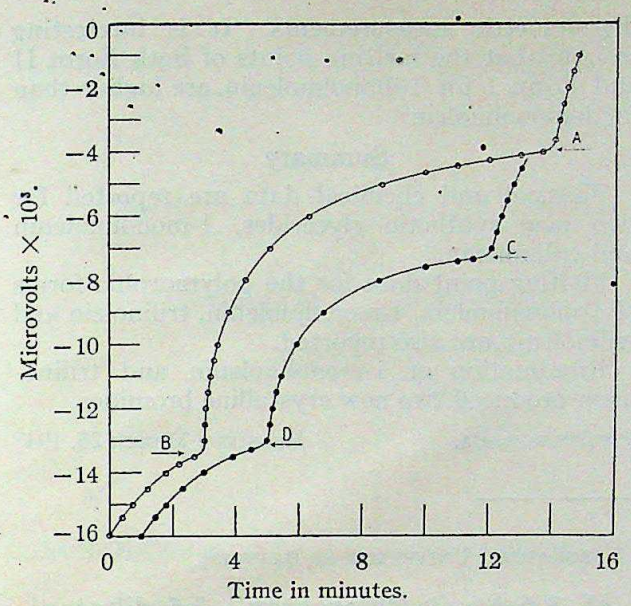

Fig. 1.—Warming curves for trilinolein and trilinolenin: trilinolein—A, 3950 microvolts = −12.9°; B, 13370 microvolts = −45.6°; trilinolenin—C, 7300 microvolts = −24.2°; D, 13100 microvolts = −44.6°.

sample at room temperature. The time required for complete melting of Form II and solidification into Form I depended on the rate of warming. To permit the change to occur sufficiently slowly for complete visual observation, the triglyceride in a small vial was cooled at −75° for thirty minutes in a dry-ice-bath; the temperature was measured with a calibrated thermel and potentiometer. At the end of thirty minutes the glyceride had completely solidified. After the vial was removed from the bath and transferred quickly to a small transparent Dewar flask cooled to −60° on the inside, it was allowed to warm spontaneously at room temperature. Complete transition of Form II into Form I, under these conditions, required approximately three minutes. In the photograph (Fig. 2) it may be seen that an actual melting of Form II occurred at the surface of the glyceride (heat leakage into the sample occurred faster through the thermel than through the sides of the vacuum flask). The progressive melting of Form II and the solidification of the liquid into Form I can be followed in the same photograph. In vials 2, 3, 4, 5 and 6, three phases are observable, solid Form II, melted Form II and solid Form I. While melting of Form II could be demonstrated in small capillary tubes on immersing them in baths of the required temperature, the evidence in Fig. 2 is much more convincing. It may be concluded, therefore, that the transition of Form II to Form I in a bulk sample of trilinolein is definitely accompanied by melting.

Transition Forms of Trilinolein

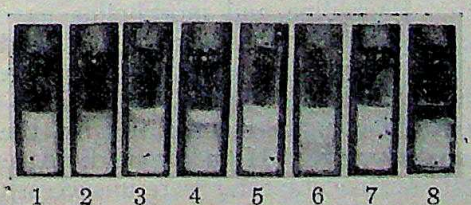

Fig. 2.—Progressive melting of the polymorphic forms of trilinolein: 1, Form II solidified at −75°; 2, Form II beginning to melt; 3, solidification of melted Form II to Form I; 4, 5, 6, progressive stages of transition; 7, completely solid Form I; 8, melting of Form I; m. p. Form II, −45.6°; m. p. Form I, −12.9°.

When the sample of trilinolein was cooled quickly to −60° in a dry-ice-bath no solidification occurred. But on removing the supercooled liquid from the bath and quickly transferring it to the small Dewar flask again cooled to −60° on the inside and allowing it to warm as before, the glyceride solidified at −45.6° in Form I which later melted normally at −12.9°.

Warming curves in Fig. 1 show that trilinolenin also may exist in at least two different forms. Cooling of a bulk sample in a similar manner to trilinolein causes solidification in Form II. Form II melts at −44.6° and Form I at −24.2°. While warming curves only are shown in Fig. 1, Form II was indicated also on cooling curves. The transition of Form II to Form I was not as sharply defined as for trilinolein and occurred much more rapidly.

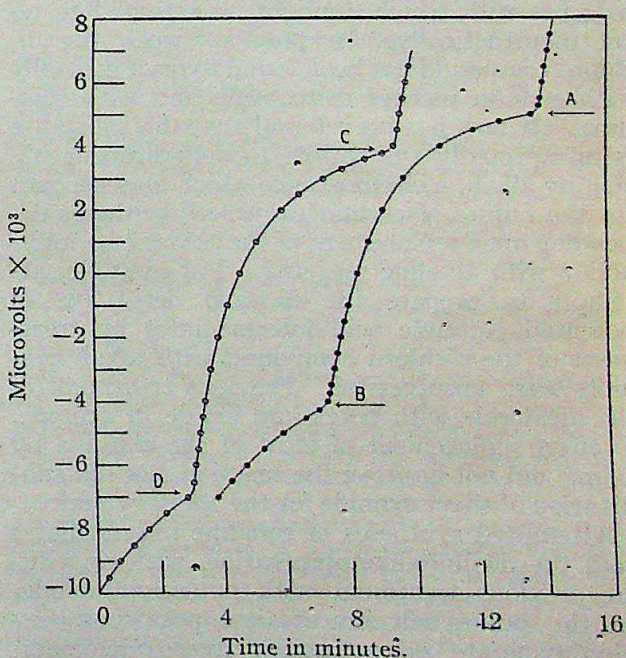

Fig. 3.—Warming curves for 1-monolinolein and 1-monolinolenin: monolinolenin—A, 5000 microvolts = 15.7°; B, 4125 microvolts = −13.5°; monolinolein—C, 3900 microvolts = 12.3°; D, 6875 microvolts = −22.8°.

Warming curves in Fig. 3 indicate the existence of two polymorphic forms for 1-monolinolenin, Form II melting at −13.5° and Form I at 15.7°. As in the case of the triglycerides, Form II was observed visually to melt in bulk sample and sub-

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sequently to solidify as Form I at −13.5°. This unsaturated monoglyceride, previously prepared in this Laboratory by Dr. T. R. Wood and one of us (A. R. B.), when exposed for a short time to air at room temperature, quickly developed a film and a decrease in iodine value. The rates of oxidation of the glycerides reported in this paper are being studied and will be reported at a later date.

Two polymorphic forms (Fig. 3) were also found for 1-monolinolein, Form II melting at −22.8 and Form I at 12.3°. While other forms were anticipated for each 1-monolinolein and 1-monolinolenin on the basis of previous experience, evidence for these forms could not be found from thermometric measurements. It is interesting to note that the melting points of both Form II and Form I for 1-monolinolenin are higher than for 1-monolinolein.

Summary

Physical and chemical data are reported for two new synthetic glycerides, 1-monolinolenin and trilinolenin.

Melting point data for the polymorphic forms of 1-monolinolein, 1-monolinolenin, trilinolein and trilinolenin are also reported.

Bromination of 1-monolinolenin and trilinolenin produced two new crystalline bromides.

PITTSBURGH, PA. RECEIVED MARCH 25, 194

[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

Synthetic Amino Acids. Some Reactions of 3,6-*bis*-(β-Chloroethyl)-2,5-diketopiperazine

BY H. R. SNYDER AND M. E. CHIDDIX[1]

In a continuation of a study[2] of the preparation of amino acids from the easily available 3,6-*bis*-(β - chloroethyl) - 2,5 - diketopiperazine[2b] (I), this substance has been treated with a number of reagents with which it might be expected to react metathetically. In previous work the dichloro compound has been found to react normally with sodium methyl mercaptide and with thiourea. It now has been found that the substance is unexpectedly susceptible to dehydrohalogenation by alkali, a circumstance which may account for the failure of certain projected syntheses depending upon replacement of the chlorine by interaction with alkaline reagents. For example, attempts to prepare the dicyano derivative (a potential glutamic acid intermediate) by treatment of the dichloro compound with alkali cyanides were unsuccessful. Previous treatment of the dichloride with potassium iodide in acetone, to effect replacement of most of the chlorine by iodine, did not improve the reaction, nor did substitution of silver cyanide for the alkali cyanide.

Attempted syntheses of canaline intermediates from the dichlorodiketopiperazine, with or without previous treatment with potassium iodide, and the sodium salt of acetoxime, potassium benzohydroxamate or potassium hydroxylaminedisulfonate likewise were unsuccessful, despite the fact that the closely related reaction of α-benzamido-γ-iodobutyric acid and potassium benzohydroxamate is reported to occur readily.[3]

The dichlorodiketopiperazine reacted readily with sodium hydroxide in refluxing ethanol to form the divinyldiketopiperazine (II). When the chloro compound was present in slight excess the reaction mixture became neutral within twenty to thirty minutes. Although some of the experiments referred to above were carried out after the properties of the divinyl compound were known, the substance was definitely isolated as a product only from the reactions with the sodium salt of acetoxime. However, some of the impure reaction products, from which no unchanged dichlorodiketopiperazine could be recovered, did yield the hydrochloride of α-amino-γ-butyrolactone when subjected to hydrolysis with hydrochloric acid. Both the *bis*-chloroethyl- and divinyldiketopiperazines are converted to the aminolactone by this treatment. In one of the attempted reactions between the dichloro compound and potassium silver cyanide the product isolated was 3,6-*bis*-(β-hydroxyethyl)-2,5-diketopiperazine. This substance also would yield the aminolactone hydrochloride on hydrolysis with hydrochloric acid.

Certain replacements of the halogen atoms in the dichlorodiketopiperazine were effected without difficulty. Piperidine and morpholine gave the corresponding *bis*-tertiary amines (IV and V). The sodium salt of benzylmercaptan reacted to give the *bis*-benzylthioldiketopiperazine (VI). Potassium thiocyanate reacted to give the *bis*-thiocyano derivative (VII) in low yield. Attempts to alkylate acetoacetic ester were unsuccessful.

Experimental

3,6-*bis*-(β-N-Morpholinoethyl)-2,5-diketopiperazine (IV).—A mixture of 5 g. of the dichloride (I) and 15 cc. of morpholine was heated on the steam-bath to 85°. A clear dark solution resulted and the temperature rose to 125°. The mixture was allowed to cool and the crystals were separated by dilution of the liquid portion with ether

(1) Present address, General Aniline and Film Corp., Easton, Pa.

(2) (a) Snyder and Cannon, THIS JOURNAL, 66, 511 (1944); (b) Snyder, Andreen, Cannon and Peters, *ibid.*, 64, 2082 (1942).

(3) Kitagawa, *J. Agr. Chem. Soc. Jap.*, 12, 871 (1936); *C. A.* 31, 1362 (1937).

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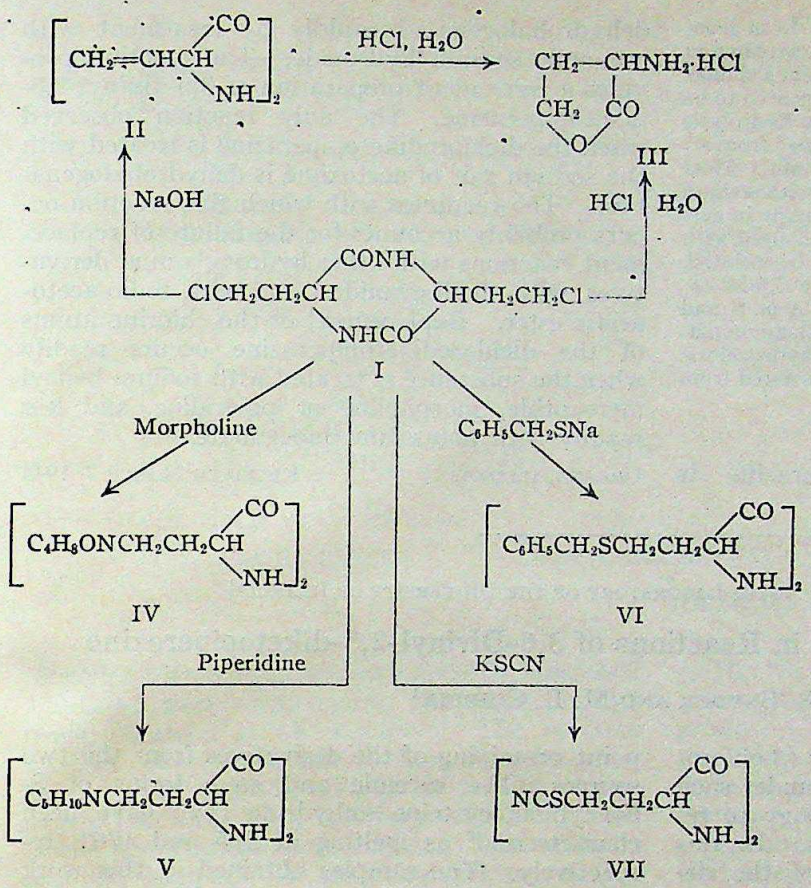

and filtration. The solid was extracted with two 50-cc. portions of chloroform, and the residue from evaporation of this solvent was recrystallized from 95% ethanol. The yield of the product, m. p. 229–232° (cor.), was about 40%.

Anal. Calcd. for $C_{16}H_{28}N_4O_4$: N, 16.45. Found: N, 16.48.

3,6-*bis*-(β-N-Piperidinoethyl)-2,5-diketopiperazine (V) was prepared in much the same way from 2 g. of the dichloride and 5 g. of piperidine. Piperidine hydrochloride and piperidine were separated from the product by water extraction, and the substance was purified by recrystallization from 60% ethanol. It melted at 242–243° (cor.).

Anal. Calcd. for $C_{18}H_{32}N_4O_2$: C, 64.20; H, 9.59. Found: C, 64.26; H, 9.63.

3,6-*bis*-(β-Thiocyanoethyl)-2,5-diketopiperazine (VII).—A mixture of 10 g. of the dichloride (I), 10 g. of potassium thiocyanate and 100 cc. of acetone was shaken mechanically at room temperature for forty hours and then heated under reflux for twenty hours. The hot mixture was filtered and the residue from the evaporation of the filtrate was extracted with hot water and recrystallized from 33% acetic acid. The yield of product, m. p. 207–208° (cor.), was about 15%.

Anal. Calcd. for $C_{10}H_{12}N_4O_2S_2$: C, 42.24; H, 4.23. Found: C, 42.51; H, 4.45.

3,6-*bis*-(β-Benzylthiolethyl)-2,5-diketopiperazine (VI).—A mixture of 5 g. of the dichloride and 100 cc. of an absolute ethanol solution containing 3.25 g. of sodium ethoxide and 6 g. of benzyl mercaptan was heated under reflux for one hour. The hot solution was filtered and the filtrate was cooled. The crystals were separated and the mother liquor was used in a second hot extraction of the original residue. The process was repeated until no additional crop was obtained. The product so obtained melted at 173–174° (cor.) after recrystallization from ethanol (lit.,[4] 165°, 176°). The yield was about 50%.

Anal. Calcd. for $C_{22}H_{26}N_2O_2S_2$: C, 63.73; H, 6.33. Found: C, 63.65; H, 6.49.

3,6-Divinyl-2,5-diketopiperazine (II).—A mixture of 88 g. (0.37 mole) of the dichloride (I) and a cold solution of 26.8 g. (0.67 mole) of sodium hydroxide in 400 cc. of absolute ethanol was stirred mechanically and gradually heated to boiling over a period of about thirty minutes. After being heated under reflux for twenty minutes, the hot mixture was filtered and the filtrate was distilled to dryness under diminished pressure. The yellow crystalline residue was dissolved in 100 cc. of hot chloroform and the solution was filtered. Dilution with 100 cc. of hot carbon tetrachloride and cooling caused crystallization. The solid was collected and washed with a mixture of chloroform and carbon tetrachloride (volume ratio, 1:2), and then with a mixture of ethanol and ether (volume ratio, 1:3). Evaporation of the filtrate and washings gave an additional crop which was treated in the same way. For complete removal of the solvents it was necessary to dry the product under a pressure of 2 mm. or less. The yield of pure, colorless 3,6-divinyl-2,5-diketopiperazine was 38 g. (62%). In ordinary melting point determinations the material darkened slowly and decomposed at temperatures above 240°; however, it melted at 192.5° (cor.) to a clear liquid when the sample tube was immersed in a bath at this temperature. The yields were inferior when other ratios of reactants were used or when sodium ethoxide was substituted for the hydroxide.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.81; H, 6.06. Found: C, 58.07; H, 6.24.

Hydrochloride of α-Amino-γ-butyrolactone (III).—A solution of 4 g. of the divinyldiketopiperazine in 30 cc. of a mixture of equal volumes of concentrated hydrochloric acid and water was heated on the steam cone for eight hours. The solution was concentrated under diminished pressure and the sirupy residue was dissolved in 50 cc. of water. The resulting solution was concentrated to a colorless crystalline residue. This was recrystallized from 95% ethanol. The lactone hydrochloride weighed 3.9 g. (59%) and melted at 199–200° (cor.) (lit.,[5] 198–200°).

Anal. Calcd. for $C_4H_8ClNO_2$: C, 34.92; H, 5.86. Found: C, 35.15; H, 6.08.

The same product was obtained when the dichlorodiketopiperazine was refluxed for two and one-half hours with 15 volumes of concentrated hydrochloric acid. The reaction mixture was diluted with water and worked up as above, to give a product of the same analysis and melting point.

Attempted Preparation of 3,6-*bis*-(β-Iodoethyl)-2,5-diketopiperazine.—Reaction occurred when the dichlorodiketopiperazine was refluxed with an acetone solution containing a slight excess of sodium iodide. The crude iodide decomposed at about 240°. A solvent for recrystallization was not found, and the pure substance was not isolated. A sample recrystallized from methylcellosolve (with apparent decomposition in the hot solvent) was free of inorganic materials and had a carbon content of 26.85% (calcd. for the diiodide, 22.75; for I, 40.0%).

Attempted Reactions of the Dichlorodiketopiperazine (I) with Inorganic Cyanides, with Derivatives of Hydroxylamine and with the Sodium Derivative of Acetoacetic Ester.—Numerous experiments with each reagent were carried out, usually with both the dichloride and the crude diiodide. The divinyldiketopiperazine (II) was definitely

(4) du Vigneaud, Patterson and Hunt, *J. Biol. Chem.*, **126**, 217 (1938).

(5) Feofilaktov and Onishchenko, *J. Gen. Chem.* (U. S. S. R.), **9**, 304, 314 (1939); *C. A.*, **33**, 878 (1940).

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isolated (identified by m. p. and mixed m. p.) from reactions of the dichloride and the sodium salt of acetoxime in absolute ethanol. The solid product isolated from a similar reaction with potassium benzohydroxamate appeared to be impure II; the oily products gave only III on hydrolysis with hydrochloric acid, as did similar oils obtained from reactions with potassium hydroxylaminedisulfonate. Most of I was recovered from attempted reactions with sodium cyanide in acetone or ethanol or potassium cyanide in acetone; dark solutions resulted when ethanol was used with potassium cyanide and no pure product could be isolated. Aqueous potassium silver cyanide and I gave 3,6-*bis*-(β-hydroxyethyl)-2,5-diketopiperazine (identified by m. p. and analysis). Treatment of the crude diiodide with ammoniacal silver cyanide, followed by hydrolysis with hydrochloric acid, gave only III. No pure substance was isolated from the reactions with sodio acetoacetic ester.

Summary

3,6-*bis*-(β-Chloroethyl)-2,5-diketopiperazine is dehydrohalogenated rapidly by treatment with ethanolic sodium hydroxide. The reaction provides a convenient preparation of 3,6-divinyl-2,5-diketopiperazine. The only reaction observed when the dichlorodiketopiperazine is treated with the sodium salt of acetoxime is dehydrohalogenation. The readiness with which this reaction occurs probably accounts for the failure of replacement reactions with other hydroxylamine derivatives, with alkali cyanides, and with sodio acetoacetic ester. Replacement of the chlorine atoms of the dichlorodiketopiperazine occurs readily when the substance is treated with sodium benzyl mercaptide, morpholine or piperidine, and less readily with potassium thiocyanate.

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[CONTRIBUTION FROM THE NOYES LABORATORY OF THE UNIVERSITY OF ILLINOIS]

Non-Markownikoff Addition in Reactions of 3,6-Divinyl-2,5-diketopiperazine

BY H. R. SNYDER AND M. E. CHIDDIX[1]

The dehydrohalogenation of 3,6-*bis*-(β-chloroethyl)-2,5-diketopiperazine[1a] proceeds under such mild conditions as to suggest an analogy to reactions of β-halocarbonyl compounds. In this paper are recorded some reactions of the dehydrohalogenation product (3,6-divinyl-2,5-diketopiperazine, I) which show its properties to resemble those of α,β-unsaturated carbonyl compounds.

The divinyldiketopiperazine (I) was found to undergo the addition of hydrogen chloride readily. The product so obtained had physical properties identical with those of the 3,6-*bis*-(β-chloroethyl)-2,5-diketopiperazine (II) from which the divinyl compound was prepared. Since the yield of the addition product was good, and since the divinyl compound was halogen-free, it is not possible that the dichloro compound isolated was present as an impurity in the unsaturated substance (I). That the addition product is indeed 3,6-*bis*-(β-chloroethyl)-2,5-diketopiperazine was proved by converting it to the known methionine anhydride (III)[2] and the known 3,6-*bis*-(β-benzylthiolethyl)-2,5-diketopiperazine (IV).[3] The same derivatives were prepared from the original dichloro compound as well, and mixed melting point determinations were made. In addition, both samples of methionine anhydride were hydrolyzed and samples of benzoylmethionine (V) were prepared. All these derivatives had approximately the melting points ascribed to them in the literature, and in no instance was there a depression of melting point on mixing of the derivatives from the two sources. The racemic and *meso* forms of S-benzylhomocysteine anhydride (IV) have been characterized[3] as melting at 165 and 176°, respectively. The samples obtained in this work melted at about 175°, so it seems likely that the diketopiperazine II is the *meso* form, or that this form preponderates if both it and the racemic variety are present in the samples of II. The only discrepancy in melting points was encountered with *dl*-S-benzylhomocysteine (VI); the sample prepared by hydrolysis of IV melted with decomposition at about 230°, whereas the recorded[4] melting point is 190–191°. The sample of VI had the expected composition.

The divinyldiketopiperazine (I) underwent addition of hydrogen bromide to give the dibromo analog of II. The 3,6-*bis*-(β-bromoethyl)-2,5-diketopiperazine (VII) so formed was identified by conversion to methionine anhydride (III). The dibromodiketopiperazine decomposed readily. It dissolved slowly in hot alcohol or hot water to give strongly acid solutions. In an experiment in which a sample was heated with water the amount of acid generated was determined by titration; it corresponded to a neutral equivalent of 181, as compared to the theoretical value of 164 calculated on the assumption that one molecule of VII yields two molecules of hydrogen bromide. The formation of the acid may be due either to dehydrohalogenation or to hydrolysis.

Treatment of the divinyldiketopiperazine with hydrogen sulfide gave an addition product containing two atoms of sulfur. Attempts to direct the reaction by carrying it out in the dark, to favor Markownikoff addition, and under strong

(1) Present address, General Aniline and Film Corp., Easton, Pa.

(1a) See preceding paper, THIS JOURNAL, 66, 1000 (1944).

(2) Snyder, Andreen, Cannon and Peters, *ibid.*, 64, 2082 (1942).

(3) du Vigneaud, Patterson and Hunt, *J. Biol. Chem.*, 125, 217 (1938).

(4) Patterson, *ibid.*, 89, 235 (1932).

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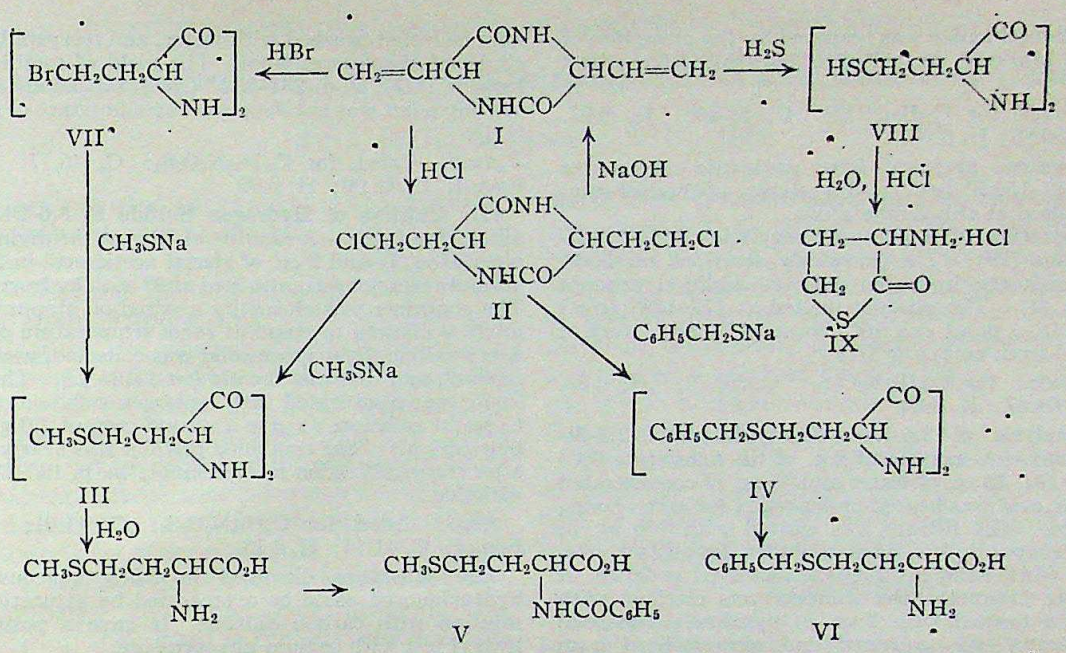

ultraviolet irradiation, to favor non-Markownikoff addition,[5] were unsuccessful, the same product being obtained in all instances. The reaction product was hydrolyzed to homocysteine thiolactone hydrochloride (IX) in good yield, so evidently the addition of hydrogen sulfide occurred in the non-Markownikoff fashion. The addition product, although of analytical purity, melted with decomposition at a temperature much lower than the recorded[3] melting point of either the *meso* or racemic homocysteine anhydride. It is possible that the material is a mixture of the two forms.

The non-Markownikoff addition observed in these instances cannot be ascribed to an effect of peroxides, since reactions of hydrogen chloride and olefins are not susceptible to such influence. An explanation can be based on the assumption that the group —CH(NH)CO— of the diketopiperazine ring polarizes the double bond of the attached vinyl group by withdrawing electrons from it. The reactive form thus would be $\left[\overset{\delta+}{CH_2}=\overset{\delta-}{CH}-CH(NH)CO\right]_2$. The effect of the diketopiperazine ring on the double bond is similar to that of a *m*-directing group in producing the polarization.[6] On this basis the addition of halogen acid is to be regarded as strictly comparable to the non-Markownikoff addition of hydrogen bromide to divinylsulfone,[7] in which the addition to the double bond is directed by a *m*-orienting group which cannot participate in 1,4-addition. It is of interest to note that in the nitration of phenylglycine the side-chain is strongly *m*-directing.[8] During the occurrence of this reaction the side-chain must be in the form of the salt —CH(NH$_3^+$)CO$_2$H. It is not surprising that this group should be *m*-directing, inasmuch as the group —CH$_2$NH$_3^+$ is *m*-orienting[6] and incorporation of the carbonyl group would be expected to increase its effectiveness in this regard. The addition of halogen acids to the divinyldiketopiperazine (I) may involve preliminary salt formation. However, the non-Markownikoff addition of hydrogen sulfide in the absence of strong acids and in the absence of ultraviolet irradiation and the extraordinary ease[1a] of dehydrohalogenation of the dichlorodiketopiperazine (II) suggest that the free diketopiperazine ring has a strong polarizing effect on groups attached at the 3 and 6 positions.

(5) Vaughan and Rust, *J. Org. Chem.*, **7**, 472 (1942).
(6) Price, *Chem. Rev.*, **29**, 37 (1941).
(7) Alexander and McCombie, *J. Chem. Soc.*, 1013 (1931).
(8) Plöchl and Loë, *Ber.*, **18**, 1179 (1885).

Experimental

(1) **Addition of Hydrogen Chloride to 3,6-Divinyl-2,5-diketopiperazine.**—Dry hydrogen chloride was bubbled into a solution of 17.5 g. of 3,6-divinyl-2,5-diketopiperazine[1a] in 150 cc. of 100% acetic acid until the gain in weight was 9.0 g. The mixture was allowed to stand for one hour, after which period it was heated on the steam-bath until a clear solution resulted. The solution was allowed to cool and the crude 3,6-*bis*-(β-chloroethyl)-2,5-diketopiperazine (II) was collected and washed with water, alcohol, and ether. It weighed 14.9 g. (59%) and melted at 233–234° (cor., with decomp.; lit.,[2] 231–232°); the melting point was not lowered by admixture of authentic II. The divinyldiketopiperazine was regenerated by heating the hydrogen chloride addition product with alcoholic sodium hydroxide.[1a]

(2) **Preparation of Methionine Anhydride (III).**—The product from the preceding experiment was treated with sodium methyl mercaptide according to the procedure described previously.[2] Methionine anhydride melting at 230–231° (lit.,[2] 231–232°) was obtained and its melting point was not depressed by admixture of an authentic sample.

Anal. Calcd. for $C_{10}H_{18}N_2O_2S_2$: C, 45.77; H, 6.92. Found: C, 46.26; H, 7.13.

(3) ***dl*-Methionine and Benzoyl *dl*-Methionine.**—The methionine anhydride so obtained was hydrolyzed as described previously. The methionine was analyzed.

Anal. Calcd. for $C_5H_{11}NO_2S$: C, 40.25; H, 7.43. Found: C, 40.71; H, 7.51.

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Benzoyl *dl*-methionine was prepared by the procedure of Windus and Marvel.[9] It melted at 151–151.5° (cor., lit.,[9] 143–145°).

Anal. Calcd. for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97. Found: C, 56.86; H, 6.20.

The derivative prepared from authentic methionine melted at 149–150.5° (cor.) and a mixture of the two samples also melted at this temperature.

(4) **Preparation of 3,6-*bis*-(β-Benzylthiolethyl)-2,5-diketopiperazine (IV).**—The previously described method[1a] was used with the hydrogen chloride addition product obtained in (1). The product melted at 177–178° (cor.) and this melting point was not depressed by admixture of IV prepared from authentic II.[1a]

Anal. Calcd. for $C_{22}H_{24}N_2O_2S_2$: C, 63.73; H, 6.33. Found: C, 64.27; H, 6.34.

(5) **Hydrolysis of 3,6-*bis*-(β-Benzylthiolethyl)-2,5-diketopiperazine.**—A mixture of 2 g. of the anhydride (IV) prepared in (4), 15 cc. of water and 45 cc. of concentrated hydrochloric acid was heated under reflux for seven hours, then filtered. The filtrate was diluted with 100 cc. of water and evaporated to dryness under diminished pressure. The white solid residue was dissolved in 20 cc. of hot absolute ethanol; the solution was clarified with charcoal and treated with 2 cc. of pyridine. The solid which separated was collected and recrystallized from water. It melted at 226–230° (cor., with dec.; lit.[4] 190–191°).

Anal. Calcd. for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.72. Found: C, 58.98; H, 6.75.

Exactly the same results were obtained in the hydrolysis of the anhydride[1a] prepared from authentic 3,6-*bis*-(β-chloroethyl)-2,5-diketopiperazine. The yield was about 75% in both instances.

(6) **3,6-*bis*-(β-Bromoethyl)-2,5-diketopiperazine (VII).**—A cold solution of 2.4 g. of dry hydrogen bromide in 6 cc. of glacial acetic acid was added slowly to a cold, stirred solution of 1.12 g. of the divinyldiketopiperazine (I) in 7 cc. of glacial acetic acid. The solution was allowed to stand without cooling for one hour, during which time crystallization occurred. The mixture was stirred in 80 cc. of cold water and the solid was collected and recrystallized from glacial acetic acid. The product (VII) melted at 221–222° (cor., with dec.) and was obtained in yields of about 50%.

Anal. Calcd. for $C_8H_{12}Br_2N_2O_2$: C, 29.27; H, 3.69. Found: C, 29.74; H, 3.69.

A sample of 0.20 g. of VII was dissolved in 20 cc. of water by heating on the steam-bath for five minutes. The clear solution was cooled and titrated with 0.0445 *N* sodium hydroxide and phenolphthalein. The end-point was fugitive. The partly neutralized solution was heated for a few minutes longer, then cooled and titrated to a permanent end-point (23.85 cc. of the standard solution required).

A mixture of 0.4 g. of the dibromo compound (VII) and a solution of 0.186 g. of sodium methyl mercaptide in 15 cc. of absolute ethanol was shaken mechanically for five hours, then allowed to stand three hours, and finally heated to boiling until a clear solution resulted. The crystals which separated when the solution was cooled were collected, washed with water, and recrystallized from 10 cc. of absolute ethanol. The yield of methionine anhydride (III), m. p. 231–232° (cor.), was about 30%; the melting point was not depressed by admixture of authentic (III).

Anal. Calcd. for $C_{10}H_{18}N_2O_2S_2$: C, 45.77; H, 6.92. Found: C, 46.09; H, 6.99.

(7) **Addition of Hydrogen Sulfide to 3,6-Divinyl-2,5-diketopiperazine.**—A solution of 10 g. of the divinyldiketopiperazine (I) and 2 cc. of glacial acetic acid in 250 cc. of absolute ethanol was saturated at 0° with hydrogen sulfide. The container was closed by a wired-on stopper and the mixture allowed to stand at room temperature overnight. A crystalline, light green solid was collected, washed with ethanol, and dried in the air (wt., 6.94 g.). The mother liquor was resaturated with hydrogen sulfide and allowed to stand as before to give a second crop of 1.0 g. of light blue crystals. The combined product was nearly colorless after recrystallization from ethanol; m. p. 185–186° (cor., with dec.).

Anal. Calcd. for $C_8H_{14}N_2O_2S_2$: C, 41.01; H, 5.98. Found: C, 41.14; H, 6.13.

The substance dissolved in 2.5% aqueous sodium hydroxide and could be regenerated by saturation of the solution with carbon dioxide. It gave a positive sulfhydryl test with sodium nitroprusside.

In similar experiments in which acetic acid was not added to the mixtures the reaction was very slow, requiring about four days to proceed to a 50% yield. No difference could be detected between runs carried out in quartz apparatus under an ultraviolet lamp and those carried out in the dark. The crude products from these runs were of darker green color than that described above, but the purified materials were nearly colorless.

(8) **Homocysteine Thiolactone Hydrochloride.**—A solution of 4 g. of the dithiol (VIII) in 60 cc. of concentrated hydrochloric acid was heated under reflux for two hours, then diluted with 100 cc. of water and evaporated to dryness under diminished pressure. The residue was dissolved in 150 cc. of water and after decolorization the solution was again evaporated under diminished pressure. The residue was washed well with absolute ethanol; the thiolactone salt (IX) weighed 3.2 g. and melted at 199–200° (lit.,[10] 200–201°).

Anal. Calcd. for C_4H_8ClNOS: C, 31.28; H, 5.25. Found: C, 31.82; H, 5.64.

Summary

3,6-Divinyl-2,5-diketopiperazine undergoes addition of hydrogen chloride, hydrogen bromide and hydrogen sulfide in the manner opposite to that predicted from Markownikoff's rule. In this regard the double bonds resemble that of an α,β-unsaturated carbonyl compound. The abnormal orientation may be attributed to polarization of the double bond by the attached —CH(NH)CO— group of the diketopiperazine ring.

URBANA, ILLINOIS RECEIVED MARCH 2, 1944

(9) Windus and Marvel, THIS JOURNAL, **53**, 3490 (1931).

(10) Riegel and du Vigneaud, *J. Biol. Chem.*, **112**, 149 (1935–1936).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF STANFORD UNIVERSITY]

Saponins and Sapogenins. XXIV. Norechinocystenol-A and Norechinocystenone-A

BY G. H. HARRIS AND C. R. NOLLER

It has been reported previously[1] that Clemmensen reduction of norechinocystenone-B[2] or of norechinocystendione gives a hydrocarbon identical with oleanene III, obtained by Winterstein and Stein[3] from oleanolic acid. This was the first direct indication that echinocystic acid and oleanolic acid have the same carbon skeleton. Since the preparations of oleanene III from echinocystic acid and from oleanolic acid involve a Clemmensen reduction, which Winterstein and Stein[3] have shown produces a molecular rearrangement, it was considered desirable to attempt to interrelate the two compounds by other methods.

In the monoacetyl derivative of methyl echinocystate prepared by direct esterification, the hydroxyl group acetylated is the one which is not "β" to the carboxyl group[4] and apparently occupies the same position in the carbon skeleton as the hydroxyl group in oleanolic acid, as evidenced by the fact that both echinocystic acid and oleanolic acid give hydroxyagathalene on selenium dehydrogenation.[5] Oxidation of this monoacetyl methyl echinocystate gives the monoacetyl monoketo ester.[4] If the carbonyl group of the keto ester could be replaced by a methylene group one should obtain a compound identical or isomeric with acetyl methyl oleanolate. Wolff–Kishner reduction seemed the most promising since it would avoid the isomerizations taking place on Clemmensen reduction. All attempts to prepare a semicarbazone failed so a direct reduction with hydrazine hydrate and sodium ethylate[6] was carried out. Analysis of the product and the formation and analysis of an acetyl derivative showed that not only had the carbonyl group been reduced to methylene but the carboxyl group was eliminated and the acetyl group alcoholyzed. To confirm this conclusion, acetylnorechinocystenolone[4] was subjected to the same treatment and an identical product obtained. This compound, which has been named "norechinocystenol-A," is isomeric with oleanol[7] but not identical with it.

It was conceivable that norechinocystenol-A is epimeric with oleanol. Accordingly the former compound was oxidized to the ketone and compared with oleanone but again the two compounds were found to be different. The new compound has been named "norechinocystenone-A." The difference in structures may arise from a difference in constitution or configuration of the carbon skeletons of oleanolic acid and echinocystic acid or to molecular rearrangements taking place during the Wolff–Kishner reductions or the decarboxylation reactions.

Attempts to carry out a Clemmensen reduction of norechinocystenolone resulted in the formation of a resin which could not be purified and from which no pure derivative could be obtained.

Experimental

Norechinocystenol-A.—A mixture of 0.93 g. of the acetyl keto methyl ester derived from echinocystic acid,[4] 5 cc. of hydrazine hydrate and 1 g. of metallic sodium dissolved in 35 cc. of absolute alcohol was heated in a sealed tube at 200° for eight hours.[6] The contents were poured into a large volume of water and the insoluble material extracted with ether. The ether solution was washed with barium hydroxide solution and water and dried over sodium sulfate. Evaporation of the ether gave a product which was recrystallized from methanol to a constant melting point of 188–191°. The product is only slightly soluble in ligroin, fairly soluble in toluene and very soluble in dioxane, acetone, chloroform and ether; $[\alpha]^{25}D$ + 15.1° in chloroform. *Anal.* Calcd. for $C_{29}H_{48}O$: C, 84.40; H, 11.71. Found: C, 83.91, 83.96; H, 11.91, 11.83.

Reduction of 0.23 g. of acetylnorechinocystenolone[4] by the above procedure gave a product which after two crystallizations from methanol melted at 187–189°. A mixture with the above product showed no depression in melting point. The reported melting point of oleanol is 216–220° and $[\alpha]^{20}D$ +59.1° in chloroform.[7]

Reaction of 0.30 g. of norechinocystenol-A with 1 cc. of acetic anhydride in 2 cc. of pyridine, precipitation in water and crystallization from methanol gave the acetate melting at 217–220°; $[\alpha]^{21}D$ +21.6° in chloroform. *Anal.* Calcd. for $C_{31}H_{50}O_2$: C, 81.88; H, 11.08. Found: C, 81.54; H, 10.87. The reported melting point for oleanol acetate is 209–210° and $[\alpha]^{21}D$ +44.7° in chloroform.[7]

Norechinocystenone-A.—A solution of 0.11 g. of norechinocystenol-A in glacial acetic acid was oxidized at 50° with a solution of 0.18 g. of chromium trioxide in glacial acetic acid. After standing one hour, 2 cc. of methanol was added to destroy the excess chromium trioxide and the product was precipitated by adding a large volume of water. The precipitate was collected in ether and the ether solution washed with alkali, dried and the solvent evaporated. The residue was crystallized twice from methanol and then from 95% ethanol to give a product melting at 159–162°; $[\alpha]^{21}D$ +30.8° in chloroform. *Anal.* Calcd. for $C_{29}H_{46}O$: C, 84.81; H, 11.30. Found: C, 84.98; H, 11.14. A mixture with an equal amount of oleanone,[8] m. p. 170–173°, melted at 157°. The melting point of oleanone has been reported to be 167–169°[8] and 168–172°[3] and $[\alpha]^{20}D$ + 95.8° in chloroform.[3]

Summary

Norechinocystenol-A has been prepared by removing the carboxyl group of echinocystic acid and the hydroxyl group "β" to the carboxyl group. It is not identical with oleanol prepared

(1) Todd, Harris and Noller, THIS JOURNAL, **62**, 1624 (1940).

(2) This compound previously has been called simply "norechinocysteneone." The carbonyl group is derived from the hydroxyl group in echinocystic acid which is "β" to the carboxyl group. The designation "B" has been added to distinguish it from norechinocystenone-A in which the carbonyl group is derived from the hydroxyl group in echinocystic acid which is not "β" to the carboxyl group.

(3) Winterstein and Stein, *Ann.*, **502**, 223 (1933).

(4) White and Noller, THIS JOURNAL, **61**, 983 (1939).

(5) Ruzicka and co-workers, *Helv. Chim. Acta*, **17**, 442 (1934); **19**, 1391 (1936); Noller, THIS JOURNAL, **56**, 1582 (1934).

(6) Longwell and Winterstein, *ibid.*, **62**, 200 (1940).

(7) Winterstein and Stein, *Z. physiol. Chem.*, **202**, 229 (1931).

(8) Bilham and Kon, *J. Chem. Soc.*, 1469 (1940).

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by the decarboxylation of oleanolic acid. Oxidation of norechinocystenol-A gives the ketone norechinocystenone-A, which is different from oleanone prepared by the decarboxylation and dehydrogenation of oleanolic acid.

STANFORD UNIV., CALIFORNIA RECEIVED MARCH 28, 1944

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, MONSANTO CHEMICAL CO., ST. LOUIS, MISSOURI]

Alkyl Sulfites—Cyclohexyl Sulfite

BY L. P. KYRIDES

In 1931 Voss and Blanke[1] reported the preparation of alkyl sulfites in high yields from primary and in fair yields from secondary alcohols. They also reported a yield of 54% of cyclohexyl sulfite—b. p. 182° (19 mm.), $n^{13.7}D$ 1.4865; S 13.16% (calcd. 13.02%). At about the same time Kitasato and Sone[2] reported that cyclohexyl sulfite made in the presence of pyridine boiled at 55° (12 mm.), which would appear to be too low for the boiling point of this ester.

Later, Carré and Libermann[3] cast doubt on the isolability of cyclohexyl sulfite, stating that cyclohexene was the only reaction product of cyclohexanol with thionyl chloride. The criticism of Carré and Libermann was countered by a subsequent report of Voss and Wachs[4] reasserting the isolation of cyclohexyl sulfite in a 42% yield, b. p. 173–173.5° at 14.5 mm.; $n^{17.3}D$ 1.48497; S, 12.85%. Finally, Carré and Libermann[5] made the categorical statement that "the new experiments have confirmed our previous results: the reaction of thionyl chloride with cyclohexanol gives mainly cyclohexene, with only a small quantity of cyclohexyl sulfite which we were unable to distil under vacuum without decomposition."

Having prepared cyclohexyl sulfite in these laboratories at three different times during the past twelve years and tested the products at intervals for stability, we concluded that, if properly prepared, the ester is stable over long periods of time. It distils within a very narrow range under a fairly good vacuum and always smells of sulfur dioxide and cyclohexene.

The procedure for the preparation of *n*-butyl sulfite given in "Organic Syntheses"[6] is not applicable to secondary alkyl sulfites. Following the reaction, distillation gives some olefin and the unchanged alcohol. Voss and Blanke obtained fair yields of secondary alkyl sulfites only by displacing the hydrogen chloride in the course of its liberation during the reaction with a stream of carbon dioxide. This elimination of hydrogen chloride appears to be of significance in driving the esterification to completion.

We have been able to improve the process, and consequently the yields, by carrying out the reaction under reduced pressure. Using the vacuum obtainable by an ordinary water pump, it was demonstrated that the halogen acid is removed quite successfully and excellent yields of both secondary and primary sulfites are obtained from the corresponding alcohols.

Since in the process for *n*-butyl sulfite referred to above 3–5% of butyl chloride is formed, we chose a lower reaction temperature in order to minimize chloride formation. At the recommended temperatures (10–20°), the reaction proceeds quite rapidly, giving the high yields desired.

The following experimental work relating to improvements in the technique of preparing sulfites in general is submitted in order to clarify the situation regarding cyclohexyl sulfite.

Experimental

The apparatus consisted of a four-necked flask carrying an efficient reflux condenser, a thermometer for following the reaction temperature, a dropping funnel and an agitator revolving in a lubricated rubber sleeve[7] for operation under vacuum.

Cyclohexyl Sulfite.—Two hundred grams of anhydrous cyclohexanol was charged into the reaction flask and cooled with agitation to incipient crystallization (25°). Vacuum was applied (24″) and 121 g. of freshly distilled thionyl chloride was slowly dropped in. As the addition progressed and the cyclohexanol liquefied, the reaction temperature was lowered gradually. When about one-half of the thionyl chloride had been added (time fifteen minutes) the temperature had fallen to 15°. At this point, further addition of thionyl chloride induced the evolution of hydrogen chloride which further lowered the temperature. External cooling was discontinued when the temperature had fallen to 5° and addition of the rest of the chloride was regulated to maintain this temperature and the pressure given. Total addition time was forty-five minutes. The vacuum was now increased to 30″ in order to expedite the more complete elimination of hydrogen chloride which in turn lowered still further the temperature (0°). After a short time the flask was immersed in a water-bath and the temperature raised slowly to 55°, taking a half-hour for this operation. After an additional reaction time of a half-hour at 55°, vacuum was broken off and the liquid was transferred into a distillation flask with an attached Vigreux column. After separating a small amount of low boiling liquid under partial vacuum, the main fraction was distilled using a high vacuum pump. The distillate weighed 217 g. and boiled constantly at 134–136° at 3 mm. The low boiling fraction upon refractionation gave 11 g. of unreacted cyclohexanol. The yield of cyclohexyl sulfite was therefore 93.5% on cyclohexanol consumed and 86% on thionyl chloride used. There was evidence of evolution of

(1) Voss and Blanke, *Ann.*, **485**, 272 (1931).
(2) Kitasato and Sone, *Ber.*, **64**, 1142 (1931).
(3) Carré and Libermann, *Bull. soc. chim.*, [5] **2**, 160 (1935).
(4) Voss and Wachs, *Ber.*, **68**, 1939 (1935).
(5) Carré and Libermann, *Bull. soc. chim.*, [5] **3**, 814 (1936).
(6) "Organic Syntheses," Coll. Vol. II, 1943, p. 112.
(7) "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., 1941, Vol. 21, p. 40.

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traces of cyclohexene and sulfur dioxide in the exit gases during the reaction and distillation. The finished product also gave positive evidence of traces of these two products. The cyclohexyl sulfite was redistilled a year later and its boiling range and refractive index ($n^{25}D$ 1.4848) were found unchanged. After another two years the material boiled constantly at 165° under 14 mm. with no change in the refractive index. Upon analysis the product contained 13.10% sulfur against 13.02% expected. These results substantiate Voss and Blanke's statements regarding cyclohexyl sulfite.

It was observed that unless the reaction is carried out to completion, as indicated, cyclohexyl sulfite cannot be distilled successfully under vacuum because of the continuous decomposition of the product to sulfur dioxide and cyclohexene. This fact would explain the inability of the French workers to isolate the product. Repeated distillation after long standing has not given evidence of deterioration, excepting for the smell of sulfur dioxide and cyclohexene. It was also observed that cyclohexyl sulfite containing very small amounts of sulfuric acid can be distilled under vacuum without decomposition.

Following the procedure given, no difficulty was experienced in the preparation of other esters such as:

Sulfite	Yield, %	Boiling range, °C.
Dimethyl	84	124–127
Diethyl	Quantitative using slight excess of anhydrous ethanol.	154–157
Isopropyl	(Refractionated) 84% on isopropanol	73–74° at 25 mm.
n-Butyl	Yield (refractionated) 92.5% on butanol	124–126° at 29 mm.
Methylhexylcarbinyl	85 (reaction temp. 20–25°)	147–149° at 5–6 mm.

It should be noted that with methanol, ethanol and isopropanol, the reaction should be carried under a lower vacuum because of their low boiling points. It is advantageous to regulate the vacuum so that the alcohol barely refluxes during the addition and later to increase the vacuum.

Summary

Sulfites are obtained in excellent yields from the reaction of primary and secondary alcohols with thionyl chloride using low pressures during the operation.

Cyclohexyl sulfite made by the above procedure is a relatively stable product and can be redistilled repeatedly without change in composition.

ST. LOUIS, MO. RECEIVED JANUARY 31, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE COLLEGE OF WASHINGTON, AND THE DEPARTMENT OF CHEMICAL ENGINEERING, COLUMBIA UNIVERSITY]

On the Thermodynamics of Azeotropic Solutions. I. Shift of Equilibrium in Binary Systems[1]

BY O. REDLICH AND P. W. SCHUTZ

Among the numerous authors who have contributed to the vast amount of experimental data on azeotropic solutions in early and recent times, several have felt the advantages which are to be expected from a thermodynamic discussion.[1a] Obviously thermodynamic predictions are apt to enhance the value of available data and the efficiency of new experimental research, especially in the field of industrial applications.

Apart from the well-known fundamental properties of azeotropic solutions, theoretical discussions either referred to the properties of solutions in general and arrived only at qualitative conclusions regarding the azeotropic properties,[2] or started from special relationships[3] between vapor pressure and composition which are necessarily of restricted validity.

Actually the problem of the shift of azeotropic equilibrium can be easily formulated in a general way and solved by straightforward thermodynamic methods.

The azeotropic equilibrium of a solution of two miscible liquids is characterized by three intensive variables: the composition, which is equal for the liquid and the vapor, the temperature and the pressure. Under the condition, that the azeotropic equilibrium should be maintained, only one of these variables is independent. The shift of equilibrium is therefore exhaustively described by two relations between the variables.

In the development it is assumed only that the vapor is a perfect gas mixture. This restriction can be removed without any essential difficulty but the practical gain would be small and by no means sufficient to justify the complication of the formulas.

In the following, the standard notation of Lewis and Randall is used, the pure components being chosen as reference states. The heats of vaporization of the two components from the solution are denoted by $\Delta H_1 = \Delta H_1^0 - \bar{L}_1$ and $\Delta H_2 = \Delta H_2^0 - \bar{L}_2$, where ΔH_1^0 and ΔH_2^0 are the heats of vaporization of the pure components, and $\bar{L}_1$ and $\bar{L}_2$ the relative partial molal heat contents.

The relationship between azeotropic pressure and temperature is represented by

$$\left(\frac{dP}{dT}\right)_{az} = \left(\frac{\partial P}{\partial T}\right)_{N_1} + \left(\frac{\partial P}{\partial N_2}\right)_T \left(\frac{dN_2}{dT}\right)_{az} \quad (1)$$

The last term is equal to zero since $(\partial P/\partial N_2)_T = 0$ constitutes one of the fundamental properties of the azeotropic equilibrium.

(1) Original manuscript received December 23, 1942.

(1a) See for instance R. W. Merriman, *J. Chem. Soc.*, **103**, 628 (1913).

(2) *Cf.* M. S. Wrewsky (Vrevskii), *Z. physik. Chem.*, **83**, 551 (1913), and previous papers.

(3) See H. C. Carlson and A. P. Colburn, *Ind. Eng. Chem.*, **34**, 581 (1942); J. J. van Laar, *Z. physik. Chem.*, **72**, 723 (1900); and refs. 7 and 8.

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Thus we obtain

$$\left(\frac{\mathrm{d}\ln P}{\mathrm{d}T}\right)_{az} = \frac{p_1}{P}\left(\frac{\partial \ln p_1}{\partial T}\right)_{N_2} + \frac{p_2}{P}\left(\frac{\partial \ln p_2}{\partial T}\right)_{N_2} \quad (2)$$

$$\left(\frac{\mathrm{d}\ln P}{\mathrm{d}\,1/T}\right)_{az} = -\frac{N_1\Delta H_1 + N_2\Delta H_2}{R} = -\frac{\Delta H}{R} \quad (3)$$

where ΔH represents the heat of vaporization of one mole of the solution.

The dependence of the azeotropic composition on the temperature is to be derived in a slightly less direct way. With the abbreviation $Q = p_1N_2/p_2N_1$ the maintenance of the azeotropic equilibrium can be represented by

$$\left(\frac{\mathrm{d}Q}{\mathrm{d}T}\right)_{az} = \left(\frac{\partial Q}{\partial T}\right)_{P,N_2} + \left(\frac{\partial Q}{\partial P}\right)_{T,N_2}\left(\frac{\mathrm{d}P}{\mathrm{d}T}\right)_{az} + \left(\frac{\partial Q}{\partial N_2}\right)_{T,P}\left(\frac{\mathrm{d}N_2}{\mathrm{d}T}\right)_{az} = 0 \quad (4)$$

since $Q = 1$ as long as azeotropic equilibrium exists.

The first of the partial differential coefficients is determined by $\Delta H_2 - \Delta H_1$. For the second we derive

$$\left(\frac{\partial \ln Q}{\partial P}\right)_{T,N_2} = \frac{\bar{v}_1' - \bar{v}_1 - \bar{v}_2' + \bar{v}_2}{RT} = \frac{-\bar{v}_1 + \bar{v}_2}{RT} = \frac{v}{P} \quad (5)$$

where the prime indicates the vapor phase and v the ratio of the difference of the partial molal volumes in the liquid to the molal volume of a perfect gas under the given conditions.

In (5) we made use of the relation

$$\bar{v}_1' - \bar{v}_2' = 0 \quad (6)$$

which results from the assumption of a perfect gas phase. The term (5) is in general entirely negligible.

The third partial differential coefficient in (4) is simplified by means of the Duhem–Margules relation

$$N_1\,\mathrm{d}\ln\frac{a_1}{N_1} + N_2\,\mathrm{d}\ln\frac{a_2}{N_2} = 0 \quad (7)$$

which yields

$$\left(\frac{\partial \ln Q}{\partial N_2}\right)_{T,P} = \frac{\partial}{\partial N_2}\left(\ln\frac{a_1}{N_1}\right) - \frac{\partial}{\partial N_2}\left(\ln\frac{a_2}{N_2}\right) = -\frac{1}{N_1}\frac{\partial}{\partial N_2}\left(\ln\frac{a_2}{N_2}\right) \quad (8)$$

Combination of (3), (4), (5) and (8) leads to[3a]

$$\left(\frac{\mathrm{d}\frac{1}{T}}{\mathrm{d}N_2}\right)_{az} = \frac{R}{\Delta H_2 - \Delta H_1 - v\Delta H}\cdot\frac{1}{N_1}\left(\frac{\partial \ln\frac{a_2}{N_2}}{\partial N_2}\right)_{T,P} \quad (9)$$

The third relationship between the three azeotropic variables is immediately derived from (3) and (9)

$$\left(\frac{\mathrm{d}\ln P}{\mathrm{d}N_2}\right)_{az} = -\frac{\Delta H}{\Delta H_2 - \Delta H_1 - v\Delta H}\cdot\frac{1}{N_1}\left(\frac{\partial \ln\frac{a_2}{N_2}}{\partial N_2}\right)_{T,P} \quad (10)$$

(3a) N_2 is chosen as the independent variable since (9) and (10) will commonly be used in this form.

Thermodynamic relations like these need no test in the proper meaning of the word. However, we wish to illustrate the practical application in an example. A complete and accurate set of the data required in equations (9) and (10) is available for hydrochloric acid.[4]

The following procedure was adopted: the data given for $\bar{L}_1$ and $\bar{L}_2$ in the range from 0 to 60° were inter- and extrapolated on $1/T$ graphs. The values (25°) of $\log(a_2/N_2)$ were interpolated for $N_2 = 0.05, 0.1, 0.2$. The corresponding values for five temperatures up to 123° were computed and represented as parabolic functions of $\log N_2$. The heats of vaporization ΔH_1 and ΔH_2 were calculated from ΔH_1^0, ΔH_2^0, $\bar{L}_1$ and $\bar{L}_2$. The term $v\Delta H$ was neglected.

The differential coefficients for five points were computed according to (3) and (9). They are listed in Table I. Three of the values of N_2, $1/T$, and $\log P$, as observed by Bonner and his collaborators, were used to calculate two parabolic functions; the values of these functions for the two other points and the differential coefficients derived from them are denoted "par." in Table I.

Considering the various inter- and extrapolations, and differentiations, the agreement between the observed ("parabolic") values and calculated ones, which were derived from entirely independent data, is very satisfactory and indicates the high accuracy of the data.

Discussion.—Equation (3) has the form of the Clausius–Clapeyron equation because the system under condition of azeotropic equilibrium acts just like a one-component system.

All conclusions which will be drawn from equation (9) can be derived in the same way from equation (10), and are therefore immediately applicable also to the pressure–composition relationship.

We discuss equation (9) in order to find the characteristic differences in the azeotropic behavior of certain types of solutions. It is convenient to consider first the factor

$$\frac{1}{N_1}\left(\frac{\partial \ln\frac{a_2}{N_2}}{\partial N_2}\right)_{T,P} = \frac{1}{N_2}\left(\frac{\partial \ln\frac{a_1}{N_1}}{\partial N_1}\right)_{T,P} \quad (11)$$

and later the denominator, $\Delta H_2 - \Delta H_1 - v\,\Delta H$.

Term (11) is zero for a perfect solution, negative if $p_1 > N_1p_1^0$, *i. e.*, especially for the maximum vapor pressure type, positive in the opposite case.

TABLE I

AZEOTROPIC FUNCTIONS OF HYDROCHLORIC ACID

N_2		0.10603	0.11088	0.11557	0.12157	0.13090
$10^3/T$	obs.	2.5247	2.6103	2.6977	2.8224	3.1073
	par.	...	2.598	...	2.826	...
$\log P$	obs.	3.0864	2.9031	2.6990	2.3979	1.6990
	par.	...	2.897	...	2.407	...
$d(1/T)/dN_2$	par.	0.0149	0.0182	0.0214	0.0255	0.0318
	calc.	.0148	.0172	.0192	.0231	.0324
$d\log P/d(1/T)$	par.	2179	2239	2299	2386	2584
	calc.	2231	2277	2298	2334	2397

If the second component dissociates in dilute solution, then

$$\lim_{N_2 = 0} a_2 = \text{const.}\,N_2^2;\quad \lim_{N_2 = 0}\frac{\partial}{\partial N_2}\left(\ln\frac{a_2}{N_2}\right) = \infty \quad (12)$$

(4) W. D. Bonner and B. F. Branting, THIS JOURNAL, **48**, 3093 (1926); W. D. Bonner and A. C. Titus, *ibid.*, **52**, 633 (1930); W. D. Bonner and R. E. Wallace, *ibid.*, **52**, 1747 (1930); M. Randall and L. E. Young, *ibid.*, **50**, 989 (1928); "International Critical Tables," Vol. V.

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Term (11) is therefore positive. This explains why azeotropic electrolytes always belong to the minimum vapor pressure or maximum boiling point type.

The equations (9) and (12) demonstrate that *dissociating* azeotropic *systems* always have an *infinite* azeotropic *temperature range.* In dilute solution, the temperature increases with decreasing concentration of the dissociating substance if its heat of vaporization is larger than that of the solvent. For dilute hydrochloric acid ΔH_2 is greater than ΔH_1 so that $\lim dT/dN_2 = -\infty$. In a diagram of the data of Table I one realizes immediately that the T–N_2 curve must have an inflection point at some concentration below the range of the table.

If neither component dissociates, term (11) is always finite.[5] One verifies easily that the left-hand side is finite for $N_2 = 0$, corresponding to a dilute solution of the second component in the first, the right-hand side for $N_2 = 1$.

The integration of (9) from $N_2 = 0$ to $N_2 = 1$ leads, therefore to a finite interval of the azeotropic temperature at least if the denominator $\Delta H_2 - \Delta H_1 - v\Delta H$ is different from zero in the whole interval. This is a matter of some practical interest as distillation at temperatures and pressures outside the azeotropic interval would lead to complete separation. At first, one is inclined to assume that the denominator will vanish or even assume a small value only in rare exceptional cases since heats of vaporization run over a fairly wide range and the denominator contains the difference of two of these quantities. It will be seen later, however, that an assumption of this kind is erroneous and that a small denominator, *i. e.*, a large azeotropic interval, may occur quite frequently and under well defined conditions.

The Isobaric Temperature.—If the vapor pressure–temperature curves of the two pure liquid components cross each other, the temperature at which $p_1^0 = p_2^0$ is of considerable interest.[6] It will be called the "isobaric temperature."

Complete miscibility presupposed, the total vapor pressure–composition curve can assume any of three forms: it may be a straight line, concave or convex. In the first case the system forms a perfect solution, in the latter cases the total vapor pressure has a maximum or minimum as the end-points of the curve are fixed at the same ordinate value. The perfect solution at the isobaric temperature is to be considered as the limiting case of a system azeotropic at any composition.

The result as required in the following discussion can be expressed by either of the statements: "Any system is azeotropic at the isobaric temperature" or: "The azeotropic temperature range always includes the isobaric temperature."

Some information on the shift of azeotropic equilibrium is derived from this fact in connection with Trouton's rule, according to which the ratio of heat of vaporization to absolute temperature is approximately equal for non-associating liquids at those temperatures where their vapor pressures are equal. Trouton's ratio is larger, usually by not more than fifty per cent., for associating substances like alcohols, water, etc.

Trouton's rule defines a family of vapor-pressure–temperature curves with the following properties: At a given temperature the heat of vaporization is greater for the less volatile liquid; with increasing temperature the vapor pressures approach one another asymptotically.

Thus a pair of ideal Trouton liquids is always below the isobaric temperature. Actually vapor pressure curves even of non-associating or "normal" liquids frequently cross in the limited interval between the melting points and critical points, the approximate validity of Trouton's rule being indicated by the small angle between the curves.

If the Trouton ratios of the two components do not deviate considerably from each other, the difference between the heats of vaporization and therefore the denominator in equation (9) $\Delta H_2 - \Delta H_1 - v\Delta H = \Delta H_2^0 - \Delta H_1^0 - \bar{L}_2 + \bar{L}_1 - v\Delta H$ is small, inasmuch as the other terms are small in any case. Thus in the neighborhood of the isobaric temperature, a small value of the denominator or a steep slope of the azeotropic temperature–composition curve is to be expected, if Trouton's rule is satisfied by both components or if only both Trouton coefficients are equal.

Small values of the denominator are also to be expected at high temperatures as the heats of vaporization vanish at the critical point. As vapor pressures increase rapidly with increasing temperatures, the formulas derived under the condition of a perfect gas phase cease to be valid at high temperatures, but this fact will hardly impair a qualitative conclusion.

Classification of Non-dissociating Azeotropic Systems.—A convenient classification starts from a "Trouton type" and describes characteristic deviations from this case.

(A) The azeotropic temperature–composition curve of a system of two non-associating liquids starts at $N_2 = 0$ or $N_2 = 1$ at a finite slope. The slope increases with increasing temperature and the curve extends to the critical temperature. The only known case of a system of this "Trouton type," benzene–cyclohexane (Fig. 1), shows a small part of this curve. It may be expected

(5) This is not a strictly thermodynamic statement. It results from the fact that the behavior of non-dissociating solutes at low concentrations can always be described by $\ln(a_2/N_2) = kN_2^s$ with $s \geqq 1$. Only for ions is $s = 1/2$, due to the long range of interionic forces. Next to these, the forces between zwitterions have the longest range. Already for this case the relation $s = 1$ holds (G. Scatchard and J. Kirkwood, *Physik. Z.*, **33**, 297 (1932)), the more for other types of solutes. However, an appreciably ionized amphoteric electrolyte would constitute an exception inasmuch as, due to the presence of ions, s were equal to 1/2 although no dissociation in the strict sense occurs.

(6) This has been realized already by W. D. Bancroft ("The Phase Rule," Ithaca, New York, 1897), and by S. Young ("Distillation Principles and Processes," London, 1922).

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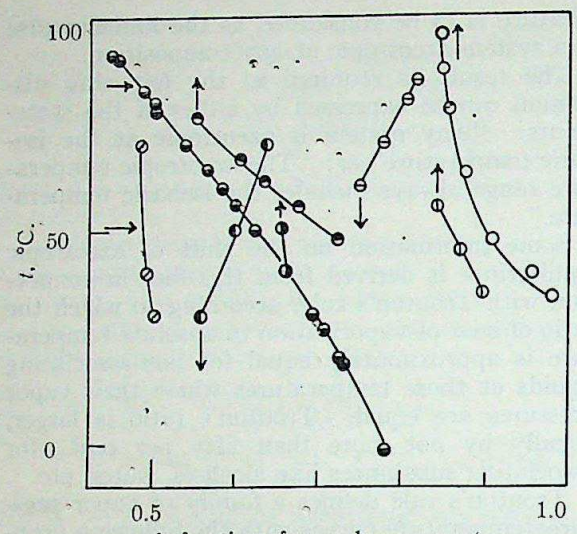

Fig. 1.—Azeotropic temperature as function of the composition. The isobaric temperature is indicated by arrows.

	Components	Isobaric temp.	Ref.
○	Water–ethanol	(high)	*a*
◐	Ethanol–chloroform	(high)	*b*
◑	Methanol–methyl acetate	(high)	*c*
◓	Ethyl acetate–carbon tetrachloride	84°	*d*
◒	Ethanol–ethyl acetate	84°	*e*
⊘	Benzene–cyclohexane	51.8°	*f*
◐	Heptane–ethanol	−2°	*g*
⊖	Toluene–ethanol	(low)	*h*

[a] J. Wade and R. W. Merriman, *J. Chem. Soc.*, **99**, 997 (1911); R. W. Merriman, *ibid.*, **103**, 628 (1913). [b] G. Scatchard and C. L. Raymond, THIS JOURNAL, **60**, 1278 (1938). [c] G. Bredig and R. Bayer, *Z. physik. Chem.*, **130**, 15 (1927). [d] P. W. Schutz and R. E. Mallonee, THIS JOURNAL, **62**, 1491 (1940). [e] R. W. Merriman, *J. Chem. Soc.*, **103**, 1801 (1913); W. Mund and Heim, *Bull. Soc. Chim. Belgique*, **41**, 349 (1932), quoted from ref. 8. [f] G. Scatchard, S. E. Wood and J. M. Mochel, *J. Phys. Chem.*, **43**, 119 (1939). [g] C. P. Smyth and E. W. Engel, THIS JOURNAL, **51**, 2660 (1929). [h] W. A. Wright, *J. Phys. Chem.*, **37**, 233 (1933).

that frequently crystallization will occur before the lower end of the curve is reached.

(B) A similar curve results from two associating liquids if the Trouton coefficients are approximately equal and the isobaric temperature is high (water–ethanol, Fig. 1).

(C) If the Trouton coefficients differ appreciably, *i. e.*, especially in systems composed of an associating and a non-associating component, the slope in general is finite. A steep slope is not strictly excluded as the heats of vaporization still may happen to be equal at some temperature. This temperature, however, must be remote from the isobaric temperature and, therefore, has no particular chance of being included in the azeotropic range. Thus a steep slope will be a rare exception as long as the gas phase is nearly perfect.

Considering the previous discussion of term (11), one is justified in extrapolating some of the experimental curves (Fig. 1) of this type to the lower end (ethyl acetate–carbon tetrachloride and ethanol–chloroform) and to the upper end (toluene–ethanol). The extrapolation is less certain in the latter case as approach to critical conditions may result in a considerable change of the slope.

Wrewsky[2] already has stated that in a system with maximum (minimum) vapor pressure the azeotropic concentration of the component with the larger heat of vaporization increases (decreases) with increasing temperature. Considering equation (9) and the previously discussed significance of the isobaric temperature, the direction of the temperature–composition curve is conveniently described also by the following statement: The azeotropic curve of a maximum (minimum) vapor pressure system ends, if at all, on the side of the more (less) volatile component. This is true both of lower and upper ends.

Frequently, though not always, the azeotropic behavior of non-dissociating systems is sufficiently described with the aid of the relationship

$$RT \ln a_2/N_2 = w N_1^2 \qquad (13)$$

where w characterizes the interaction between the two components. This has been shown by Herzfeld and Heitler[7] and recently in more detail by Kirejew.[8]

From a practical viewpoint, a thermodynamic examination of ternary systems is perhaps more interesting inasmuch as the experimental investigation requires so much more labor. The thermodynamic discussion, of course, is more complicated, too. Equations for ternary solutions similar to (13), derived by Porter[9] and by Scatchard,[10] greatly simplify the discussion which will be presented in a following paper of this series.

Acknowledgment.—The authors are indebted to Professor George Scatchard, the reviewer of this paper, for important critical advice.

Summary

1. The two thermodynamic relationships connecting the three azeotropic variables (composition, temperature, pressure) of a binary system are expressed in terms of common quantities with the only restriction that the vapor is a perfect gas mixture (equations 3, 9, 10).

2. The azeotropic temperature–composition curves depend in a characteristic way on whether one or both components are normal, dissociating or associating.

3. Dilute azeotropic solutions of a dissociating substance belong necessarily to the minimum vapor pressure type. The slope of the azeotropic

(7) K. F. Herzfeld and W. Heitler, *Z. Elektrochemie*, **31**, 536 (1925).

(8) V. A. Kirejew, *Acta Phys. Chim., U. R. S. S.*, **13**, 552 (1940); **14**, 371 (1941).

(9) A. W. Porter, *Trans. Faraday Soc.*, **16**, 336 (1921).

(10) G. Scatchard, *ibid.*, **33**, 160 (1937).

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temperature–composition curve decreases or increases without limit with decreasing concentration in dilute solutions of a dissociating component, and only of a dissociating component.

4. The term "isobaric temperature" is proposed for the temperature at which the vapor pressures of the pure components are equal. The slope of the azeotropic temperature–composition curve is steep at the isobaric temperature if the deviations from Trouton's rule are small for both components.

5. If the azeotropic temperature–composition curve of a maximum (minimum) vapor pressure system extends to a pure component, this component is the more (less) volatile one. The rule holds both for upper and lower limits of the azeotropic temperature range. In connection with the fact that this range includes the isobaric temperature, the rule conveniently indicates the direction of the curve.

PULLMAN, WASHINGTON
NEW YORK, N. Y. RECEIVED FEBRUARY 12, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK UNIVERSITY]

The Ternary System Barium Bromate–Barium Chlorate–Water at 25°

BY J. E. RICCI AND S. H. SMILEY

Introduction.—During various attempts to determine bromate in the presence of chlorate by precipitation with excess of barium chloride, it became apparent that the precipitated barium bromate was repeatedly and almost reproducibly contaminated with barium chlorate, despite all precautions for its proper formation in the pure state. The weight of the solid obtained, after the usual drying, was always too high, and its oxidizing equivalent, determined by iodometry, was also too high, indicating the presence of some chlorate. It was consequently suspected that the two salts, barium bromate and barium chlorate, isomorphous and both mono-hydrated, were forming solid solutions from their aqueous solutions. This was verified by a phase rule study of the ternary system involved. Since the resulting solid solution turned out to be a continuous one, the data were therefore used in testing the applicability of a semi-empirical relationship previously reported as describing the distribution of such isomorphous salts in solubility equilibrium between liquid and solid phases.[1]

Experimental Procedure.—The barium bromate used was a C. P. grade of the monohydrate, the purity of which was checked, with the following results: by iodometry, 95.73% $Ba(BrO_3)_2$, and by dehydration to constant weight at 110°, 95.53%. The theoretical value is 95.60%. A C. P. grade of $Ba(ClO_3)_2 \cdot H_2O$ also was used, found to contain 5.69% of water (by drying at 110°) as compared with the theoretical 5.60%. A qualitative test for bromate or other strong oxidizing agents proved negative (<0.001% as $Ba(BrO_3)_2$).

The experimental procedure for the solubility determinations has been described in similar publications. The temperature of the determinations was 24.95 ± 0.02°. Equilibrium was approached from two directions, in about half of the experiments from undersaturation, *i. e.*, lower temperature, and in the others from higher temperature. In most cases equilibrium was proved by the constancy of the composition of the liquid on repeated analysis. In other cases, although such direct proof was not possible since the solution was all consumed in repeated analyses before actual constancy was established, it is felt that the systems must have been very close to if not at true equilibrium, because care was taken to keep the relative amount of solid phase in the complexes very low, and because of the long period of stirring generally used (one to six, averaging three and one-half, months).

The liquid solution was analyzed after sampling by means of calibrated pipets fitted with filtering tips. The wet residues were either pressed between coarse filter paper or centrifuged briefly, before weighing and analysis.

Water was determined by drying at 110° and bromate was determined iodometrically (in the presence of chlorate) by a procedure already described[2] for a similar investigation on the system sodium bromate–sodium chlorate–water. The correction there reported for the effect of relatively high concentrations of chlorate was verified and applied in the present case. These two determinations allowed the calculation of the percentage of each salt in the various solutions and residues.

A slight complication arose from the fact that final traces of water were not easily driven off at 110°, but required a brief treatment at about 300°. Since this temperature would also cause a slight decomposition of the two salts, especially of the barium bromate, experiments were made to determine the rate of loss of weight of each salt at 300°. The results indicated that after the initial expulsion of traces of water, barium chlorate suffered no measurable loss of weight in one or two hours, while barium bromate lost almost 4 mg. per gram per hour at this temperature, a correction which was then applied in the actual analyses.

Results.—The results are tabulated in Table I, which lists all compositions in weight per cent. The density of the saturated liquid solution was not always measured. Some of the values listed were read from a plot of the density, d, against c, the total percentage of salt in the saturated solution; the dependence was in fact found to be roughly linear, with an average error of about 0.002, according to the expression

$$d = 0.993 + 0.00935c \qquad (1)$$

The solubility of barium chlorate here found is the same as the accepted value in the literature.[3] The solubility of barium bromate here reported, 0.791%, also agrees well with the important literature values: 0.788%, by Trautz and Anschütz,[3a] and 0.796%, by Harkins.[4]

(1) Hill, Durham and Ricci, THIS JOURNAL, 62, 2723 (1940).

(2) Swenson and Ricci, *ibid.*, 61, 1974 (1939).

(3) (a) Trautz and Anschütz, *Z. physik. Chem.*, 56, 238 (1906); 27.53%; (b) Foote and Hickey, THIS JOURNAL, 59, 648 (1937); 27.58%.

(4) Harkins, *ibid.*, 33, 1807 (1911).

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TABLE I

SYSTEM $Ba(BrO_3)_2$–$Ba(ClO_3)_2$–H_2O AT 25°

No.	Liquid solution Wt. % $Ba(BrO_3)_2$	Liquid solution Wt. % $Ba(ClO_3)_2$	Density[a]	C:Original complex R:Wet residue Wt. % $Ba(BrO_3)_2$	C:Original complex R:Wet residue Wt. % $Ba(ClO_3)_2$	Solid phase by extrapolation[b] Wt. % $Ba(BrO_3)_2$	Solid phase by extrapolation[b] Wt. % $Ba(ClO_3)_2$
1	0.791 (±0.001)	....	1.001				
2	.609	1.292	1.011	C:2.270	1.274	95.2	0.26
3	.553	2.304	1.016	C:2.829	2.258	95.1	.40
4	.491	4.850	(1.043)	C:2.94	4.74	94.9	.61
5	.446	7.019	1.060	C:3.00	6.90	92.4	3.1
				R:74.9	4.10		
6	.423	9.370	(1.085)	C:1.908	9.302	90.2	5.3
7	.402	10.50	(1.095)	C:5.84	10.47	84.6	10.8
				R:64.6	11.4		
8	.347	14.41	(1.131)	C:6.79	14.65	78.0	17.3
9	.347	14.56	(1.132)	C:2.92	14.81	73.5	21.9
				R:53.8	20.0		
10	.310	16.83	1.151	C:1.97	16.99	71.5	23.7
11	.282	18.07	1.165	C:2.47	18.74	59.2	36.0
12	.249	19.53	(1.178)	C:3.31	20.84	52.0	43.2
				R:38.5	37.6		
13	.235	20.50	1.186	C:1.92	21.53	46.4	48.6
14	.207	21.72	1.202	C:2.07	23.39	39.2	55.7
				R:29.3	47.8		
15	.176	22.91	(1.209)	C:2.93	25.56	32.5	62.4
				R:17.6	46.2		
16	.145	23.85	(1.217)	C:2.27	28.03	24.0	70.7
				R:16.8	58.7		
17	.112	24.87	(1.227)	C:2.93	31.67	19.2	75.5
				R:15.5	61.7		
18	.078	25.87	1.242	C:2.28	36.02	13.0	81.6
				R:9.15	66.8		
19	.057	26.51	(1.241)	C:1.00	37.82	5.7	88.8
				R:5.66	85.3		
20		27.54	1.249				

[a] Densities in parentheses are interpolated. [b] Average of two extrapolations, where wet residue analysis is reported; otherwise extrapolation through liquid solution and original complex.

The composition of the solid solution in equilibrium with the saturated liquid solution was calculated by the algebraic extrapolation,[5] to the line joining the compositions of the two separate monohydrates, of appropriate tie-lines through the liquid composition and the original complex, and also through the liquid composition and that of the wet residue whenever the latter was analyzed.

Figure 1 is the usual graphical representation of the isothermal relations of the ternary system, showing principally the disposition of the tie-lines for the distribution of the two isomorphous salts between the two continuous conjugate solutions. The shape of the solubility curve itself cannot be shown on such a scale. It is therefore presented separately on Fig. 2, which brings out an inverted S-shape similar to that of the 25° isotherm of the corresponding system sodium bromate–sodium chlorate–water.[2] The dip in the curve near the chlorate end, accompanied with divergence of the tie-lines in the direction of the solid solution, indicates, as in the sodium salt system, a tendency toward discontinuity of the solid solution and the formation of an isothermally invariant liquid. This is borne out by the mathematical analysis of the distribution of the salts between liquid and solid phases, in which it is inferred that the solid solution involves positive deviations from Raoult's law.

Distribution between the Aqueous and the Solid Solutions.—According to a relation already shown to hold with at least approximate correctness in a number of cases of pairs of isomorphous salts, the distribution of the salts of the present investigation, at equilibrium between their solid solutions, is given by the expression

$$\log R_l = \log K + m \log R_s \qquad (2)$$

in which R_l is the mole ratio of chlorate to bromate in the liquid solution, R_s is the same ratio in the solid solution, K represents the square root of the ratio of the thermodynamic solubility product of barium chlorate to that of barium bromate, and m is an empirical constant characteristic of the particular pair of salts and representing some measure of the degree of non-ideality of the solid

(5) Hill and Ricci, THIS JOURNAL, 53, 4305 (1931).

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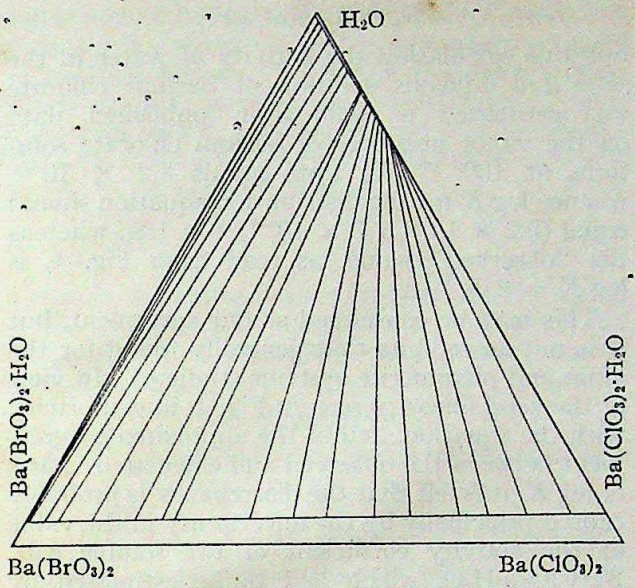


Fig. 1.—System $Ba(BrO_3)_2$–$Ba(ClO_3)_2$–H_2O at 25°.

solution formed by them. With ideal relations, $m = 1$. The equation has been found to apply to a number of systems both of alums and of picromerites.[1]

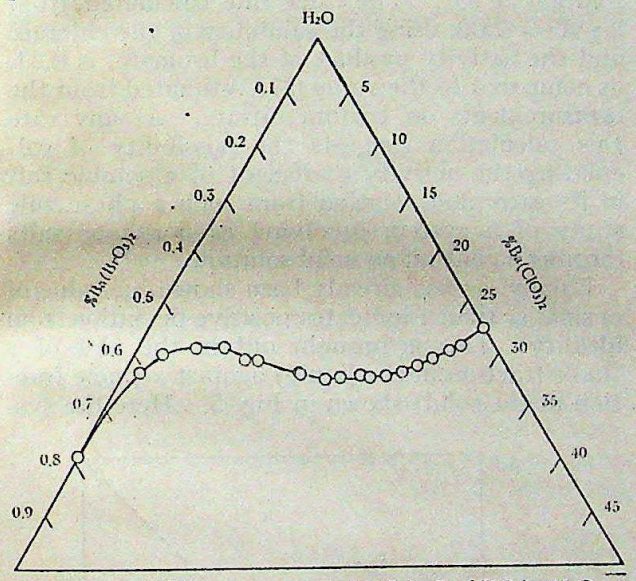


Fig. 2.—Solubility curve: $Ba(BrO_3)_2$–$Ba(ClO_3)_2$–H_2O at 25°.

The quantities required for testing this distribution equation in the present system are listed in Table II. Here R_l and R_s are the ratios already explained, and x and y are the mole fractions of barium chlorate in the solid and in the liquid phases, respectively, excluding water.

These quantities were first plotted to see whether the solid solution of these salts constituted a "regular" solution in the Hildebrand sense.[6] This would require a linear relation between log (R_l/R_s) and x, the mole fraction of one of the salts in the solid. Figure 3 shows

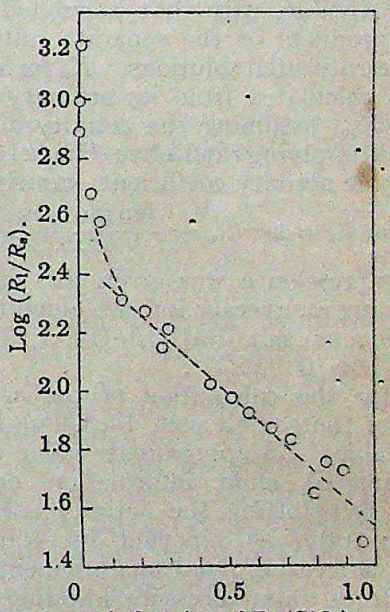
(6) Hildebrand, "Solubility of Non-Electrolytes," Reinhold Publishing Company, New York, N. Y., 1936, p. 65.

TABLE II

DISTRIBUTION BETWEEN LIQUID AND SOLID SOLUTIONS

No.	Log R_l	Log R_s	y	x
1			0	0
2	0.4380	−2.4523	0.733	0.00352
3	.7309	−2.2648	.843	.00541
4	1.1059	−2.0807	.927	.00824
5	1.3082	−1.3708	.954	.0408
6	1.4567	−1.1229	.967	.0701
7	1.5283	−0.7827	.971	.142
8	1.7297	− .5428	.982	.223
9	1.7342	− .4145	.984	.278
10	1.8460	− .3683	.986	.300
11	1.9180	− .1047	.988	.440
12	2.0058	+ .0308	.990	.518
13	2.0520	+ .1314	.991	.575
14	2.1322	+ .2639	.993	.648
15	2.2258	+ .3946	.994	.713
16	2.2274	.5805	.995	.792
17	2.4578	.7059	.996	.836
18	2.6320	.9091	.998	.890
19	2.7790	1.3038	.999	.953
20			1	1

that while the relation is linear for values of x above 0.2, it is distinctly non-linear at lower mole fractions of the chlorate.



x = the mole fraction of $Ba(ClO_3)_2$.

Fig. 3.—Test of "regularity" of the solid solution.

Figure 4 shows the data plotted to test equation (2). The over-all linearity of the relation between log R_l and log R_s is evident, especially with respect to intermediate values of the ratios. The scattering from linearity toward the extreme values is not necessarily significant, since the ratios at either end are more sensitive to experimental errors in the analytical determinations. Since the percentage of $Ba(ClO_3)_2$ is calculated by difference the error in the determination of R_s is relatively high when the solid phase approaches

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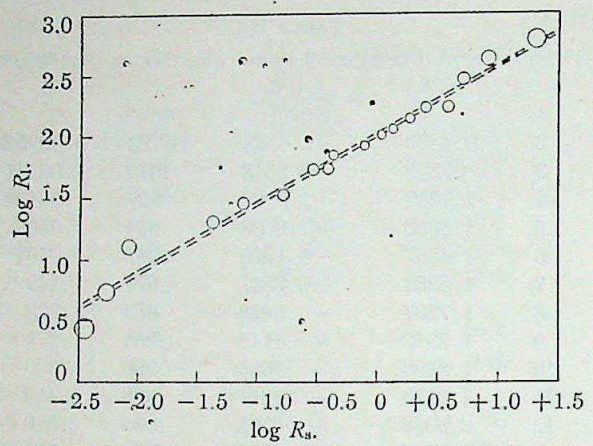

Fig. 4.—Distribution curve according to equation [4].

pure $Ba(BrO_3)_2 \cdot H_2O$. At the other extreme R_1 becomes uncertain because of the decreasing precision of the determination of the small solubility of the bromate. Fortunately the important region of the plot of Fig. 4 is that near $\log R_s = 0$, and here the precision of the measurement of the ratios is high and the linearity is definite, giving a value of $m = 0.58$. At $\log R_s = 0$, $\log R_1 = \log K = 2.0_0$.

This "observed" value of $\log K$ is to be compared, if possible, with that calculated from the activity products of the separate salts in their respective saturated solutions. K_a for $Ba(BrO_3)_2 \cdot H_2O$ was calculated from its ordinary solubility product, K_m, assuming the activity of water to be one, and applying the Debye–Hückel expression for the ionic activity coefficient, namely

$$\log K_a = \log K_m - \frac{6(0.510)(\mu)^{1/2}}{1 + 0.329a(\mu)^{1/2}} \qquad (3)$$

In this expression a was given the value of 2.5 Å., assuming an average ion size equal to that for the analogous salt $Ba(IO_3)_2 \cdot H_2O$.[7] This gives $K_a = 7.74 \times 10^{-6}$ at 25°.

Data for the calculation of the activity coefficient of the soluble salt, $Ba(ClO_3)_2 \cdot H_2O$, were not available. An approximate value was therefore estimated from information on barium nitrate. By plotting the activity coefficient of barium nitrate, as reported by Randall and Scott[8] from freezing point measurements, and by Ratner[9] from vapor pressure lowerings, at 70°, of solutions up to 1 M in concentration, against the square root of the ionic strength, and extrapolating to the solubility of the chlorate, (1.13 M), a value of $f_\pm = 0.18$ was obtained. The applicability of the estimate is subject to uncertainty both because the two salts differ in respect to hydration and because an extrapolation was involved to a concentration somewhat beyond the range of Ratner's measurements. At any rate, using this value for the ionic activity coefficient, K_a for $Ba(ClO_3)_2 \cdot H_2O$ is calculated as

$$K_a = K_m a_{H_2O} (f_\pm)^3 \qquad (4)$$

For this calculation the activity of water in the saturated aqueous solution of barium chlorate was estimated as 0.95 from published data on the vapor pressures of barium chlorate solutions at 100°.[10] K_a thus equals 3.2×10^{-2}, whence $\log K$ for the distribution equation should equal $(3.2 \times 10^{-2}/7.7 \times 10^{-6})^{1/2} = 1.8_1$, whereas the "observed" value, as read from Fig. 4, is $\log K = 2.0_0$.

This may be considered as fair agreement, but it is not as good as that generally found for the alum and picromerite systems studied.[1] In view of the good linearity seen in Fig. 4, in conformity with the equation, and of the approximate agreement between the observed and calculated values of $\log K$, it is felt that the discrepancy is probably caused principally by the uncertainty in the value of the activity coefficient of the soluble salt, $Ba(ClO_3)_2 \cdot H_2O$, which had to be estimated by analogy only. Since the equation probably does describe the actual relations, it may be suggested that the observed value of $\log K$ can be used to estimate the unknown activity coefficient of $Ba(ClO_3)_2 \cdot H_2O$ in its pure saturated aqueous solution at 25°. The value thus calculated, from $\log K = 2.00$, using the solubility of the chlorate and the activity product of the bromate, is 0.24, as compared to the value 0.18 estimated from the measurements on barium nitrate. At any rate this calculation suggests the possibility of calculating the activity coefficient of a soluble salt in its saturated solution from such a phase rule study of a system involving isomorphous salts forming a continuous solid solution.

Finally, as has already been shown,[1] a value of m smaller than 1 indicates positive deviation from ideality. This is brought out in the plot of y (mole fraction in the liquid) against x (mole fraction in the solid) shown in Fig. 5. Here the sys-

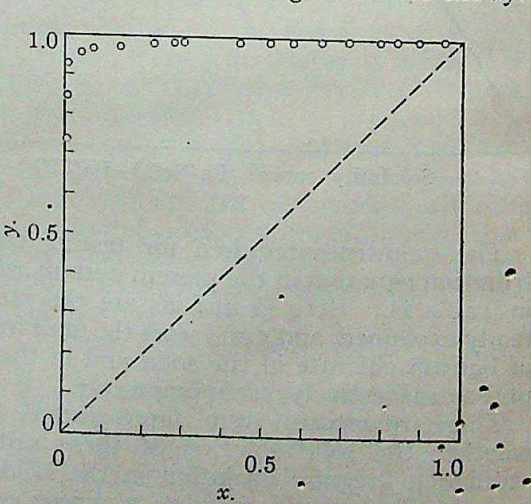

Fig. 5.—Distribution curve in mole fractions: x, mole fraction of chlorate in solid solution; y, in liquid solution.

(7) Ricci and Nesse, THIS JOURNAL, 64, 2305 (1942).
(8) Randall and Scott, *ibid.*, 49, 647 (1927).
(9) Ratner, *J. Phys. Chem., U. S. S. R.*, 9, 257 (1937).
(10) Measurements by Tammann, as listed in "International Critical Tables," Vol. III, 1926, p. 296.

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tem is seen to belong to Type II of the Roozeboom classification of such distributions between liquid and solid solutions. Although the experimental points do not actually cross the diagonal as x and y approach 1, as is demanded by Roozeboom's Type II, it may be calculated that with $m = 0.6$ and $K = 100$ in the equation

$$\frac{y}{1-y} = K\left(\frac{x}{1-x}\right)^m \qquad (5)$$

which is derivable from equation (2), the curve of Fig. 5, plotting y against x, will cross the diagonal at $x = 0.99999$, a value beyond experimental handling.

Summary

1. The solubility equilibrium relations in the system $Ba(BrO_3)_2$–$Ba(ClO_3)_2$–H_2O were studied at 25°.

2. The formation of a continuous solid solution of the monohydrates of the two salts at this temperature explains the difficulties in the attempted analytical determination of bromate in the presence of chlorate by precipitation with excess of some barium salt such as barium chloride.

3. The system is found to belong to Type II of Roozeboom's classification of solid solutions, involving positive deviations from ideality.

4. The distribution constant for the two isomorphous salts between their aqueous solutions and the saturating solid solution was determined from a plot of the data. Log K so found = 2.0_0, in fair agreement with the value calculated from the separate aqueous solubilities of the two salts, namely, log $K = 1.8_1$.

5. The disagreement between calculated and observed distribution constants is attributed chiefly to the uncertainty of the value of the activity coefficient for $Ba(ClO_3)_2 \cdot H_2O$, and it is suggested that the distribution constant derived from this type of equilibrium study may be used for the calculation of such an activity coefficient.

NEW YORK, N. Y. RECEIVED MARCH 1, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, NEW YORK UNIVERSITY]

The Systems $NaClO_3$–NaBr–H_2O, $NaClO_3$–NaI–H_2O and $NaClO_3$–$NaNO_3$–H_2O, at 25°C.

BY J. E. RICCI

The solubility measurements here reported[1] have been made as additions to the systematic study of the equilibrium relations in aqueous systems involving sodium halates, particularly sodium chlorate.[2]

The experimental procedure was that already described for similar investigations. The salts were all C. P. or "reagent" materials, used without further purification. Equilibrium was established in representative instances by constancy of composition upon repeated analysis. Complexes were stirred for at least two days in every case, at a temperature of 25 ± 0.05°.

In the first two systems (I, $NaClO_3$–NaBr–H_2O; II, $NaClO_3$–NaI–H_2O) the analysis of the saturated aqueous solution involved argentometric titration of the halide salt, with eosin as adsorption indicator, determination of water in a separate sample by evaporation, and calculation of the sodium chlorate by difference. A few of the halide determinations for the isothermally invariant points were verified by the Volhard method. In the third system (III, $NaClO_3$–$NaNO_3$–H_2O) the chlorate was determined independently by treatment with standard arsenite solution and, after heating with hydrochloric acid, titration of the excess of arsenite by means of standard potassium bromate solution, using indigosulfonic acid as indicator; the sodium nitrate was then calculated by difference, after determination of water by evaporation. The solubilities of the individual salts (with the exception of sodium nitrate) were determined both volumetrically and by evaporation, with very close agreement between the two methods throughout.

The solid phases were in each case the pure separate salts or their respective hydrates stable at 25°, and were easily identified by means of tie-lines, on the ternary diagrams, drawn through the compositions of the original complex and of the corresponding saturated solution. The algebraic extrapolation of these tie-lines shows deviations from the points representing the pure salts or their hydrates, averaging 0.20, 0.21 and 0.34% in the three systems, respectively. This indicates, on the average, a relatively much smaller error in the total experimental procedure involving preparation of complexes, establishment of equilibrium and sampling and analysis of saturated solutions.

The numerical results are listed in Tables I, II and III, in terms of weight per cent. Densities were determined for the whole range of concentration only for the sodium nitrate system. These densities were obtained by using calibrated

(1) The greater part of the experimental work here reported was performed by A. C. Campbell (system $NaClO_3$–NaBr–H_2O), P. Mockridge (system $NaClO_3$–NaI–H_2O) and G. J. Moore (system $NaClO_3$–$NaNO_3$–H_2O), as candidates for the Bachelor's degree at New York University.

(2) Ricci and Yanick, THIS JOURNAL, **59**, 491 (1937); Ricci, **60**, 2040 (1938); Swenson and Ricci, **61**, 1974 (1939); Ricci and Weltman, **64**, 2746 (1942).

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TABLE I

SYSTEM $NaClO_3$–NaBr–H_2O AT 25°

Original complex, wt. % $NaClO_3$	NaBr	Saturated solution, wt. % $NaClO_3$	NaBr	Solid phase
...	0	50.10	0	$NaClO_3$
58.52	7.99	37.93	11.86	$NaClO_3$
51.96	14.17	29.54	20.72	$NaClO_3$
47.30	20.52	20.87	30.75	$NaClO_3$
43.02	25.08	16.29	36.77	$NaClO_3$
35.05	29.26	15.37	38.10	$NaClO_3$
29.92	34.79	13.87	40.32	$NaClO_3$ + $NaBr{\cdot}2H_2O$
25.00	37.00	13.97	40.18	$NaClO_3$ + $NaBr{\cdot}2H_2O$
15.59	42.68	13.85	40.36	$NaClO_3$ + $NaBr{\cdot}2H_2O$
13.02	46.07	14.03	40.11	$NaClO_3$ + $NaBr{\cdot}2H_2O$
12.14	46.78	13.98	40.18	$NaClO_3$ + $NaBr{\cdot}2H_2O$
Average		13.89	40.28	$NaClO_3$ + $NaBr{\cdot}2H_2O$
8.91	50.42	12.38	41.16	$NaBr{\cdot}2H_2O$
6.48	49.96	8.07	43.74	$NaBr{\cdot}2H_2O$
6.14	49.24	7.22	44.28	$NaBr{\cdot}2H_2O$
0	...	0	48.49	$NaBr{\cdot}2H_2O$

TABLE II

SYSTEM $NaClO_3$–NaI–H_2O AT 25°

Original complex, wt. % $NaClO_3$	NaI	Saturated solution, wt. % $NaClO_3$	NaI	Solid phase
...	0	50.10	0	$NaClO_3$
55.03	9.11	38.72	12.40	$NaClO_3$
42.93	19.86	27.62	25.23	$NaClO_3$
40.31	26.79	18.67	36.53	$NaClO_3$
28.30	38.98	10.28	48.78	$NaClO_3$
30.14	41.13	7.11	54.63	$NaClO_3$
34.01	41.07	5.44	58.56	$NaClO_3$
16.93	54.77	4.50	61.52	$NaClO_3$ + $NaI{\cdot}2H_2O$
25.92	52.02	4.28	61.74	$NaClO_3$ + $NaI{\cdot}2H_2O$
15.31	60.91	4.08	61.79	$NaClO_3$ + $NaI{\cdot}2H_2O$
8.33	63.92	4.20	61.73	$NaClO_3$ + $NaI{\cdot}2H_2O$
4.93	64.13	4.51	61.61	$NaClO_3$ + $NaI{\cdot}2H_2O$
Average		4.32	61.68	$NaClO_3$ + $NaI{\cdot}2H_2O$
2.12	67.63	2.83	62.65	$NaI{\cdot}2H_2O$
1.29	65.92	1.43	63.67	$NaI{\cdot}2H_2O$
0.95	67.43	1.22	64.00	$NaI{\cdot}2H_2O$
0	...	0	64.80	$NaI{\cdot}2H_2O$

TABLE III

SYSTEM $NaClO_3$–$NaNO_3$–H_2O AT 25°

Original complex, wt. % $NaClO_3$	$NaNO_3$	Saturated solution, wt. % $NaClO_3$	$NaNO_3$	Density	Solid phase
...	0	50.10	....	1.432	$NaClO_3$
56.99	7.06	43.98	9.26	1.481	$NaClO_3$
49.82	14.31	38.82	17.47	1.517	$NaClO_3$
48.96	18.09	35.72	22.65	1.528	$NaClO_3$
43.93	22.98	34.28	25.96	1.549	$NaClO_3$ + $NaNO_3$
38.95	30.03	34.29	25.95	1.557	$NaClO_3$ + $NaNO_3$
34.10	33.77	34.28	25.90	1.552	$NaClO_3$ + $NaNO_3$
30.23	40.44	34.28	25.91	...	$NaClO_3$ + $NaNO_3$
27.93	40.05	34.28	25.96	1.554	$NaClO_3$ + $NaNO_3$
Average		34.28	25.94	1.553	$NaClO_3$ + $NaNO_3$
27.59	37.32	32.15	27.08	1.548	$NaNO_3$
22.11	43.02	27.34	29.72	1.505	$NaNO_3$
9.65	68.90	20.96	33.94	1.468	$NaNO_3$
10.04	54.94	13.85	38.66	1.440	$NaNO_3$
4.99	59.98	6.93	43.27	...	$NaNO_3$
0	...	0	47.87	1.389	$NaNO_3$

pipets in the sampling of the saturated liquids for analysis; they are relatively less precise and dependable than the analytical results themselves.

The data are not shown graphically since the relations involve no unusual features: The values, however, all lie on smooth curves; and the systems are seen to be of the simplest type, each with two branches for the solubility curve, one for each of the separate component salts, and with no indication of the formation of either solid solutions or double salts. The isothermally invariant solutions saturated with two salts have the compositions

	% $NaClO_3$	% 2nd salt	Density
I	13.89	40.28 (NaBr)	1.583
II	4.32	61.68 (NaI)	1.911
III	34.28	25.94 ($NaNO_3$)	1.553

A few determinations were also made on the equilibrium relations of the first system, $NaClO_3$–NaBr–H_2O, at 50°, enough to show that the principal isothermally invariant point, at this temperature, containing 43.0% sodium chlorate and 16.2% sodium bromide, involves as solid phases sodium chlorate and anhydrous sodium bromide, instead of the dihydrate of the latter salt, which in the binary aqueous system is stable up to ~ 51.0°.

The absence of complexity in the sodium nitrate system is in some contrast with the relations in the system $KClO_3$–KNO_3–H_2O at the same temperature. These salts form a limited series of solid solutions consisting of potassium chlorate containing (at 25°) up to 14.37 *M* % of potassium nitrate, while no potassium chlorate is found to dissolve in the potassium nitrate phase.[3] This behavior seems to be related to the dimorphism of potassium nitrate. While the stable rhombic form of potassium nitrate changes to a monoclinic variety only at 129°, the solid solution seems to involve the unstable monoclinic form since potassium chlorate is itself monoclinic at room temperature. On the other hand, the stable rhombic potassium nitrate, which is the actual potassium nitrate phase of the ternary aqueous system, does not take up any of the monoclinic chlorate. For the sodium salts, however, the nitrate is simply rhombohedral, and while the chlorate appears to be at least dimorphous, its usual form is cubic, and no solid solution at all is observed in the system as studied at 25°.

Summary

Solubility measurements are given for the systems I, $NaClO_3$–NaBr–H_2O, II, $NaClO_3$–NaI–H_2O and III, $NaClO_3$–$NaNO_3$–H_2O, at 25°. These salt pairs form neither double salts nor solid solutions at this temperature.

NEW YORK, N. Y. RECEIVED MARCH 6, 1944

(3) At 25°: Toda, *J. Chem. Soc.* (Japan), **43**, 320 (1922), in "International Critical Tables," Vol. 4, p. 314 (1926). At 16°: Herbette, *Compt. rend.*, **143**, 128 (1906).

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[CONTRIBUTION FROM THE MALLINCKRODT CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

The Viscosity of Aqueous Solutions of Electrolytes as a Function of the Concentration. VIII. Potassium Ferricyanide

BY GRINNELL JONES AND SCHUYLER M. CHRISTIAN

This paper is an extension of the work on the viscosity of solutions of electrolytes which has been reported in a series of earlier papers.[1]

Potassium ferricyanide was selected because it gives a good example of a salt of the 1–3 valence type. Measurements of the viscosity of solutions of this salt have been carried out by Wagner,[2] by Abegg,[3] and by Rankin and Taylor,[4] but the available data do not cover as wide a range of concentration or have as great precision as is desired for our purposes. It is of interest that Rankin and Taylor found that although at 25° the solutions of this salt are more viscous than water, yet at 1.6° the solutions are less viscous than water with a minimum in the viscosity–concentration curve.

The best grade of salt available by purchase was further purified by crystallization and carefully dried. The viscometer, thermostats, timing apparatus and experimental procedure were the same as those used by Jones and Stauffer. Two minor changes were made in the calculation of the corrections to the experimental data. In the previous papers of this series the kinetic energy correction has been calculated by the method recommended by Bingham, using the value $m = 1.12$ for the coefficient of the correction term. The value for this coefficient has recently been determined experimentally for this particular instrument by T. W. Dakin[5] and found to be $m = 0.98$, and this new value was used in the computation of the correction. For a nearly saturated solution (3.5 N) at 25° the kinetic energy correction computed by the old value of m is +0.00297, which is reduced to +0.00266 by the use of the new value of m, or a change of less than 0.03% of the viscosity. However, the correction decreases rapidly with dilution. Thus for the 1 N solution at 25° the correction is only +0.00011 with the old value of m and +0.00010 with the new value. At 0° the kinetic energy correction itself is much smaller than at 25° owing to the fact that the efflux time is approximately doubled and furthermore the viscosity of the solutions is much closer to that of water, so that for relative measurements the effect is substantially reduced. The kinetic energy correction for the strongest solution studied at 0° (2 N) was only −0.00025 and the difference in the correction caused by the change in the value of m is only 0.004%. We have not yet recomputed the correction for the data on other salts which have been determined in this Laboratory by the use of this instrument but these examples indicate that the error in this correction due to the use of $m = 1.12$ will not be significant except perhaps in a few of the most concentrated solutions studied. The situation is even more favorable in the cases of the measurements made with another viscometer designated as the T Instrument because (1) the kinetic energy correction is smaller because of a greater efflux time; and (2) Dakin's determination of the value of m for this instrument gave a value of 1.16 which is nearer to the assumed value of 1.12 used in the computation of the published data obtained with this instrument.

A surface tension correction is applied to the data by the use of a correcting factor computed by the formula $f = 1 + 0.0076\left(1 - \frac{\sigma_c \rho_0}{\sigma_0 \rho_c}\right)$ given by Jones and Fornwalt.[1] The surface tension data for 25° are taken from the paper by Jones and Ray.[6] Jones and Ray did not make any measurements at 0° but some approximate measurements made at 0° with a DuNouy tensiometer gave results for the relative surface tension which agree well with those at 25°. In contrast to the kinetic energy correction this surface tension correction is nearly independent of the temperature and is approximately linear with respect to the concentration. It amounts to +0.027% for a 1 N solution.

In a few cases a correction not exceeding 0.003% has been applied to the viscosity data and density data to bring the results to a round concentration. In all cases where the correction exceeded 0.003% the data as obtained are published and the estimated values at a round concentration are given in parentheses.

Interpretation of the Results

The experimental data on the density of potassium ferricyanide solutions may be expressed by equations having the form suggested by Root[7] with an average deviation of only 0.0023%.

$$d^{25}_4 = 0.99707_4 + 0.181448c - 0.0204195c^{3/2}$$

$$d^{0}_4 = 0.99987_0 + 0.193367c - 0.0204495c^{3/2}$$

The viscosity and fluidity of these solutions can be expressed by equations of the form suggested by Jones and Dole, as is shown in Table III. It is interesting that the viscosity–concentration curve at 0° has both a maximum (at $c = 0.0034$; $N =$

(1) Grinnell Jones and Associates, VII, THIS JOURNAL, 62, 338 (1940). For references to earlier articles see *ibid.*, 62, 335 (1940).

(2) J. Wagner, *Z. physik. Chem.*, 5, 31 (1889).

(3) R. Abegg, *ibid.*, 11, 248 (1893).

(4) C. Rankin and W. W. Taylor, *Trans. Roy. Soc. Edin.*, 45, 401 (1905).

(5) T. W. Dakin, Harvard University Dissertation, 1940 (not yet published).

(6) Grinnell Jones and W. A. Ray, THIS JOURNAL, 63, 288 (1941).

(7) W. C. Root, *ibid.*, 55, 850 (1933).

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TABLE I

VISCOSITY OF POTASSIUM FERRICYANIDE SOLUTIONS AT 25°

c	N	Density	$\frac{d_c t_c}{d_0 t_0}$	KE Correction $\times 10^6$	Surface tension correction $\times 10^6$	$\frac{\eta_c}{\eta_0} = \eta$	$\varphi = 1/\eta$	$(\eta - 1)/c$
0.000333	0.001	0.99714	1.000461	+ 5	0	1.00047	0.99953	+1.41
.000667	.002	.99721	1.000648	+ 6	0	1.00065	.99935	+ .97
.001667	.005	.99739	1.001196	+ 10	+ 1	1.00121	.99879	+ .726
.003333	.010	.99768	1.001774	+ 13	+ 3	1.00179	.99821	+ .537
.006667	.020	.99830	1.002777	+ 17	+ 5	1.00280	.99721	+ .420
.016667	.050	1.00009	1.004992	+ 22	+ 13	1.00503	.99500	+ .301
.03333	.100	1.00305	1.008232	+ 25	+ 26	1.00828	.99179	+ .248
.097772	.29332	1.01439	1.019284	+ 22	+ 84	1.01939	.98098	+ .198
(.100)	.300	(1.01478)				(1.01978)	(.98060)	.1978
.16667	.500	1.02632	1.031468	+ 24	+ 149	1.03164	.96933	.1898
.33333	1.000	(1.05472)				(1.06678)	(.93740)	.2003
.33349	1.00048	1.05474	1.066429	+ 96	+ 300	1.06682	.93737	.2004
.66604	1.99814	1.11002	1.169455	+ 619	+ 597	1.17067	.85421	.2562
.6667	2.000	(1.11012)				1.1709	(.85403)	.2563
.9996	2.99883	1.16399	1.333798	+1763	+ 920	1.33648	.74823	.3356
1.000	3.000	(1.16405)				(1.3367)	(.7481)	.3367
1.166666	3.500	(1.19038)				(1.4489)	(.6902)	.3848
1.1677	3.50321	1.19055	1.445938	+2600	+1102	1.44964	.68983	.3851

TABLE II

VISCOSITY OF POTASSIUM FERRICYANIDE SOLUTIONS AT 0°

c	N	Density	$\frac{d_s t_s}{d_0 t_0}$	KE correction $\times 10^6$	Surface tension correction $\times 10^6$	η	$\varphi = \frac{1}{\eta}$	$\eta = \frac{1}{c}$
0.000333	0.001	0.99998	1.000376	+ 1		1.00038	0.99962	+1.14
.000667	.002	1.00000	1.000447	+ 1	+ 1	1.00045	.99955	+0.67
.001667	.005	1.00021	1.000588	+ 1	+ 2	1.00059	.99941	+ .35
.003333	.010	1.00053	1.000681		+ 5	1.00069	.99931	+ .21
.006667	.020	1.00111	1.000540	- 2	+ 10	1.00055	.99945	+ .082
.016667	.050	1.00305	0.999839	- 10	+ 20	0.99985	1.00015	- .009
.033333	.100	1.00616	.999178	- 23	+ 41	.99820	1.00180	- .054
.098143	.29443	1.01823	.992206	- 76	+115	.99224	1.00782	- .079
.100	.300	(1.01857)				(.99210)	1.00796	- .079
.16667	.500	(1.03074)				(.98818)	1.01196	- .0715
.167383	.50215	1.03088	.988148	-124	+182	.98820	1.01194	- .0705
.33333	1.00	(1.06036)				(.98879)	1.01134	- .0336
.33538	1.00615	1.06071	.988822	-212	+318	.98891	1.01121	- .0331
.66667	2.000	1.11763	1.032548	-251	+607	1.03289	0.96816	+ .0498

TABLE III

EQUATIONS FOR VISCOSITY AND FLUIDITY OF AQUEOUS SOLUTIONS OF POTASSIUM FERRICYANIDE

	Range of validity	Average deviation
25°C.		
$\eta = 1 + 0.0244\sqrt{c} + 0.1141c$	$c \longrightarrow 0.0333$ ($N = 0.1$)	0.000025
$\eta = 1 + .0244\sqrt{c} + .10785c + 0.13262c^2$	$c \longrightarrow .1667$ ($N = .5$)	.000043
$\varphi = 1 - .0245\sqrt{c} - .1114c$	$c \longrightarrow .033$ ($N = .1$)	.000026
$\varphi = 1 - .0245\sqrt{c} - .102371c - .129818c^2$	$c \longrightarrow .666$ ($N = 2.0$)	.000066
0°C.		
$\eta = 1 + 0.02113\sqrt{c} - 0.1701c$	$c \longrightarrow .033$ ($N = .1$)	.00003
$\eta = 1 + .02113\sqrt{c} + .18133c + 0.35368c^2$	$c \longrightarrow .1667$ ($N = .5$)	.00003
$\varphi = 1 - .02113\sqrt{c} + .1701c$	$c \longrightarrow .033$ ($N = .1$)	.00003
$\varphi = 1 - .02113\sqrt{c} + .18151c - .34973c$	$c \longrightarrow .1667$ ($N = .5$)	.00003
$\varphi = 1 - .02113\sqrt{c} + .17736c - .31959c^2$	$c \longrightarrow .33$ ($N = 1.0$)	.000056

0.01) and a minimum (at $c = 0.17$; $N = 0.5$). This behavior is unusual but has been obtained at 0° for solutions of potassium chloride (Jones and Talley) and of silver nitrate (Jones and Colvin).

In order to compute the coefficient of the square root term (A) in the viscosity equation by the use of the Falkenhagen and Vernon equation,[8] reliable values for the equivalent conductance of the potassium and ferricyanide ions at 25 and 0°

(8) H. Falkenhagen and E. L. Vernon, *Physik. Z.*, **23**, 140 (1932).

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are needed. For 25° we shall use the values 73.52 for the potassium ion and 101.0 for the ferricyanide ion given by MacInnes,[9] based on measurements of the conductance of potassium ferricyanide solutions by Hartley and Donaldson.[10] These measurements were evidently well done and cover a very low range of concentration; N = 0.00004 to 0.0002. The results are supported by the measurement of Hölzl[11] which cover the range from N = 0.001 N to 0.03 N but when plotted appear to be consistent with those of Hartley and Donaldson. On the other hand, the earlier measurements of Harry C. Jones and C. Watkins[12] are inconsistent with the others by nearly 7%, and deserve no further consideration.

Unfortunately, the available information as to the mobility of the ferricyanide at 0° is far less satisfactory. The only measurements of the conductance of a ferricyanide solution at 0° which we have found in the literature are those of Harry Jones and Watkins which, as explained above, are grossly in error at 25°. There is a strong presumption that an error of this magnitude is due to a wrong choice of the reference standard used in the determination of their cell constants. This is supported by the values for potassium chloride given by Harry C. Jones[13] which are also substantially below the correct values at both 25 and 0°. It is necessary to multiply his values for potassium chloride by a factor 1.067 to obtain the correct values. We have, therefore, applied this factor to his data on potassium ferricyanide and plotted the results against $\sqrt{c}$. Extrapolation gives a value of 94.4 for the limiting conductance at infinite dilution. The values thus obtained are consistent with the values given in the "International Critical Tables" which are stated to be based on Jones and Watkins and, therefore, the process of adjustment described above must have been used in preparing the "International Critical Tables." Subtracting the mobility of the potassium ion at 0°, 40.4, gives 54 for the ferricyanide ion.

TABLE IV

	25°C.	0°C.
T	298.18	278.18
D	78.8	88.0
η	0.008949	0.01792
$l_1(K^+)$	73.52	40.4
$l_2(Fe(CN)_6^{---})$	101.0	54
A computed	0.0222	0.020
A experimental	.0244	.0211

The other parameters used in the calculation and in the results are shown in Table IV. The agreement between the computed and experimental results is about as close as usual[14] and shows that the formula of Falkenhagen and Vernon correctly evaluates the influence of valence type and of the temperature.

Summary

1. Data are given for the density and viscosity of potassium ferricyanide solutions at 25 and 0° covering the range up to saturation.

2. Equations expressing the density, viscosity and fluidity as functions of the concentration are given.

3. The predictions of the Falkenhagen and Vernon equation are verified for this case.

(9) D. A. MacInnes, "The Principles of Electrochemistry," Reinhold Publishing Company, N. Y., 1939, p. 342.

(10) G. H. Hartley and G. W. Donaldson, *Trans. Faraday Soc.*, **33**, 465 (1937).

(11) F. Hölzl, *Monatsh.*, **55**, 137 (1930).

(12) Harry C. Jones and C. Watkins, THIS JOURNAL, **37**, 2631 (1915).

(13) H. C. Jones, Carnegie Institute at Washington, Pub. 130, p. 20.

(14) See H. S. Harned and B. B. Owen, "The Physical Chemistry of Electrolytic Solutions," Reinhold Publishing Company, New York, N. Y., 1943, p. 177, for a tabulation of the available data in other cases.

CAMBRIDGE, MASSACHUSETTS RECEIVED MARCH 18, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF ANATOMY, CORNELL UNIVERSITY MEDICAL COLLEGE]

The Characterization of Capillaries Used for Dropping Mercury Electrodes in Polarographic Studies

BY OTTO H. MÜLLER

The best identifying characteristics of a capillary are its length and internal diameter, provided that it has a truly uniform bore. While some factory made capillaries fulfill this condition, all laboratory made capillaries do not, because they are drawn from wider stock and are consequently more or less tapered. Even if capillaries of uniform bore were used exclusively, the means for measuring with sufficient accuracy diameters varying from 10–50 μ, or for determining the uniformity of the bore are not available to most chemists. The present study was therefore undertaken to find certain characteristics which would (a) be peculiar to *all* kinds of capillaries, (b) be determinable without special apparatus, (c) permit comparison of straight and tapered capillaries and a prediction of their performance, and (d) give enough information for the duplication of any given capillary. It was found that the capillary constant, κ, and the radius of the capillary orifice, ρ, are two factors which meet all of these requirements. Some simple techniques for their precise determination and some incidental observations made during this study will be discussed in this

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paper. The value of incorporating these factors in the Ilkovič equation will be described in another communication.

The capillary constant,[1] κ, represents the pressure of mercury necessary to force 1 mg. of mercury through the capillary per second. It is defined by means of the following equation

$$\kappa = \frac{p}{m} = \frac{8\eta l}{d\pi r_c^4} \qquad (1)$$

where p is the pressure (in dynes cm.$^{-2}$) producing a flow per second of m mg. of mercury of viscosity η and density d, through a capillary of length l and with uniform radius r_c. When this pressure is expressed in cm. of mercury and other known values (for 25°) are substituted in this equation, it reduces to

$$\kappa = 2.1567 \times 10^{-10}\, l/r_c^4 \qquad (2)$$

where κ is expressed in cm. sec. mg.$^{-1}$, and l and r_c in cm.

The effect of temperature on this constant is negligible, as may be seen by differentiation of equation (1) with respect to temperature. Using known temperature coefficients of the viscosity and density of mercury, one finds the temperature coefficient of the capillary constant equal to -0.0034 deg.$^{-1}$.

If the radius of the orifice, ρ, is substituted for r_c, the above equations also become applicable to capillaries without uniform bore; l then represents the length of an equivalent hypothetical capillary with a uniform bore of radius ρ. In other words, by means of equation (2) it is possible to calculate the dimensions of a capillary of uniform bore needed to replace a given laboratory made capillary.

Determination of κ.—The value of κ is easily obtained as the ratio of P/m, where P is the pressure (in cm. of mercury) producing a flow of m mg. of mercury per second through the capillary. Even fairly rough measurements of these quantities give practically constant values for κ under a variety of conditions.[1] As will be shown presently, a slight drift in the κ values with changing pressures can be eliminated in more accurate measurements by making appropriate corrections for the applied pressure.

In Tables I and II are given the results of two typical experiments in which the capillary was dropping in air and in a solution of 0.1 N potassium nitrate. The apparent or applied pressure ($P_{app.}$) was measured accurately to 0.1 cm. from the tip of the capillary to the level in the mercury reservoir. The capillary used was 6.32 cm. long and had an essentially uniform diameter of 54.0 μ. W, t and m were determined as before.[1] Although the drops in air are abnormally large and not as reproducible as drops falling in an electrolyte, the flow of mercury, m, at a given pressure, is constant. Yet, in both experiments, the values for the capillary constant, $\kappa_{app.}$, calculated from m and the apparent pressure, $P_{app.}$, show a small drift with changing pressure. This and the small but definite difference between corresponding m values of Tables I and II are caused by the back pressure of the mercury drops.

(1) O. H. Müller, *J. Chem. Education*, 18, 172 (1941).

TABLE I

MEASUREMENTS MADE WITH CAPILLARY NO. 1, DROPPING IN AIR

$P_{app.}$, cm.	t, sec.	W, mg.	m, mg./sec.	$\kappa_{app.}$, cm. sec./mg.	$W,^{1/3}$ mg.$^{1/3}$	P_{back}, cm.	P, cm.	κ, cm. sec./mg.
70.0	27.2	71.2	2.61	26.8	4.14	0.7	69.3	26.6
70.0	24.1	63.0	2.61	26.8	3.98	.8	69.2	26.5
70.0	26.6	69.5	2.61	26.8	4.11	.8	69.2	26.5
70.0	27.4	71.6	2.61	26.8	4.15	.7	69.3	26.6
60.0	35.2	78.7	2.23	26.9	4.28	.7	59.3	26.6
50.0	42.6	79.0	1.85	27.0	4.29	.7	49.3	26.6
40.0	59.1	87.5	1.48	27.0	4.44	.7	39.3	26.5
30.0	71.8	78.9	1.10	27.3	4.29	.7	29.3	26.6
60.0	44.3	98.6	2.23	26.9	4.62	.7	59.3	26.6
60.0	43.7	96.9	2.22	27.0	4.59	.7	59.3	26.7

TABLE II

MEASUREMENTS MADE WITH CAPILLARY NO. 1, DROPPING IN 0.1 N POTASSIUM NITRATE SOLUTION

$P_{app.}$, cm.	t, sec.	W, mg.	m, mg./sec.	$\kappa_{app.}$, cm. sec./mg.	$W,^{1/3}$ mg.$^{1/3}$	P_{back}[a], cm.	P, cm.	κ, cm. sec./mg.
70.0	2.64	6.77	2.56	27.3	1.89	1.7	68.3	26.6
70.0	2.64	6.77	2.56	27.3	1.89	1.7	68.3	26.6
70.0	2.65	6.77	2.55	27.4	1.89	1.7	68.3	26.7
70.0	2.64	6.76	2.56	27.3	1.89	1.7	68.3	26.6
60.0	3.04	6.66	2.19	27.4	1.88	1.7	58.3	26.6
50.0	3.66	6.66	1.82	27.5	1.88	1.7	48.3	26.5
40.0	4.63	6.66	1.44	27.8	1.88	1.7	38.3	26.6
30.0	6.27	6.62	1.06	28.3	1.87	1.8	28.2	26.6

[a] P_{back} includes a correction of 0.1 cm. for loss in hydrostatic pressure, because the capillary was immersed into the solution to a depth of 1.3 cm.

It should be remembered that not all of the pressure measured is effective in forcing mercury through the capillary. A small fraction of it has to be expended in overcoming the back pressure caused by the surface tension of the expanding drop of mercury. The back pressure is greatest before the drop forms and may amount to tens of centimeters, depending on the capillary bore (see, *e. g.*, the critical pressure values given in Table III). Unless the total pressure exceeds this maximum value of the back pressure, the capillary stops dropping. As soon as a drop is formed, the back pressure diminishes; it becomes minimal as the drop reaches its maximum size before falling off.

According to Kučera,[2] the back pressure is equal to $2\sigma/r_d$, where σ is the surface tension of mercury and r_d is the radius of the mercury drop. Kolthoff and Lingane[3] have evaluated this equation in terms of m and t (the drop time) for the *average* size of the drop and for a surface tension of 400 dynes cm.$^{-1}$ and found

$$\text{Average } P_{back} = 3.1/m^{1/3}t^{1/3} \qquad (3)$$

Assuming, as a first approximation, the same surface tension, the data of Tables I and II were

(2) G. Kučera, *Ann. Physik*, 11, 529 (1903).

(3) I. M. Kolthoff and J. J. Lingane, "Polarography," Interscience Publishers Inc., New York, N. Y., 1941.

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corrected. In column 6 is given $W^{1/3}$ (equal to $m^{1/3}t^{1/3}$), and in column 8, P, the pressure corrected for back pressure and any loss in hydrostatic pressure. The new value of κ (Column 9) is now constant within the experimental error and identical for the two media.

To test the validity of the corrected κ value, a further experiment was performed which involved no back pressure. For a carefully measured length of time the capillary was immersed into a pool of mercury contained in a small beaker which was weighed before and after the experiment. The increase in weight represented the quantity of mercury flowing through the capillary in the elapsed time under a pressure equal to the difference between the mercury levels in the reservoir and the beaker. In two experiments the following results were obtained

Pressure, cm.	Weight, g.	Time, sec.	Rate of flow, mg./sec.	κ, cm. sec./mg.
38.6	1.0432	720	1.45	26.6
67.1	2.4261	960	2.53	26.5

Upon substitution of the corrected κ and the known l values in equation (2), r_c was found to be 26.7 μ in good agreement with the direct measurement.

The Attachment of Mercury to Glass.—If the pressure is expressed in cm. of mercury, Kučera's equation becomes

$$P_{back} = 2\sigma/gdr_d \quad (4)$$

where d is the density of mercury and g the acceleration of gravity. For the present study it was desirable to evaluate this equation in terms of ρ. By combining the two well-known equations relating W, the drop weight, to r_d, the radius of the drop, and to ρ, the radius of the capillary orifice

$$W = 4/3\pi r_d^3 d \quad (5)$$

and

$$W = 2\sigma\pi\rho/g \quad (6)$$

one gets r_d expressed in terms of ρ

$$r_d = \sqrt[3]{3\sigma\rho/2dg} \quad (7)$$

Substituting this in equation (4), which is multiplied by 4/3 to represent the *average* back pressure[3] in cm. of mercury, we get

$$\text{Average } P_{back} = 4.1576 \times 10^{-3}\sigma^{2/3}\rho^{-1/3} \text{ cm.} \quad (8)$$

The average back pressure calculated by means of this equation for the capillary used in the above experiments is 1.6 cm. Since this agrees with the data of Table II only, the value of ρ must undergo some change when the capillary is dropping in air, because the surface tension of mercury cannot differ much from 400 dynes cm.$^{-1}$. Substituting in equation (8) the value of P_{back} from Table I, one finds that ρ must be about 320 μ instead of the known 27.0 μ.

This difference became understandable upon microscopic examination of the drops. As long as the mercury was dropping in a solution of 0.1 N potassium nitrate, it was suspended only from the thin column of mercury in the capillary bore. However, mercury dropping in air was attached mainly to the glass of the capillary. These observations are represented schematically in Fig. 1. It could be estimated that the attachment to the glass was over an area with a diameter about ten times that of the capillary orifice.

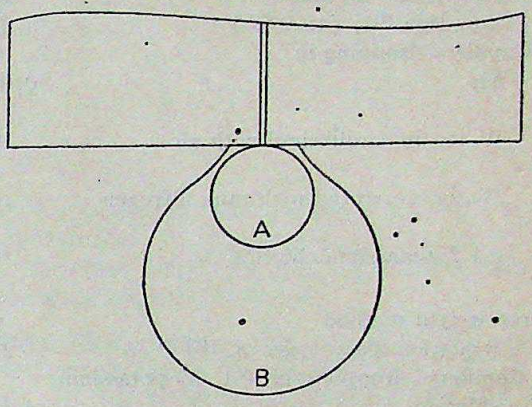

Fig. 1.—Schematic representation of mercury drops formed at a capillary whose orifice is 54 μ in diameter: A, in 0.1 N potassium nitrate—the drop is suspended from the mercury column only; B, in air—the drop is attached to the glass of the capillary.

Kolthoff and Kahan[4] have observed a similar attachment of mercury to the capillary glass when electrically disconnected mercury was dropping in oxygen-containing water. This they explained on the basis of interaction between the negatively charged glass/water double layer and the water/mercury double layer which is charged positively by the adsorption of oxygen from the water. They believe that an aqueous film exists between the attached mercury and the glass. This is probably not the case when the electrode is dropping in air, because the abnormalities are much greater than when it is dropping in water. Hence, a gaseous layer between mercury and glass must be assumed.

Since mercury does not wet glass, it is probable that neutralization of the electrostatic forces acting between mercury and glass cannot take place by direct transfer of the charges but must be effected by means of a conductor, such as an electrolyte. Only partial neutralization of these charges is possible in the presence of the poor conductor, water. Thus we have the paradox: under suitable conditions mercury is attracted to glass because it does not wet glass. Not much can be said without further study about the cause for the opposite charges. Experiments in this Laboratory have shown that the abnormalities persist when the mercury is dropping in an atmosphere of hydrogen gas instead of air; on the other hand, no abnormalities were found in benzene or in absolute ethyl alcohol, although the latter is known to contain much dissolved oxygen and is a poor conductor.

(4) I. M. Kolthoff and G. J. Kahan, THIS JOURNAL, 64, 2553 (1942).

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TABLE III

DETERMINATION OF THE RADIUS OF THE CAPILLARY ORIFICE

Methods	Factor	Capillaries: No. 1 P_c, cm.	No. 1 W, mg.	No. 1 ρ, μ	No. 2 P_c, cm.	No. 2 W, mg.	No. 2 ρ, μ	No. 3 P_c, cm.	No. 3 W, mg.	No. 3 ρ, μ
Direct measurement with microscope				27.0			14.1			8.1
Critical pressure method[a] (equation (9); *factor*/P_c)	$\frac{2\sigma}{dg}$									
Capillary dropping in										
Air	0.0695	25.1		27.7	47.7		14.6	81.5		8.5
		25.0		*27.8*	*40.5*		*17.2*	*74.5*		*9.3*
Water, in equilibrium with air	.0564	21.6		26.1	41.7		13.5	74.5		7.6
		20.3		*27.8*	*23.5*		*24.0*	*71.5*		*7.9*
Water, deaerated with tank nitrogen	.0644				42.0		15.3	73.0		8.8
		22.4		*28.8*	*37.0*		*17.4*	*65.0*		*9.9*
0.1 *N* potassium chloride	.0573	21.1		27.2	40.0		14.3	74.0		7.7
		21.1		*27.2*	*39.8*		*14.4*	*70.5*		*8.1*
Drop weight method (equation (6a); *factor* × W)	$\frac{g}{2\pi\sigma}$									
Capillary dropping in 0.1 *N* potassium chloride	4.11		6.66	27.4		3.52	14.5		1.95	8.0

[a] Values in italics were obtained by lowering the mercury reservoir, the other values by raising it.

Determination of ρ.—In equation (2), the capillary radius—or the radius of the capillary orifice—appears raised to the fourth power. It is therefore essential that this radius be determined as accurately as possible. Besides direct measurement under the microscope, there are available two indirect methods involving well-known equations relating to surface tension.

The *critical pressure method* is based on the equation

$$\rho = 2\sigma/gdP_c \qquad (9)$$

in which σ is the surface tension and P_c is that critical pressure (in cm. of mercury), which is necessary to stop the flow of mercury and which leaves the meniscus of the mercury just at the capillary orifice.

The *drop weight method* is based on equation (6), rewritten as follows

$$\rho = Wg/2\pi\sigma \qquad (6a)$$

Both of these methods have been tried with different capillaries and in different media. Because of the attachment of mercury to glass, irregularities were found unless the medium was a satisfactory electrolyte such as 0.1 *N* potassium chloride.[4] Some typical examples are presented in Table III and compared with the directly determined radius (accurate to $\pm 0.5\ \mu$). Capillary no. 1 was factory made, while the other two were drawn in this Laboratory from 0.5 mm. capillary tubing. Nos. 1 and 2 represent capillaries suitable for general polarographic work, while capillary no. 3 should be used for special studies only because its orifice is too narrow and the bore is too tapered. In the calculations, the following values were assumed for the surface tension, σ: in water,[5] in equilibrium with air, 374 dynes cm.$^{-1}$; in water,[6] free from air, 427 dynes cm.$^{-1}$; in air,[7] 461 dynes cm.$^{-1}$; in 0.1 *N* potassium chloride,[8] 380 dynes cm.$^{-1}$.

In view of the sensitivity of these measurements to slight vibrations and the uncertainty of some of the surface tension values, the results show a satisfactory agreement as long as the critical pressure is attained by gradually *raising* the mercury reservoir. When the critical pressure was determined by *lowering* the reservoir, erroneous results were often obtained because, in this case, the drops did not "break clean" from the mercury column, but left some residual mercury outside the capillary orifice attached to the glass (see also Kučera[2]). When the pressure was lowered sufficiently that the dropping finally did stop, it was found that the mercury column receded into the capillary for a considerable distance. Gradual increase in the mercury pressure forced the mercury column nearer the capillary orifice until the critical pressure was exceeded and the capillary began to drop. In the potassium chloride solution, such complications were minimal.

Position of the Capillary.—That the capillary should be vertical and the cut surface perfectly horizontal is a foregone assumption in all polarographic work. Yet no clear-cut test has heretofore been described to safeguard against errors from this source. Actually, photographs of capillaries with hanging mercury drops, published by several investigators,[4,9] indicate that this prerequisite was not fully appreciated.

If the capillary is cut off at an angle or tilted, the drops cannot fall freely and become deformed. Under such conditions equation (6a) no longer

(5) H. Brown, THIS JOURNAL, **56**, 2564 (1934).

(6) D. C. Henry and J. Jackson, *Nature*, **142**, 616 (1938).

(7) T. R. Hogness, THIS JOURNAL, **43**, 1621 (1921).

(8) Determined in this Laboratory as the most probable value.

(9) W. M. MacNevin and E. W. Balis, THIS JOURNAL, **65**, 660 (1943).

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holds and should give a value for ρ different from that obtained by means of equation (9). However, if the capillary is so adjusted that the plane of the cut surface is horizontal, the value for ρ obtained by both equations should be identical. This phenomenon has been actually observed and is represented diagrammatically in Fig. 2.

The capillary used here had been cut off improperly so that the cut surface formed an angle of 70° instead of 90° with the longitudinal axis of the capillary. The capillary radius was found equal to 13.4 μ by direct measurement of the smallest diameter of the oval orifice. In all subsequent calculations, this orifice was considered round and with a radius equal to the one measured. The critical pressure in water and the drop weight in a 0.1 N potassium chloride solution were then determined, first, when the capillary was vertical and the plane of the cut surface slanted, and, second, when the capillary was slanted to bring the orifice on a horizontal plane. The results and the calculated values were

Position of capillary	P_c, cm.	ρ, μ	W, mg.	ρ, μ
Straight	42.0	13.6	2.37	9.7
Slanted	39.5	14.5	3.32	13.7

From this, one must conclude that the ρ values obtained by the drop weight and critical pressure methods should certainly agree within 1μ to insure proper functioning of the capillary. It should be mentioned here that even this type of capillary can be used for some special polarographic work and will give good results as long as its position is rigidly fixed. Because of its extreme sensitivity to slight changes in position, it cannot be recommended for general use.

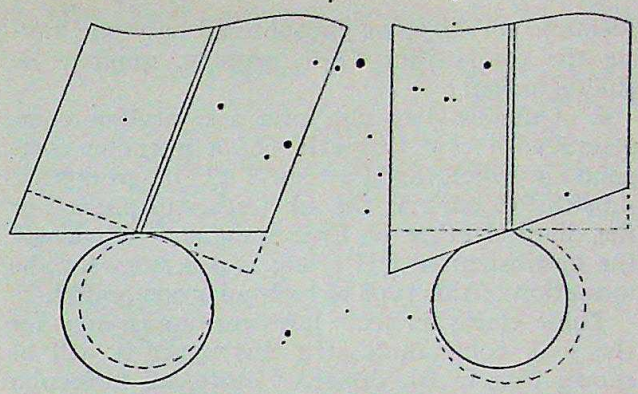

Fig. 2.—Graphical demonstration of the effect of position and improper cutting of the capillary on the drop size. Note that normal drops are obtained whenever the cut surface is perfectly horizontal.

Acknowledgment.—The author wishes to thank Mr. Howard Phipps and Dr. John Staige Davis, Jr., for financial support of this investigation.

Summary

Two factors have been proposed to serve as simple means for the complete characterization of all kinds of capillaries used for dropping mercury electrodes. These are the radius of the capillary orifice, ρ, and the capillary constant, κ, which is the pressure of mercury (in cm.) necessary to force 1 mg. of mercury through the capillary per second.

Various methods for their determination have been described which serve as checks for the proper behavior of the capillary.

Some abnormalities in the behavior of capillaries have been discussed.

NEW YORK, N. Y. RECEIVED MARCH 31, 1944

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

Molecular Compounds of the Quinhydrone Type in Solution

BY LEONOR MICHAELIS AND S. GRANICK

The intensely colored molecular compounds of the quinhydrone type are best known in the crystalline state.[1] In solution all of them dissociate to a very high degree, although not completely. Such compounds usually consist of two components of which one is on a higher oxidation level than the other. One component may be a quinone, or an aromatic nitro compound; the other a phenol, an amine, or even a hydrocarbon such as hexamethylbenzene. Most of the studies here reported were carried out with compounds of a quinone with some phenolic compound. Crystalline compounds of this kind have the following characteristics:

1. When quinone combines with hydroquinone, the stoichiometrical composition of the compound is Q_1B_1, where Q stands for the quinoid and B for the benzenoid component.

2. When quinone combines with a phenolic compound having only one unsubstituted OH group, the molecular compound is Q_1B_2. Examples are the quinone compound of phenol and of *p*-methoxyphenol.

3. Some quinhydrone-like compounds of "anomalous composition" have been described.[2] Their compositions were inferred, not from a straight-forward analysis of the solid, but by indirect methods involving dubious interpretations. Among all such compounds which can be prepared in the crystalline state, and which are of

(1) P. Pfeiffer, "Organische Molekülverbindungen," Stuttgart, 1927. Some references to more recent papers are: I. Palacios and O. R. Foz, *Anales soc. espan. fis. quim.*, **34**, 799 (1936); G. Weiss, *J. Chem. Soc.*, 245 (1942) and 462 (1943); H. M. Powell, G. Huse and P. M. Cookc, *ibid.*, 153 (1943) and 435 (1943).

(2) R. Kremann, S. Sutter, F. Sitte, H. Strezelba and A. Dobotzky, *Monatsh.*, **43**, 259 (1922).

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adequate stability, we encountered only one having the composition Q_2B_1, namely, quinone + phloroglucinol.

4. Quinone does not form a crystalline compound with any derivative of a phenolic compound in which the H atoms of all OH groups are substituted, such as the alkyl ether of phenol, or the di-alkyl ether of hydroquinone. Obviously the unsubstituted OH group is necessary for the formation of this type of molecular compound.

These characteristics, however, apply only for the solid compounds. In this paper it will be shown that in the dissolved state, all molecular compounds of the quinhydrone type are always of the composition Q_1B_1, regardless of their composition in the solid state, and even in such cases where no molecular compound exists at all in the solid state. As far as a comparison of various compounds in the same solvent can be carried out, one arrives at the conclusion that in the dissolved state the affinity of quinone is nearly the same for hydroquinone, its monomethyl ether, its dimethyl ether and its diethyl ether. It follows that problems concerning the composition and steric configuration of such compounds in the dissolved state cannot be dealt with on an equal footing with those holding for the solid state. The latter has been the subject of many experimental and theoretical studies[3] without a full understanding of the problem having been reached either with respect to the nature of the chemical bond, or to an explanation of the intense color, or to the general principle underlying the crystalline structure. Neither do the writers claim to have solved the problem, yet they have arrived at some definite experimental facts concerning the dissolved state which should have a bearing on any future general theory pertaining to the nature of such compounds.

It will be shown that all of the compounds of the quinhydrone type are highly dissociated in solution, and that the equilibrium within the limits of error can be expressed always as follows

$$qb/m = k \qquad (1)$$

where q and b are the total molar concentrations of the quinonoid and benzenoid components and m is the concentration of the molecular compound, instead of according to the more exact equation

$$(q - m)(b - m)/m = k \qquad (2)$$

In all cases, under all experimental conditions that can reasonably be applied, m is small, usually negligibly small, as compared with q and b. No method is available for the determination of the absolute value of m; only relative values can be obtained. This fact precludes any accurate determination of the association constant, k, for any one of these compounds. In solutions no evidence has yet been found for the existence of any compound other than Q_1B_1, both with respect to stoichiometrical composition and molecular size. The fact that, in the dissolved state, the substitution of the H in the OH group by the much more spacious CH_3 or C_2H_5 group, has no noticeable influence upon the formation of a molecular compound with a quinone, shows that, at least in the dissolved state, a hydrogen bond is not essential, as demonstrated by the formation of compounds such as quinone + hydroquinone-diethyl ether. The lack of any conspicuous steric hindrance caused by the alkyl group is compatible only with the assumption that in the dissolved state the molecular compound is always formed by superimposing the two rings upon each other, and not by a coplanar arrangement of the two rings.

The study of these molecular compounds in solution, where they exist only in extremely low concentration in equilibrium with their free components, depends on the relative intensity of their color. The free components absorb usually in the ultraviolet, and even where there is an additional absorption band in the visible spectrum as for quinone (with peak at 420 to 435 mμ, and with varying degree of fine structure (Fig. 5), according to the solvent) the molar absorption coefficient of this band at its maximum is very low. It is, for quinone, 17 to 19.8 depending on the particular solvent (whereas, for example, for regular dyestuffs of equivalent resonance structure it is of the order 10^4 to 10^5 at the peak of absorption). The quinhydrones also have a very high absorption coefficient at the peak of absorption, in or near the visible spectrum. Since the concentration of the molecular compound cannot be determined, its molar absorption coefficient cannot be determined either. However, it is always so large that even at those low concentrations at which they exist in equilibrium with the components, the optical density of the solution in or near the visible usually is due almost completely to the molecular compound alone, except for a small, sometimes negligible correction for the absorption due to the free components. This correction, then, consists in subtracting from the total optical density of the solution, that of its free components. Since always only a very small fraction (say 5% *in maximo* and usually very much less) of the components is used for the formation of the compound and the whole correction is usually small, no appreciable error is involved in subtracting the optical density due to the total concentration of the two components instead of subtracting the concentration of the uncombined part of the components. This correction is carried out by measuring the absorption against the pure solvent as a blank and subtracting the absorption due to the free components by calculation. Often a solution of one of the components in a proper concentration was used as a blank, and the correction for the other component was made by calculation. The

(3) In addition to references quoted,[1] special attention should be given to some brief remarks on the subject in a paper by L. Pauling.[4] The authors are indebted to Professor Pauling also for further discussion and advice with respect to the problems involved.

(4) L. Pauling, *Proc. Natl. Acad. Sci.*, **25**, 577 (1939).

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absorption was measured with the Beckman[5] photoelectric spectrophotometer which allows rapid and very precise readings of the transmission reproducible to within a fraction of 1%, from 215 to 1275 mμ.

The optical density, δ, of any solution is

$$\delta = \frac{I}{d} \log \frac{I_0}{I}$$

where I_0 is the intensity of light transmitted across the blank; I, that across the solution; and d, the thickness of the absorption cell in cm. The molar absorption coefficient of any single molecular species is $\epsilon_{mol} = \delta/c$ where c is the concentration of the substance in moles per liter.

The claim that all such molecular compounds in the dissolved state have the composition Q_1B_1, is based on the fact that the optical density due to the molecular compound is in all cases proportional to the concentration both of the Q component and of the B component, so that within the limits of error

$$\delta/qb = C$$

where the constant, C, depends on the particular compound and on the particular solvent used. This constant will, in what follows, be designated as ϵ_{st}, the "absorption coefficient of the molecular compound under standard conditions," in the particular solvent. Its significance will be discussed later.

Experimental Part

All substances were freshly purified either by sublimation, distillation, steam distillation, or recrystallization, and only quite fresh solutions were used, which is especially important for quinone.

In the diagrams, the corrected optical density of the solution, δ, is plotted against wave length in mμ. A few absorption spectra, in terms of the molar absorption coefficient, ϵ_m, for the single components are added.

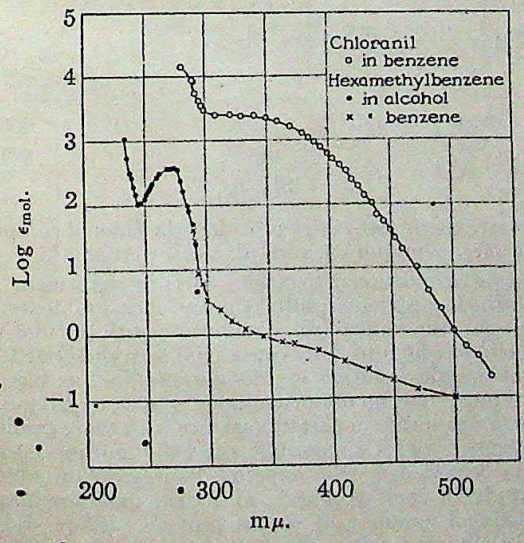

Fig. 1.

(5) H. H. Cary and A. O. Beckman, *J. Optical Soc. Am.*, **31**, 682 (1941).

1. Examples of Compounds Having, in the Solid State, the Composition Q_1B_1

(a) **Tetrachloroquinone + Hexamethylbenzene.**—In Fig. 1, the molar absorption coefficient for either component separately is plotted logarithmically against wave length. The maximum absorption of the molecular compound (Figs. 2 and 3) is at 510 mμ. Here the contribution, to the density, of the free components is negligible and no correction is required. For all wave lengths > 450 mμ, the optical density of the mixture (Figs. 2 and 3) is solely due to the molecular compound. This optical density is shown in Fig. 2 to be proportional to the concentration of tetrachloroquinone, and, in Fig. 3, to be proportional to the product of the two concentrations if both are varied.

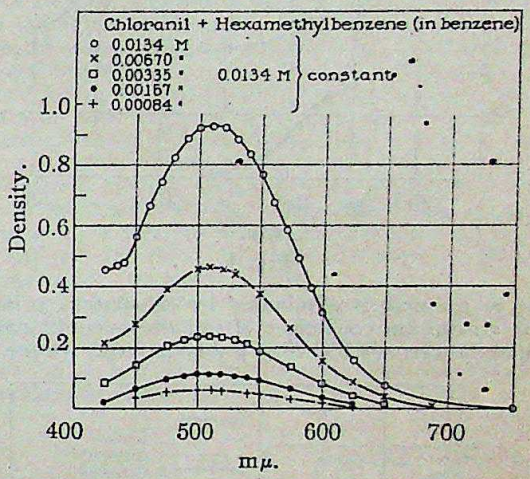

Fig. 2.

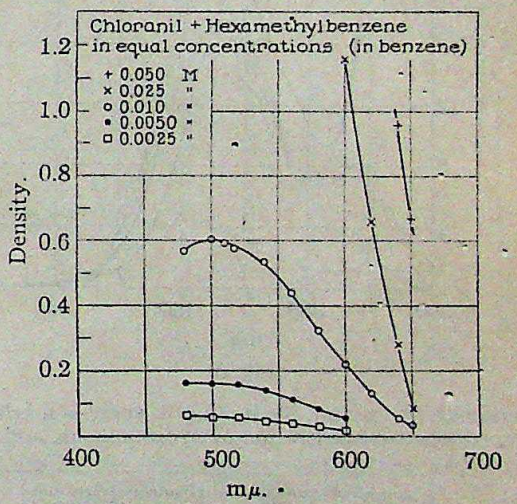

Fig. 3.

(b) **Quinone + Hydroquinone.**—The molar absorption coefficients are plotted, logarithmically, in Fig. 4, for the components singly. That part which is most important for this problem, in the violet region of the visible spectrum, is shown on a larger scale for quinone (not logarithmically) in Fig. 5. The molar absorption coefficient of quinone at its maximum around 430 mμ is 17 to 19.8 according to the solvent. Since the peak of absorption for quinone and for quinhydrone lie almost at the same wave length, the correction for the effect of quinone is always necessary. Although this correction is small in general, subtraction of the density due to the total quinone, instead of the uncombined quinone only, may cause a slight error. The effect of quinone is eliminated in Figs. 7 and 8, by taking as a blank a quinone solution of the same concentration but without hydroquinone. On the other hand, in Fig. 6, the

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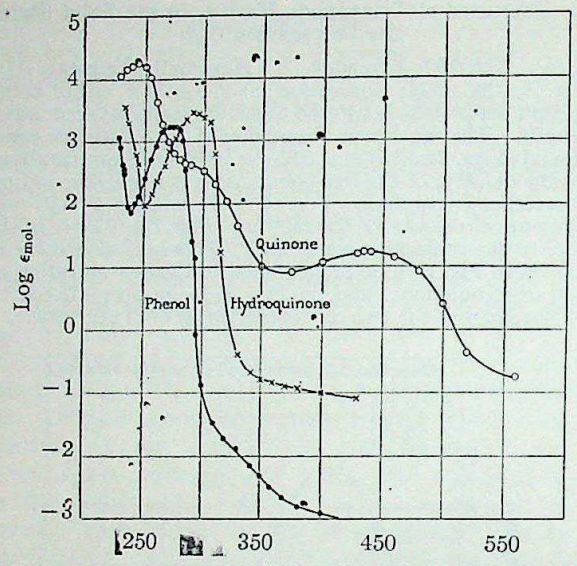

Fig. 4.

effect of quinone is eliminated by calculation, using the molar absorption coefficient of quinone according to the original data from which Fig. 5 was derived. In the three

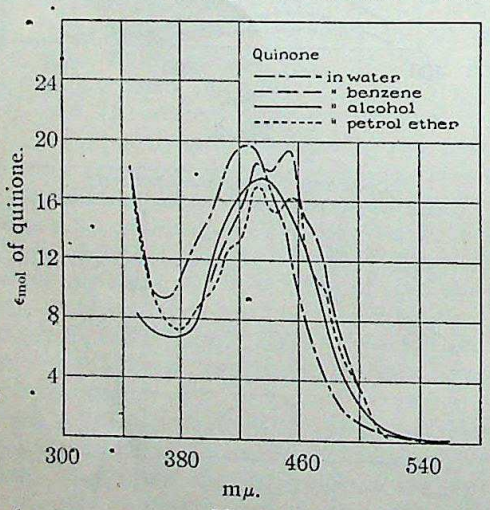

Fig. 5.

experiments ⊙, x and +, in Fig. 6, there is a relatively large, constant concentration of hydroquinone, and a low,

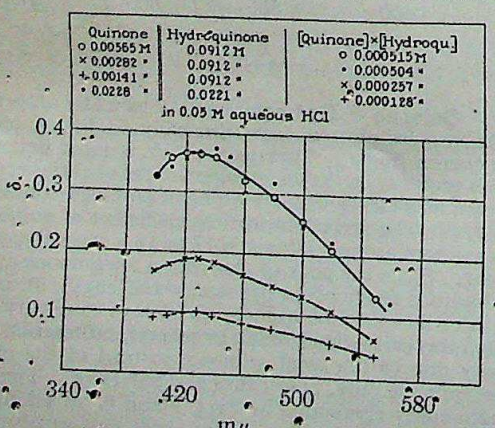

Fig. 6.

varied concentration of quinone. Here the optical density is proportional to the quinone concentration. In experiment ●, an equimolar concentration of both components is used. Considering the fact that for the latter experiment the quinone correction is unusually great, involving a larger uncertainty, it can be stated that in all four experiments of Fig. 6 the density is proportional to the product of the concentrations of the two components, within the limits of error. The fact that this is true whether hydroquinone is nearly at the same concentration as quinone, or in excess, is important with reference to an observation made by other authors which will be discussed presently.

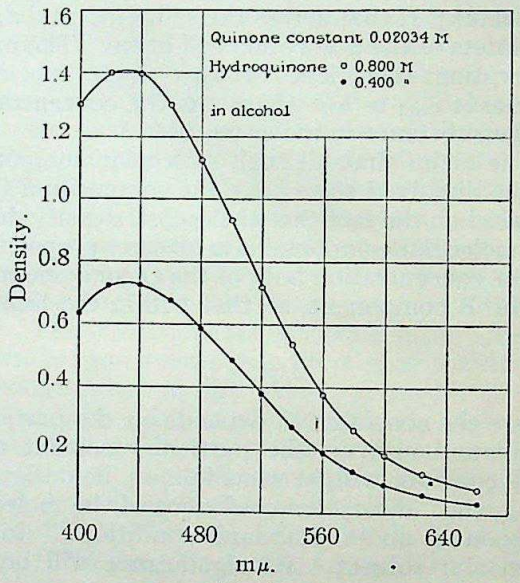

Fig. 7.

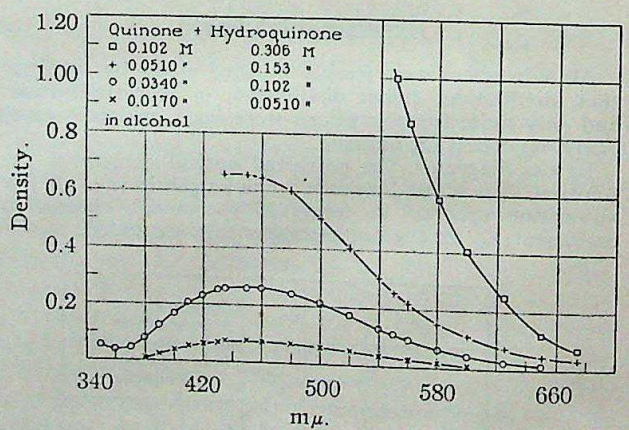

Fig. 8.

These experiments show also that the colored compound is not a free semiquinone radical. If it were so, the density would be proportional to $\sqrt{qb}$. It is in agreement with the authors' previous results[6] that no measurable amount of semiquinone radical is in equilibrium with the molecular compound (which may be considered as a dimerized radical) unless the solution is strongly alkaline, as has been shown for a solution of duroquinone + durohydroquinone.

These results are in part at variance with those published by Wagner and Grünewald,[7] the only authors, to the writers' knowledge, who have used spectrophotometry in the study of such problems, and then only for aqueous solutions of quinone + hydroquinone. They did not establish a continuous absorption curve nor locate the

(6) L. Michaelis, M. P. Schubert, R. K. Reber, J. A. Kuck and S. Granick, THIS JOURNAL, **60**, 1678 (1938).

(7) C. Wagner and K. Grünewald, *Z. Elektrochem.*, **46**, 265 (1940).

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maximum absorption but measured the optical density of aqueous solutions only at the wave length of three mercury lines. In equimolar mixtures of the components, the optical density was approximately proportional to the product of the two concentrations. On the ground of the small deviations from proportionality they calculated the dissociation constant of quinhydrone, which, however, they could not corroborate with measurements on mixtures with excess of hydroquinone. They refrain from making a decision as to whether this was due to some unknown optical effect or to the establishment of a compound different from Q_1B_1, say Q_1B_2. They agree with the writers that there is no measurable amount of semiquinone radical in equilibrium with the molecular compound. It can be seen that the present results do not coincide with those of the earlier authors' in several respects.

(c) **Duroquinone + Durohydroquinone.**—In one of the previous papers in this series (5) it was claimed that duroquinone + durohydroquinone do not combine to form any quinhydrone-like compound. This statement must be revised. To be sure, a mixture of the two substances in 20% pyridine or alcohol + 80% water, does not produce any precipitate, yet a very slight intensification of the color, compared with that of duroquinone alone, takes place. The steric hindrance for the formation of a quinhydrone due to the methylation at the ring is very conspicuous indeed, but it is not quite complete. Under proper conditions even a solid crystalline quinhydrone can be prepared. On dissolving equivalent amounts of either component at a high concentration in acetone, mixing both, and adding water slowly, a brownish precipitate arises, consisting of long, rod-shaped crystals, dichroitic blue and yellow. The dissociation of this quinhydrone in solution is extremely great. Judging from the appearance of color in a test-tube experiment, when a mixture of quinone + hydroquinone is compared with that of duroquinone + durohydroquinone at the same conditions, the dissociation of the latter is very much greater indeed. However, accurate spectrophotometric measurements cannot be carried out because durohydroquinone is so highly autoxidizable that the readings of the optical density rapidly change during the period of time necessary for an experiment.

Previous magnetic measurements[6,8] did not reveal any polymerization of the semiquinone radical of duroquinone as it arises in strongly alkaline solution. However, the crystalline, solid duroquinhydrone obtained as just described, from a non-alkaline solution, is diamagnetic. The susceptibility was measured with the method previously described[9] and found to be $= -140 \times 10^{-6}$ c.g.s.u., per equivalent (or half a mole). It is expected to be -124×10^{-6} according to Pascal's rules, on the assumption that the susceptibility of durohydroquinone is suitable for comparison. Considering the fact that this is just one single measurement and that the finely ground duroquinhydrone is a remarkably fluffy powder which can be packed homogeneously into the cylindrical vessel only with difficulty, the agreement is satisfactory. There is decidedly no paramagnetic semiquinone radical component in the crystals. The crystalline state, just as for the aromatic diamines,[9] is entirely in one of the two possible magnetic states, either fully diamagnetic or fully paramagnetic. This compound is fully diamagnetic. The previous magnetic measurements with the free radical in the dissolved state did not reveal any dimerization of the paramagnetic radical because they were carried out at *p*H 12, where the radical has the composition, $[OC_6(CH_3)_4O]^-$, but in the present investigations the solutions were neutral and so the radical has the composition $HOC_6(CH_3)_4O$, which is utterly unstable due to lack of equivalent resonance and which exists only, if at all, as the dimeric, diamagnetic quinhydrone with the H atom acting as a hydrogen bond involving dimeric resonance.[9] It may be added that in the meantime also the free radical, as a sodium salt, has been prepared in the solid state. In agreement with expectation, it is paramagnetic, however not to the full extent expected due to the fact that the solid preparation was not pure nor homogeneous.

(d) **Quinone + Resorcinol.**—The compound quinone + resorcinol is listed in Pfeiffer's book[1] among the compounds of composition Q_2B_1, according to indirect evidence presented by Kremann and associates.[2] These authors did not succeed in preparing the solid compound. It is however easy to prepare the intensely red, crystalline compound by mixing solutions of the components in acetone. One sample was prepared by mixing 1 g. of quinone (in 4 cc. acetone) with 1 g. of resorcinol (in 2 cc. of acetone), whereby the crystalline compound is obtained directly in pure form. Another preparation was obtained by mixing 0.4 g. of resorcinol (in 0.5 cc. of acetone) and a large excess of quinone, 1 g. (in 4 cc. of acetone). After slight evaporation of acetone, crystals of the free quinone are obtained. After addition of benzene the quinone dissolves and gradually brown crystals appear. Both samples of the quinhydrone were of the accurate composition, Q_1B_1. The analysis for quinone was made by dissolving the crystals in a little alcohol, diluting with water and titrating with titanous chloride. The stock solution of the latter diluted with a suitable volume of 6 *N* hydrochloric acid was standardized against quinone with methylene blue as internal indicator. It was ascertained that addition of resorcinol to a solution of quinone does not disturb the titration of quinone. So, the crystalline compound always has the composition Q_1B_1.

The spectrophotometric analysis of the solution containing quinone and resorcinol shows (Fig. 9 and Table I) that the optical density is proportional to the quinone concentration and also to the resorcinol concentration. The maximum absorption is at 370 mμ.

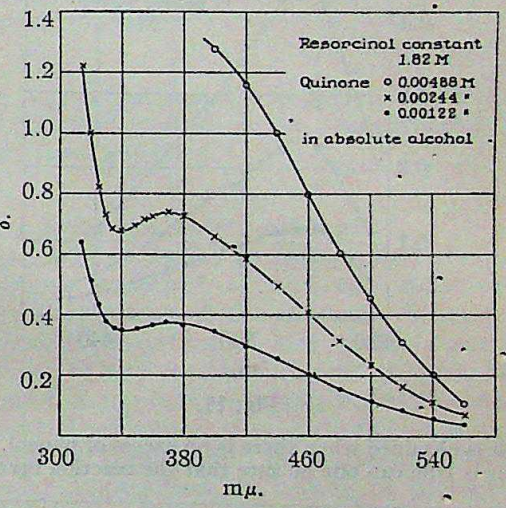

Fig. 9.

2. Examples of Compounds Having the Composition Q_1B_2 in the Solid State

(a) **Quinone + Phenol.**—First of all it was ascertained that solid "phenoquinone" has always the composition Q_1B_2 even when prepared from a solution, in petrolic ether, with a large excess of quinone. The analysis for quinone was made in the same manner as just described. The color of "phenoquinone" in solution is yellow, and the peak of absorption is not in the visible spectrum, but at 320 mμ. In Fig. 10 (disregarding for the time being the experiment marked △), it is shown that in alcoholic solution the optical density is proportional to the quinone concentration if the phenol concentration is kept constant. The same is true in petrol ether solution (Fig. 11). In Fig. 12 it is shown that on varying only the phenol concentration the density is proportional to the latter. So, in Fig. 12 the densities, corrected for the effect of both free components, for instance at 450 mμ, in the four experiments plotted, are in the ratio, 5.88:4.02:2.00:1.00, while the ratios of the phenol concentrations are, 6.1:4.0:2.00:1.00.

(8) L. Michaelis, THIS JOURNAL, **63**, 2446 (1941).
(9) L. Michaelis and S. Granick, *ibid.*, **65**, 1747 (1943).

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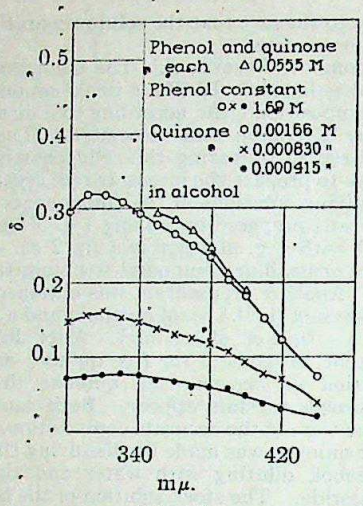

Fig. 10.

In these experiments although the concentrations have been varied, there is always an excess of phenol with respect to quinone. It is important to show that the same

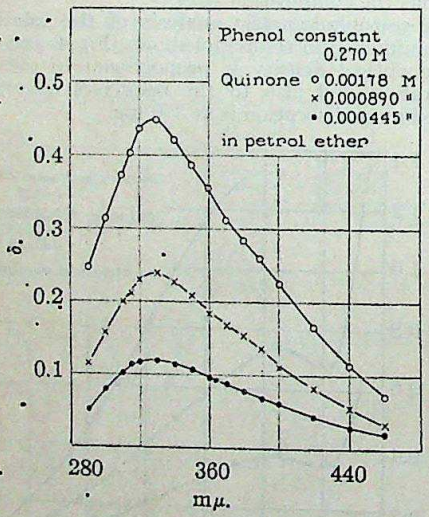

Fig. 11.

result is obtained when there is no excess of phenol. Only if this is true can one be sure that the reaction involved is always $Q + B \rightleftharpoons QB_1$ and that another reaction, $QB_1 + B \rightleftharpoons QB_2$, does not occur. Such an experiment is shown in Fig. 10, marked Δ, where the concentration ratio is 1:1.

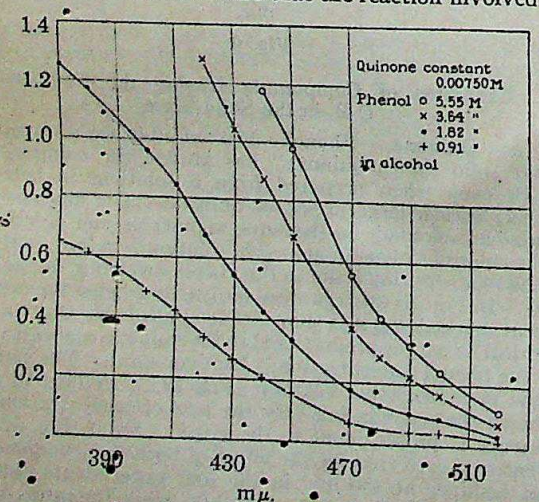

Fig. 12.

TABLE I

Q-Component and its molar concentration	B-Component and its molar concentration	Solvent	Wave length mμ at maximum absorption	δ	$\delta/qb = \epsilon_{at}$
Chloranil	Hexamethylbenzene				
0.0134				0.921	512
.00670	all			.468	520
.00335		Benzene	512	.239	530
.00167	0.0134			.116	515
.00084				.61	540
Quinone	Hydroquinone				
0.00565	0.0912	Water (0.05 *M* HCl)	425	.345	670
.00282	.0912			.181	705
.00141	.0912			.097	730
.0228	.0221			.37	720
.0203	.800	Alcohol	430	1.40	86
.0203	.400			0.72	89
Quinone	Methylhydroquinone				
0.000167	4.15			.60	86
.0000875	4.15	Alcohol	420	.284	82
.0000417	4.15			.143	83
.00176	3.67			.463	72
.00176	1.22			.171	80
Quinone	Dimethylhydroquinone				
0.0200	0.250			.501	100
.0200	.125	Alcohol	410	.252	101
.0200	.0625			.131	105
Quinone	Diethylhydroquinone				
all	0.171			.357	100
0.0203	.0855	Alcohol	420	.181	104
	.0427			.089	90
all	.400			.509	57
0.0222	.200	Benzene	420	.268	60
	.100			.145	65
Quinone	Phenol				
0.00166	all			0.321	114
.000830	1.69	Alcohol	320	.165	117
.000415				.085	122
.00178	all	Petrol ether		.446	93
.000890	0.270		330	.237	99
.000445				.118	98
Quinone	Anisol				
all	2.34			1.084	163
	1.17	Alcohol	320	0.534	161
0.00284	0.585			.280	169
all	3.82			1.398	67
	1.91	Petrol ether	350	0.770	72
0 00550	0.955			.377	72
Quinone	Phenetol				
all	3.26	Petrol ether		1.301	76
	1.63		350	0.745	84
0.00525	0.815			.398	93
Quinone	Resorcinol				
0.00488	1.82			1.385	156
.00244	1.82	Alcohol	379	0.728	164
.00122	1.82			.374	169
.00534	1.81			1.361	151
.00534	0.905			0.754	156
Quinone	Phloroglucinol				
0.0274	0.238	Alcohol	420	0.124	190
.0137	.119			.031	190

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The absorption due to free quinone is so strong here that the optical density due to the molecular compound can be measured only at wave lengths > 350 mμ, but not at the maximum of absorption at 320 mμ. On looking at the results, *e. g.*, at 360 mμ, the corrected density was found to be 0.284. This, divided by the product of the two concentrations, yields $\epsilon_{st} = 92$. For the same wave length, the other experiments gave values ranging from 92 to 96, a satisfactory agreement.

(b) **Quinone + Hydroquinone Monomethyl Ether.**—The composition of the crystalline compound, a long time ago,[10] was found to be Q_1B_2. This can be easily confirmed by the method of analysis just described. For the dissolved state, however, it is shown (Table I) that the optical density of the mixture is proportional, at constant concentration of the hydroquinone ether, to the concentration of quinone. The maximum of absorption is at 420 mμ, very close to that of quinone + hydroquinone, and very far from that of phenol + quinone which is at 320 mμ. In Table I the density is shown to be proportional also to the concentration of hydroquinone monomethyl ether. So, the composition in solution is Q_1B_1.

3. Example for a Case Where the Solid Compound is Q_2B_1

Among the tri-hydroxybenzenes only phloroglucinol combines with quinone to form a crystalline compound stable enough to allow an analysis both in the solid and in the dissolved states. The solid compound is perfectly stable, the solution at least stable enough to permit of spectrophotometry with freshly prepared solutions. The crystalline compound has always the composition Q_2B_1, a composition which has heretofore not been known, nor even expected. One sample was prepared by mixing 1 g. of quinone (in 4 cc. of acetone) with 1.1 g. of phloroglucinol (in 2 cc. of acetone). Crystallization proceeds slowly but copiously. Another sample was prepared with an excess of quinone, by mixing 1.5 g. of quinone (in 6 cc. of acetone) with 0.5 g. of phloroglucinol (in 1 cc. of acetone). This mixture yields directly only quinone crystals. After adding an equal volume of benzene and slight evaporation at room temperature the red-brown quinhydrone crystals appear. Both samples of the solid quinhydrone, when titrated with titanous chloride, were found to have accurately the composition Q_2B_1.

A mixture of the two components in alcohol shows the formation of a brownish compound with maximum absorption at 420 mμ, close to that of quinone + hydroquinone, and very different from quinone + resorcinol (360 mμ). Freshly prepared alcoholic solutions gave the results presented in Table I. In another experiment, in which only the quinone concentration was varied, the optical density was proportional to that concentration, within the limits of error. So, the optical density due to the molecular compound is proportional to the product of the concentrations of the two components, hence its composition in the dissolved state is Q_1B_1.

4. Examples of Molecular Compounds Which do not Exist in the Solid State

(a) **Quinone + Hydroquinone Dimethyl Ether.**—No molecular compound of phenol + hydroquinone dimethyl ether has been obtained. However, a remarkable phenomenon can be observed in this case, which throws much light on the difference in behavior in the solid and in the liquid state. When a mixture of solid phenol and dimethylhydroquinone is melted, an intensely red liquid is obtained which remains so, even after supercooling. As crystallization sets in, all the red color disappears. The solid material is yellow and consists of two kinds of crystals, the light yellow ones of quinone and the colorless ones of hydroquinone dimethyl ether. This process is reversible. In alcoholic solution a mixture of quinone + dimethylhydroquinone shows an orange color, very much more intense than that of quinone alone, and here again the absorption due to this strongly colored substance is proportional both to the concentration of quinone and, as shown in Table I, to that of dimethylhydroquinone, so, the composition of the colored compound is Q_1B_1, but this compound exists only in solution.

The absorption maximum of this molecular compound in alcohol solution is, at 410 mμ, close to but not quite equal to that of quinhydrone.

(b) **Quinone + Hydroquinone Diethyl Ether.**—This case is quite analogous in every respect to that of the dimethyl ether. The larger volume of the ethyl group, as compared with the volume of the methyl group, does not influence the properties of the molecular compound. Table I shows the values both for alcohol and for benzene solutions.

(c) **Quinone + Anisole.**—No crystalline molecular compound of quinone and anisole can be prepared. In solution, however, such a compound does exist to a slight extent. When a solution of quinone, in alcohol or in petrol ether is mixed with anisole, the color is intensified. The maximum absorption of the compound in alcohol is at 320 mμ (Table I), just as for phenoquinone, and at 350 mμ in petrol ether. Here again the absorption due to the molecular compound is very much stronger than that of quinone alone, and the optical density is rather accurately proportional to the concentration of anisole. So, the molecular compound again is Q_1B_1.

(d) **Quinone + Phenetol.**—The result is similar to that obtained in the preceding case.

Significance of the ϵ_{st}, the Standard Absorption Coefficient

Since the optical density due to the molecular compound must be

$$\delta = \epsilon_{mol} \times m$$

where ϵ_{mol} is the molar absorption coefficient of the compound and m is its concentration, one obtains from equation 1

$$\epsilon_{st} = \epsilon_{mol} \times k$$

where k is the association constant.

There is good reason to assume that the molar absorption coefficient of any one substance is nearly independent of the solvent. Whenever a considerable variation of the molar absorption coefficient of any dye in different solvents is encountered, it can be always attributed to a change in chemical structure, say, a change of a quinonoid–lactoid equilibrium, or a different state of molecular aggregation, according to the solvent. There is no reason to assume that the molar absorption coefficients of molecular compounds of composition Q_1B_1 should vary appreciably according to the solvent. Consequently, the values of ϵ_{st} for any one compound in different solvents may be considered approximately as relative values of the association constant of that compound in various solvents. For instance, Table I shows that the association constant of quinone + hydroquinone is about eight times greater in water than in alcohol, probably due to the fact that in the competition among the affinities of the components for the solvent and for each other, the association is more inhibited by alcohol than by water.

On the other hand, on comparing the various values of ϵ_{st} for a series of molecular compounds in the same solvent, it is not possible, in general,

(10) H. Wichelhaus, *Ber.*, **12**, 1501 (1879): for the correction of his result, see O. Hesse, *Ann.*, **200**, 254 (1880).

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to decide whether the variation is due to a change of ϵ_{mol}, or of k, or of both. However, on comparing a homologous series, such as the compounds of quinone and, on the other hand, either hydroquinone or its ethers, in the same solvent, the values of ϵ_{st} are found to vary but little within this homologous series. It does not seem probable that the variation of ϵ_{mol} should be always just inversely proportional to the variation of k. It may rather be inferred from this fact, with high probability, that both ϵ_{mol} and k are approximately constant within the homologous series. For instance, both the molar absorption coefficients and hence the association constants are found to be almost alike for the compounds formed by quinone either with hydroquinone, its monoether, or its di-ethers, in alcohol. The substitution in the OH group is no steric hindrance to the formation of the molecular compound in solution.

In benzene the situation is slightly different. Quinone + hydroquinone cannot be compared with the other compounds of quinone because in benzene even at extremely low concentration precipitation of crystalline quinhydrone occurs. However, the compounds of quinone with the various ethers of hydroquinone can be mixed at proper concentration without any precipitation occurring. It can be seen that ϵ_{st} for the monomethyl ether compound is about twice that for a di-alkyl ether compound. In all probability this is due, not to any appreciable change of ϵ_{mol}, but to a slight change in the association constant, k, which in its turn is probably due to competition between the mutual affinity of the components and the affinity between components and solvent.

Summary

Highly colored molecular compounds of the quinhydrone type exist, not only in the crystalline state, but, to a slight extent, also in solution, in equilibrium with their free components. Because of their intense color such compounds lend themselves to a study by spectrophotometric methods. The compounds studied here consist usually of a quinone (Q) and another component of benzenoid structure (B), usually a phenolic compound. In the crystalline state the stoichiometric composition of the compound may vary, according to the particular phenolic compound used. It may be Q_1B_1, Q_1B_2, or Q_2B_1. No solid compound is formed when the OH group of phenol, or all OH groups in a poly-phenol, are alkylated. In the dissolved state, however, all of these compounds have the composition Q_1B_1, and molecular compounds exist just as well with unsubstituted as with alkylated phenols. This conclusion is based on the fact that the absorption of light due to the molecular compound is always proportional to the concentration of either component. It is furthermore shown that the affinity of quinone for a phenolic compound in solution is not essentially altered by alkylation of the phenolic OH groups. It is inferred from this that in the dissolved state the rings of the two components are superimposed upon each other and are not coplanar, and that no hydrogen bond plays any essential role in the establishment of these compounds. The crystalline compounds may differ from the dissolved ones, both in their stoichiometrical composition and in their spatial structure.

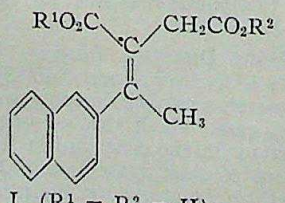
NEW YORK 21, N. Y. RECEIVED MARCH 1, 1944

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

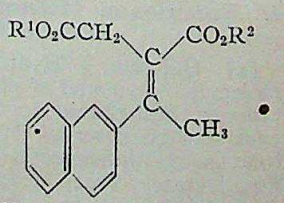
The Condensation of 2-Acetylnaphthalene with Diethyl Succinate[1]

BY WILLIAM S. JOHNSON AND ARTHUR GOLDMAN

In the course of certain synthetic work being carried out in this laboratory the occasion arose to investigate the condensation of 2-acetylnaphthalene with diethyl succinate. Through the efforts of Stobbe and his collaborators it has been well established that the alkoxide-catalyzed reaction of succinic ester with a ketone proceeds not by the acetoacetic ester type but mainly by an aldol type of condensation between the carbonyl group of the ketone and a methylene group of the ester. Stobbe and Lenzner[2] have reported that this condensation with 2-acetylnaphthalene gave a crystalline half-ester, m. p. 103–104° (yield unspecified). Saponification yielded a dicarboxylic acid, m. p. 165° (dec.), which they presumed to be an itaconic acid (formula I or II) by analogy with the products formed in similar condensations.[3]



I ($R^1 = R^2 = H$)
Ia ($R^1 = C_2H_5$, $R^2 = H$)
Ib ($R^1 = H$, $R^2 = C_2H_5$)
Ic ($R^1 = R^2 = C_2H_5$)



II ($R^1 = R^2 = H$)
IIa ($R^1 = H$, $R^2 = C_2H_5$)
IIb ($R^1 = C_2H_5$, $R^2 = H$)
IIc ($R^1 = R^2 = C_2H_5$)

In the present investigation when the condensation was conducted in ether solution with alcohol-free sodium ethoxide according to the reported

(1) This work was assisted in part by a grant from the Wisconsin Alumni Research Foundation.

(2) Stobbe and Lenzner, *Ann.*, **380**, 93 (1911).

(3) *Cf.* the reaction with acetophenone: (a) Stobbe, *Ann.*, **308**, 114 (1899); (b) *Ber.*, **37**, 1619 (1904); (c) *Ann.*, **380**, 36 (1911).

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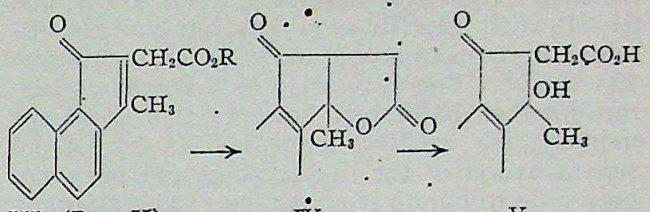
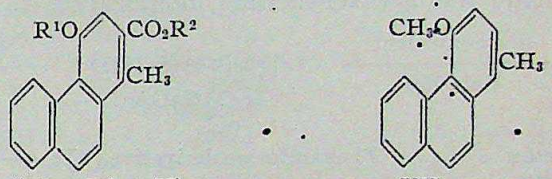
procedure,[2] an acidic mixture was produced from which a crystalline half-ester could be separated in 18% yield. This substance in contrast to that of Stobbe and Lenzner melted at 119–119.6° (pure). No other crystalline products could be isolated at this stage. The reaction proceeded similarly when carried out in ethanol with approximately one equivalent instead of excess sodium ethoxide. The latter procedure was easier and gave the 119° half-ester in 21% yield. Saponification yielded a dibasic acid, m. p. 179.5–180.5° (dec.), which gave an anhydride, m. p. 155.5–156°.

The oily mixture remaining after removal of the 119° half-ester was saponified with barium hydroxide, and the acidic material was treated with acetyl chloride. Fractional crystallization of the neutral material first gave a fraction which appeared to contain some of the previously mentioned 156° anhydride, followed by a more soluble fraction which consisted largely of a new isomer, m. p. 116°. This separation was inefficient, but did serve as a source of pure materials. From a study of the reactions, however, an indirect method was evolved for estimating the relative amounts of materials in the original mixture. This is described later.

Hydrolysis of the 116° anhydride gave a dibasic acid, m. p. 167–168° (dec.). The position of the ethylenic bond in this and in the 180° acid was shown by ozonolysis of derivatives which gave 2-acetylnaphthalene in each case. This proves that these are the geometrically isomeric γ-methyl-γ-(2-naphthyl)-itaconic acids. Stobbe[3b] determined the configurations of the two corresponding γ-methyl-γ-phenylitaconic acids from their behavior with sulfuric acid. One of the acids was converted to its anhydride, while the other was cyclized to give 3-methyl-1-indone-2-acetic acid (and the corresponding lactone), indicating that it had the *allo*-cinnamic acid configuration. The method of Stobbe was not successful when applied to the present case, probably because the higher polycyclic nuclei are more susceptible to sulfonation by the reagent.[4] When hydrogen fluoride[5] was used instead of sulfuric acid satisfactory yields of cyclized products were obtained. The 180° acid gave a mixture of 3-methyl-6,7-benz-1-indone-2-acetic acid (III) and the corresponding lactone IV. It is therefore assigned the configuration shown in formula I. The 168° acid was converted to 4-hydroxy-1-methylphenanthrene-2-carboxylic acid (VI), and is therefore represented by formula II. The cyclization of II to form the phenanthrol instead of the anhydride (as with the phenylitaconic acid analog[3b]) may be explained by the greater reactivity of the naphthalene nucleus or/and a cyclizing action of hydrogen fluoride which is different from that of sulfuric acid. The proof of structure of the cyclization products III and VI is considered later.



III (R = H) IIIa (R = C_2H_5) IV V



VI ($R^1 = R^2 = H$)
VIa ($R^1 = COCH_3$, $R^2 = C_2H_5$)
VIb ($R^1 = H$, $R^2 = C_2H_5$)
VIc ($R^1 = CH_3$, $R^2 = H$)
VId ($R^1 = CH_3$, $R^2 = C_2H_5$)

VII

When the anhydride of I was treated with ethanol containing a drop of sulfuric acid it was converted into a new half-ester, m. p. 118°, which was different from the 119° isomer as shown by the melting point depression of the mixture. The 118° half-ester could be prepared also in good yield by mild esterification of the dibasic acid (I). Exhaustive esterification of the 118° half-ester gave the di-ester (Ic) which on partial saponification with one equivalent of barium hydroxide yielded the 119° half-ester, thus completing the cycle (see Fig. 1). The mode of formation of the two half-esters suggests that the 119° substance has the structure Ia and that the 118° isomer is Ib. These structures were substantiated by cyclization experiments. When heated with acetic anhydride and sodium acetate the 118° half-ester was converted into the red indoneacetic ester IIIa. Upon the same treatment the 119° isomer, in contrast, was recovered largely unchanged. The small neutral fraction contained the anhydride of I and none of the indone derivative. The above transformations are indicated in the accompanying chart (Fig. 1):

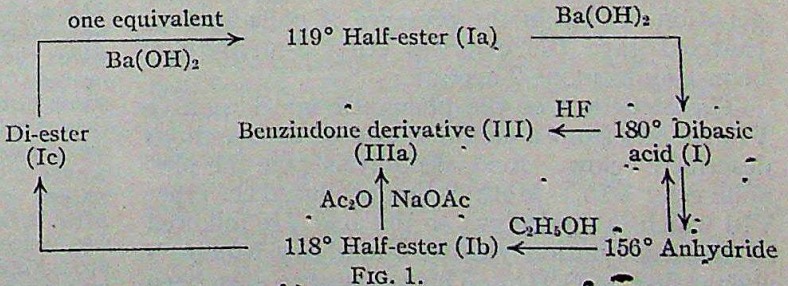


FIG. 1.

A sequence of transformations analogous to those described above for the dibasic acid I was developed from the stereoisomeric acid II (see

(4) *Cf.* how attempts to cyclize certain reactive γ-arylbutyric acids with sulfuric acid resulted in sulfonation: Krollpfeiffer and Schäfer, *Ber.*, **56**, 620 (1923).

(5) Fieser and Hershberg, THIS JOURNAL, **61**, 1272 (1939); **62**, 49 (1940).

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Fig. 2). Although the half-ester IIb obtained by alcoholysis of the 116° anhydride melted at 102–102.5°, its mode of formation makes improbable its identity with the material of Stobbe and Lenzner. This same argument seems to rule out the 118° half-ester Ib, even though it has been obtained in a polymorphic modification melting at 105–105.5°. This leaves IIa as a possible structure for their half-ester; however, this also seems unlikely, for we have prepared IIa by partial saponification of the di-ester IIc, and have not been able to obtain it crystalline. The alternate possibility still remains that their substance actually was a lower-melting modification of Ia,

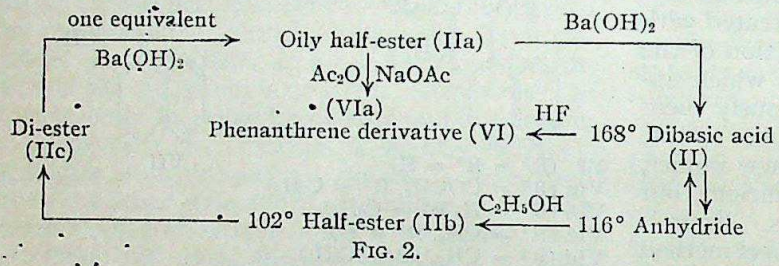

Fig. 2.

and that coincidentally their dibasic acid was similar to a low-melting (163–165°) fraction of I isolated in the present work.

The structures of the half-esters IIa and IIb were assigned on the basis of their behavior toward acetic anhydride and sodium acetate. The former was cyclized to ethyl 4-acetoxy-1-methylphenanthrene-2-carboxylate (VIa), while the isomeric half-ester IIb was converted largely to the anhydride.

The structure of the red indoneacetic ester IIIa was assigned on the basis of the following transformations. Oxidation with nitric acid gave benzene-1,2,3,4-tetracarboxylic acid which proved that ring closure took place into the 1-position of the naphthalene nucleus. On acid hydrolysis of IIIa the color (which is characteristic of an indone) was dispelled and the colorless lactone IV was produced. This was identical with the material obtained by the cyclization of the itaconic acid I. Alkaline cleavage gave the hydroxy acid V which reverted easily to the lactone on heating. Hydrogenation of IIIa in the presence of palladium on charcoal gave the colorless ethyl 3-methyl-6,7-benz-1-hydrindone-2-acetate.

The structure of the phenanthrene derivative VIa follows from a consideration of the reactions described below. Acid alcoholysis gave the phenolic ester VIb. Methylation produced the ether VId which on hydrolysis to the acid VIc followed by decarboxylation yielded 4-methoxy-1-methylphenanthrene (VII). This substance has been prepared previously[6] by the Pschorr synthesis, and the reported melting points of VII and of the picrate are in agreement with those found in the current work. Alkaline hydrolysis of VIa produced 4-hydroxy-1-methylphenanthrene-2-carboxylic acid (VI) which was the product of cyclization of the itaconic acid II.

A rough estimation of the amounts of the itaconic half-esters present in the original reaction mixture was made by treating the crude oily fraction which remained after the separation of the half-ester Ia (in 21% yield), with acetic anhydride and sodium acetate. The half-ester IIa thus was cyclized to the phenanthrol acetate VIa which crystallized in 30%[7] yield from the neutral fraction. On working up the acidic residues additional half-ester Ia was accounted for, raising the amount of this isomer in the original mixture to 29% of the theoretical. The total amount of itaconic half-esters thus accounted for is 59% of the theoretical based upon 2-acetylnaphthalene. This is in fair agreement with the yield (65%) of the mixture of itaconic di-esters obtained from the crude reaction mixture by esterification and fractional distillation. Partial saponification of this product gave a mixture which was rich in respect to the itaconic half-esters as shown by analysis according to the procedure described above for the crude mixture. About 47% of Ia and 38% of IIa were accounted for in this way.

Experimental Part[8]

The Condensation of Diethyl Succinate with 2-Acetylnaphthalene

(*a*) *By the Procedure of Stobbe and Lenzner.*[2]—The reported procedure has been repeated several times, and the results of a typical run are given herewith. When 19.5 g. (0.112 mole) of diethyl succinate, 19.1 g. (0.112 mole) of 2-acetylnaphthalene and 0.20 mole of alcohol-free sodium ethoxide (from 4.6 g. of sodium) were used, all but about 10% of the product was alkali-soluble. The oily acidic fraction was dissolved in ether, petroleum ether[9] was added to the point of incipient cloudiness and crystallization was induced. The crude product was filtered and then recrystallized from ether–petroleum ether.[9] The first and second crops of colorless crystals both had the same m. p., 118–119°, and amounted to 6.0 g., a yield of 18%.

(*b*) *With Alcoholic Sodium Ethoxide.*—To a solution of 6.4 g. (0.28 mole) of sodium in 120 cc. of absolute alcohol were added 43.5 g. (0.25 mole) of diethyl succinate and 42.5 g. (0.25 mole) of 2-acetylnaphthalene. The mixture was refluxed on the steam-bath for fifteen hours during which the solution turned brown and a heavy precipitate formed. Water was added, and the alcohol removed by steam-distillation. Ether extraction of the alkaline solution gave 5.9 g. of dark neutral oil which was not further investigated. The aqueous layer was acidified, and the orange oil which separated was taken up in ether and washed with water followed by saturated salt solution. After drying over anhydrous sodium sulfate the solution was concentrated and treated with petroleum ether[9] to precipitate the crude half-ester Ia. By recrystallization from ether–petroleum ether[9] a total of 15.3 g. (21% yield) of colorless plates, m. p. 117.5–118.5°, was obtained. The nature of the residues is considered later.

(6) Higginbottom, Hill and Short, *J. Chem. Soc.*, 263 (1937).

(7) The amount of IIa in the original mixture is probably more than indicated by this yield, since the cyclization of relatively pure IIa to VIa was not quantitative. See experimental part.

(8) Unless otherwise stated, all melting points are corrected.

(9) Boiling range 60–68°.

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3-Carbethoxy-4-(2-naphthyl)-*cis*-3-pentenoic Acid (Ia).—Material obtained in the preceding experiment was recrystallized to constant m. p. from ether–petroleum ether.[9] It formed colorless plates, m. p. 119–119.5°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.60; H, 5.82.

3-Carboxy-4-(2-naphthyl)-*cis*-3-pentenoic Acid (γ-Methyl-γ-(2-naphthyl)-isoitaconic Acid) (I).—A mixture of 9.10 g. of the above half-ester (m. p. 117–118°), 13 g. of barium hydroxide, 75 cc. of alcohol and 100 cc. of water was heated under reflux on the steam-bath for six hours. The colorless barium salt was filtered from the cooled solution, washed with water, then with alcohol. Treatment with dilute hydrochloric acid gave 8.10 g. of crude dibasic acid, m. p. 169–171° (dec.). The first crop obtained by recrystallization from dilute alcohol amounted to 5.40 g. of colorless crystals, m. p. 176.5–178.5° (dec.). Repeated recrystallization from acetone–petroleum ether[9] gave material of constant m. p., 179.5–180.5° (dec.).

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.40; H, 5.26.

The mother liquor from the dilute alcohol crystallization yielded an additional 2.50 g. of acid, m. p. 163–165° (dec.), which could not be purified readily. The m. p. of a mixture with the analytical sample was not depressed (165–167°). When mixed with the stereoisomeric acid II (m. p. 167–168°) the m. p. was depressed (150–155°). This second crop of the dibasic acid I corresponds in m. p. to the acid of Stobbe and Lenzner.[2] This suggests that their half-ester possibly could have been a lower-melting polymorphic modification of the 119° half-ester.

The anhydride of I was prepared by Stobbe's general procedure[3a] with acetyl chloride at room temperature. From 0.670 g. of I (m. p. 179–180°) was obtained 0.552 g. of bicarbonate-insoluble material, m. p. 153–154°. The pure anhydride was obtained as colorless blades, m. p. 155.5–156°, from chloroform–petroleum ether.[9]

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80. Found: C, 76.30; H, 4.94.

Ethyl 3-Carboxy-4-(2-naphthyl)-*cis*-3-pentenoate (Ib). (*a*) *From the Anhydride of I.*—A mixture of 1.04 g. of the anhydride described in the preceding experiment and 20 cc. of ethanol containing one drop of concentrated sulfuric acid was warmed on the steam-bath until solution was nearly complete. After standing overnight the solution was evaporated in a stream of air, and the solid residue was taken up in ether. The solution was washed with water, and then extracted with portions of 5% sodium bicarbonate solution. Acidification of these extracts gave 1.17 g. (95% yield) of colorless half-ester, m. p. 117–118°.

(*b*) *From the Dibasic Acid I.*—A mixture of 4.90 g. of the itaconic acid I (m. p. 177–179°), 40 cc. of alcohol and 60 cc. of benzene containing three drops of sulfuric acid was allowed to reflux through a system which included a constant water separator of the type described by Cope, Hofmann, Wyckoff and Hardenbergh.[10] After nineteen hours water had ceased to separate. The solvent was removed, and the product worked up as in (*a*) above. The crude half-ester was colorless and amounted to 5.03 g. (93% yield), m. p. 116–117.5°. The pure substance, m. p. 118.5–119°, formed fine colorless needles from ether–petroleum ether.[9] When mixed with the half-ester Ia, it melted at 98–105°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.45; H, 6.03.

On slow crystallization from dilute solution the half-ester Ib sometimes formed prisms, m. p. 105–105.5°. The polymorphic nature of this product was established by adding to the clear melt at 110° a seed of the higher-melting modification. Solidification occurred immediately, and the material then melted at 116.5–117.5°.

In order to show that no structural or configurational change had occurred in the acid portion of the molecule during the above alcoholysis reactions, the half-ester Ib was saponified with barium hydroxide, and the dibasic acid (I) was reconverted to the original anhydride, m. p. 154.5–155°.

Ethyl 3-Carbethoxy-4-(2-naphthyl)-*cis*-3-pentenoate (Ic).—The diethyl ester Ic can be prepared from either half-ester Ia or Ib. From structural considerations it was expected that the former would be easier to esterify. This was borne out by the fact that Ia could be esterified under conditions to which Ib already has been shown to be stable.

(*a*) *From Half-ester Ia.*—To esterify 7.51 g. of Ia (m. p. 117–118°) the procedure described in the preceding experiment, part (*b*), was followed. The quantities of solvents and catalyst were the same as before. The di-ester Ic was obtained from the neutral fraction; yield 6.95 g. of material boiling at 184–186° (0.05–1 mm.), $n^{22}D$ 1.5667. Partial saponification with one equivalent of barium hydroxide according to the procedure described below part (*b*), regenerated the half-ester Ia.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.80. Found: C, 73.87; H, 6.82.

(*b*) *From Half-ester Ib.*—A solution of 0.650 g. of the half-ester Ib in 15 cc. of ethanol was saturated with hydrogen chloride and heated under reflux for twenty-four hours. Only a trace of acidic material remained, and the crude diester amounted to 0.639 g. This was characterized by partial saponification (of the di-ester Ic) to the half-ester Ia with 0.32 g. of barium hydroxide octahydrate in 9 cc. of alcohol and 6 cc. of water. After refluxing for six hours the insoluble barium salt of the dibasic acid was filtered. Decomposition with hydrochloric acid gave 0.113 g. of crude I characterized by conversion to the anhydride, m. p. 152–153°. The alcoholic filtrate containing the half-ester was evaporated, and the residue was treated with dilute hydrochloric acid, taken up in ether, washed with water and finally extracted with 5% sodium bicarbonate solution. The colorless half-ester obtained on acidification amounted to 0.295 g., m. p. 117–118°, not depressed on mixing with authentic Ia. Unchanged diester amounting to 0.120 g. was recovered from the ether solution.

3-Carboxy-4-(2-naphthyl)-*trans*-3-pentenoic Acid (γ-Methyl-γ-(2-naphthyl)-itaconic Acid) (II).—A condensation of 2-acetylnaphthalene (68.0 g.) and diethyl succinate (69.6 g.) was carried out according to procedure (*b*) described above. The crude half-ester remaining after crystallization of about 16 g. of Ia was hydrolyzed for five hours with 135 g. of barium hydroxide in 800 cc. of alcohol and 700 cc. of water. The mixture of acids obtained by decomposing the barium salt with hydrochloric acid was dried and treated with excess acetyl chloride at room temperature. The bicarbonate-insoluble mixture of anhydrides amounted to 62.0 g. (59%) of dark-brown solid material. Eleven grams of this material was distilled rapidly in a two-bulb flask under reduced pressure. The red, viscous distillate (9.6 g.) was crystallized from chloroform–petroleum ether[9] to yield the following fractions: (a) 2.6 g. (m. p. 85–108°); (b) 1.1 g. (m. p. 90–113°); (c) 2.1 g. (113–115°). Only crude anhydride of I (m. p. 141–148°) could be isolated from fractions (a) and (b) by recrystallization. Fraction (c), however, consisted largely of the anhydride of II, which after several recrystallizations had the constant m. p. 116–116.5°; colorless prisms from chloroform–petroleum ether.[9]

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80. Found: C, 76.05; H, 4.89.

Hydrolysis of the above anhydride (0.105 g.) with 5 cc. of 2% sodium hydroxide solution yielded on acidification 0.091 g. of the dibasic acid II, m. p. 165–167° (dec.). The pure substance forms colorless microscopic crystals from dilute alcohol and melts at 167–168° (dec.).

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.29; H, 5.03.

With acetyl chloride this acid could be reconverted to the anhydride in practically quantitative yield.

Ethyl 3-Carboxy-4-(2-naphthyl)-*trans*-3-pentenoate (IIb).—Alcoholysis of 3.88 g. of the anhydride of II (m. p.

(10) Cope, Hofmann, Wyckoff and Hardenbergh, THIS JOURNAL, 63, 3452 (1941).

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115–116°) described in the preceding experiment was effected with 100 cc. of ethanol containing 4 drops of sulfuric acid. The procedure already described for the stereoisomer was followed, and 4.06 g. of colorless half-ester, m. p. 100–101.5° was obtained. Pure IIb crystallized from ether–petroleum ether[9] in colorless prisms, m. p. 102–102.5°.

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.54; H, 6.25.

This half-ester was reconverted to the anhydride, m. p. 115–116° (not depressed on mixing with anhydride of II prepared as above) in 77% yield by the usual saponification with barium hydroxide followed by dehydration of the dibasic acid with acetyl chloride.

Ethyl 3-Carbethoxy-4-(2-naphthyl)-*trans*-3-pentenoate (IIc).—Esterification of 3.09 g. of the above half-ester (IIb) was effected according to the procedure already described for the stereoisomer Ib. Thirty cubic centimeters of ethanol saturated with hydrogen chloride was used, and the yield of liquid di-ester IIc was 2.72 g. (81%) after a rough distillation in a two-bulb flask under reduced pressure; $n^{22}D$ 1.5670.

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.80. Found: C, 73.81; H, 6.77.

This ester gave a pale yellow color with concentrated sulfuric acid. In contrast the isomeric *cis* di-ester Ic gave a dark-red brown color. These observations are compatible with those of Stobbe[3o] regarding the color reactions and configurations of the methylphenylitaconic esters.

Partial saponification of IIc (1.52 g.) was effected with 0.76 g. of barium hydroxide octahydrate, 25 cc. of alcohol and 15 cc. of water. The procedure described above for the stereoisomer Ic was followed. Thus was obtained 0.30 g. of the dibasic acid II, m. p. 165–167°, which was converted to the anhydride, m. p. 113–115°, no depression on mixing with original anhydride of II. The neutral fraction amounted to 0.41 g. of unchanged di-ester, and the yield of oily **3-carbethoxy-4-(2-naphthyl)-*trans*-3-pentenoic acid (IIa)** was 0.64 g. All attempts thus far to crystallize this material have failed. It is easily characterized by conversion to ethyl 4-acetoxy-1-methylphenanthrene-2-carboxylate (VIa) which is described below, or by preparation of the crystalline **anilide**, m. p. 153–154°, which forms fine colorless needles from acetone–petroleum ether.[9]

Anal. Calcd. for $C_{24}H_{23}O_3N$: N, 3.75. Found: N, 4.06.

Ozonolysis. (*a*) *Of 3-Carbethoxy-4-(2-naphthyl)-cis-3-pentenoic Acid (Ia).*—A slight excess of ozone (detected by starch–iodide test), was introduced into a cold (ice-bath) solution of 1.00 g. of the pure half-ester Ia in 25 cc. of ethyl acetate. The ozonide was decomposed[11] by stirring with 1–2 g. of Raney nickel for two hours at room temperature, then at refluxing temperature for three hours. The filtered solution was extracted thoroughly with 5% sodium bicarbonate solution and dried over anhydrous potassium carbonate. The neutral oil obtained on evaporation was dissolved in 10 cc. of methanol and treated with 0.5 g. of semicarbazide hydrochloride and 0.42 cc. of pyridine by refluxing for twenty minutes. The semicarbazone was obtained as tan needles, m. p. 229–230° (dec.); yield 0.294 g. (39%). The mixed m. p. with authentic 2-acetylnaphthalene semicarbazone (m. p. 234–235° (dec.)) was not depressed. The above semicarbazone was cleaved by warming with 20% hydrochloric acid to give 0.201 g. of yellow ketone, m. p. 48.5–50°. Recrystallization from petroleum ether[9] containing a little benzene gave material having the m. p. 52–53° which was not depressed on mixing with authentic 2-acetylnaphthalene (m. p. 53–54°).

(*b*) *Of Ethyl 3-Carboxy-4-(2-naphthyl)-cis-3-pentenoate (Ib).*—One gram of the half-ester Ib was ozonized according to the preceding procedure. The semicarbazone amounted to 0.321 g., m. p. 228–230° (dec.). This and the ketone obtained by hydrolysis showed no depression of m. p. on mixing with authentic specimens.

(11) Cook and Whitmore, THIS JOURNAL, 63, 3540 (1941).

(*c*) *Of Ethyl 3-Carboxy-4-(2-naphthyl)-trans-3-pentenoate (IIb).*—The results of ozonolysis of IIb were practically identical with those described in the preceding experiment. The yield of 2-acetylnaphthalene semicarbazone was 0.320 g. or 42%.

Cyclization of Ethyl 3-Carboxy-4-(2-naphthyl)-*cis*-3-pentenoate (Ib).—A solution of 0.800 g. of the half-ester and 0.2 g. of sodium acetate in 7 cc. each of acetic anhydride and acetic acid was boiled under reflux for three hours. The deep-red solution was evaporated in a current of air, and the residue (which was insoluble in cold bicarbonate) was boiled for thirty minutes with 25 cc. of 5% sodium bicarbonate solution to decompose the anhydride of I. The undissolved portion was filtered, dried, and crystallized from petroleum ether.[9] Thus was obtained 0.111 g. of **ethyl 3-methyl-6,7-benz-1-indone-2-acetate (IIIa)** m. p. 95.5–97°. An additional 0.023 g., m. p. 93–95° was obtained from the filtrate. A purified sample crystallized from dilute alcohol as orange needles, m. p. 96.5–97°.

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 77.15; H, 5.75.

Acidification of the sodium bicarbonate solution gave an oily acid which was converted to anhydride by the acetyl chloride treatment. Crystallization from chloroform–petroleum ether[9] yielded 0.120 g. of good material, m. p. 154–155°.

Oxidation of Ethyl 3-Methyl-6,7-benz-1-indone-2-acetate.—A mixture of 0.5 g. of the indoneacetic ester IIIa, 1.5 cc. of water and 2 cc. of concentrated nitric acid was heated in a sealed tube at 190–200° for sixteen hours. The crude product which was filtered on a sintered-glass plate amounted to 0.18 g., m. p. 229–236°. Once recrystallized from concentrated nitric acid, it melted at 232–237°. For benzene-1,2,3,4-tetracarboxylic acid the reported[12] m. p. is 238° with softening at 225°. The methyl ester was prepared with diazomethane. After sublimation and recrystallization twice from methanol, tetramethylbenzene-1,2,3,4-tetracarboxylate was obtained as colorless needles, m. p. 129.5–131° (reported[12] 133–135°).

For comparison a sample of 1-keto-1,2,3,4-tetrahydrophenanthrene kindly supplied by Dr. A. L. Wilds was oxidized in the same way. The crude acid produced therefrom melted at 228–231°, and the purified tetramethyl ester had the m. p. 130–131°. No depression of the m. p. of a mixture of the two samples was observed. When mixed with an authentic specimen of tetramethylbenzene-1,2,4,5-tetracarboxylate, m. p. 137–139°, each of the above products depressed the m. p. to 109–126°.

Lactone (IV) of 3-Methyl-3-hydroxy-6,7-benz-1-hydrindone-2-acetic Acid.—A solution of 1.84 g. of ethyl 3-methyl-6,7-benz-1-indone-2-acetate (IIIa) in 15 cc. of acetic acid and 10 cc. of concentrated hydrochloric acid was boiled under reflux overnight. The hot mixture which had turned from a deep red to a pale yellow color was diluted with water to the point of incipient cloudiness, and on cooling the lactone IV crystallized in straw-colored plates. It amounted to 1.35 g. (81% yield), m. p. 167–168°. An additional 0.14 g. of less pure material, m. p. 164–166°, was obtained from the filtrate. After three recrystallizations from benzene–petroleum ether[9] the lactone was obtained as thick, colorless plates, m. p. 168.5–169°. It is insoluble in, but is cleaved slowly by, dilute alkali.

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80. Found: C, 76.36; H, 5.01.

An attempt to prepare the semicarbazone of the above lactone (IV) gave a product which after recrystallization from dilute alcohol melted at 244° (dec.) (introduced in bath at 239°). The analysis of this material is compatible with a hydrazide structure which could result from cleavage of the lactone ring by the semicarbazide.

Anal. Calcd. for $C_{17}H_{17}O_4N_3$: C, 62.37; H, 5.24. Found: C, 62.06; H, 5.15.

(12) Bamford and Simonsen, *J. Chem. Soc.*, 1904 (1910).

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3-Methyl-3-hydroxy-6,7-benz-1-hydrindone-2-acetic Acid (V).—A suspension of 2.02 g. of the above lactone IV (m. p. 167–168°) in 20 cc. of 5% sodium hydroxide was allowed to stand overnight at room temperature. The clear red solution was filtered, carefully acidified in the cold with dilute hydrochloric acid, and the gummy red precipitate was extracted with ether–ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfate and concentrated. The residue was treated with hot benzene which dissolved all but 0.27 g. of amorphous red material, m. p. 227–235° (dec.) which was not further investigated. The filtrate deposited 0.61 g. of orange microscopic crystals, m. p. 146–150° (dec.). Unlike the lactone this material was soluble in sodium bicarbonate solution. After one recrystallization from benzene it melted sharply at 148.5–150° (dec.). On a second recrystallization the m. p. jumped to 168–169° (dec.) (polymorphic form ?). The best sample was obtained as buff-colored, flat rods, m. p. 169–169.5° (dec.).

Anal. Calcd. for $C_{16}H_{14}O_4$: C, 71.10; H, 5.22. Found: C, 71.20; H, 5.42.

In the crystallizations described above it was necessary to use glassware which had been washed with alkali and thus rinsed free of traces of acid which catalyze the lactonization of the hydroxy acid V. Even with this precaution the dehydration was not eliminated completely, for the more soluble lactone was usually found in the mother liquors.

Ethyl 3-Methyl-6,7-benz-1-hydrindone-2-acetate.—A solution of 1.44 g. of the indoneacetic ester (IIIa) in 25 cc. of ethyl acetate was hydrogenated in the presence of 0.250 g. of 30% palladium-charcoal.[13] After shaking for one-half hour one molecular equivalent of hydrogen was absorbed. The residue obtained after filtration and evaporation was recrystallized from petroleum ether[9] giving 0.803 g. of colorless plates, m. p. 68.5–70°. A second crop obtained from the mother liquor amounted to 0.280 g., m. p. 66–68°, making the total yield 75%. The residue was oily and may have contained the diastereoisomer. Pure ethyl 3-methyl-6,7-benz-1-hydrindone-2-acetate was obtained by two recrystallizations from petroleum ether[9] from which it formed colorless plates, m. p. 70.2–70.6°.

Anal. Calcd. for $C_{18}H_{18}O_3$: C, 76.58; H, 6.42. Found: C, 76.63; H, 6.36.

Cyclization of 3-Carbethoxy-4-(2-naphthyl)-*cis*-3-pentenoic Acid (Ia). (*a*) *By the Acetic Anhydride–Sodium Acetate Method.*—The half-ester Ia (0.512 g.) was treated with 0.14 g. of sodium acetate in 3 cc. each of acetic anhydride and acetic acid just as described above for the stereoisomer Ib. In distinct contrast to the case of Ib, the reaction mixture of Ia, even after the heating was complete, was pale yellow. No trace of the red color which is characteristic of the indone derivative was detected. Acidification of the sodium bicarbonate extracts gave back 0.310 g. (61%) of unchanged half-ester, m. p. 117–118°. The neutral fraction was a yellow oil from which could be crystallized a small amount, 0.019 g., of crude anhydride of I, m. p. 135–142°. One recrystallization brought the m. p. to 149–151°, which was not depressed on mixing with authentic anhydride. No more crystalline material was obtained from the residues, but the lack of red color was considered sufficient evidence for the absence of the indone derivative.

(*b*) *With Hydrogen Fluoride.*—This reagent effects cleavage of the ester group, and therefore promotes cyclization to the expected (see later experiments on the dibasic acid I) lactone IV. Thus 0.44 g. of half-ester Ia after standing in about 20 g. of hydrogen fluoride at room temperature for five hours, yielded 0.291 g. of neutral crystalline material, m. p. 167–168.5°. The m. p. of a mixture with lactone IV was not depressed.

Cyclization of 3-Carbethoxy-4-(2-naphthyl)-*trans*-3-pentenoic Acid (IIa).—When 0.560 g. of the crude oily half-ester IIa was treated with 0.15 g. of sodium acetate in 5 cc. each of acetic acid and acetic anhydride according to cyclization procedures described above, very little (0.016 g.) acidic material remained. The neutral material consisted of ethyl 4-acetoxy-1-methylphenanthrene-2-carboxylate (VIa) obtained by crystallization from ethyl acetate–petroleum ether.[9] The first crop amounted to 0.339 g., m. p. 127–128°, and the second 0.133 g., m. p. 125.5–127°, making the total yield 78%. The analytical sample of VIa formed colorless prismatic rods from dilute alcohol and melted at 127.5–128°.

Anal. Calcd. for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.66; H, 5.72.

Ethyl 4-hydroxy-1-methylphenanthrene-2-carboxylate (VIb) was prepared by acid alcoholysis of 5.00 g. of the above acetoxy derivative (VIa) in 100 cc. of ethanol saturated with hydrogen chloride. After refluxing for five hours, the solution was concentrated, and water was added. The crystalline precipitate amounted to 4.00 g., m. p. 175–178°. An additional 0.21 g., m. p. 174–176°, was obtained by concentrating the filtrate. Recrystallization of the combined crops from dilute alcohol gave 4.01 g. (92% yield) of colorless blades, m. p. 177–179°. Material recrystallized three times from the same solvent had the constant m. p. 178.5–179°.

Anal. Calcd. for $C_{18}H_{16}O_3$: C, 77.12; H, 5.75. Found: C, 76.80; H, 5.76.

Ethyl 4-methoxy-1-methylphenanthrene-2-carboxylate (VId) was prepared in 95% yield by methylaton of the above phenolic ester (5.0 g.) with excess dimethyl sulfate in cold dilute sodium hydroxide. The crude product amounted to 5.0 g., m. p. 70–73°. The analytical sample crystallized from dilute alcohol in the form of colorless needles, m. p. 74–74.5°.

Anal. Calcd. for $C_{19}H_{18}O_3$: C, 77.53; H, 6.16. Found: C, 77.40; H, 5.76.

4-Methoxy-1-methylphenanthrene-2-carboxylic acid (VIc) was obtained by hydrolysis of 5.0 g. of crude VId with 100 cc. of 5% alcoholic potassium hydroxide. After refluxing for four hours the acidic material amounted to 4.29 g. (95% yield), m. p. 222–225.5°. After several recrystallizations from dilute alcohol a sample was obtained as colorless needles, m. p. 225–225.5°.

Anal. Calcd. for $C_{17}H_{14}O_3$: C, 76.67; H, 5.30. Found: C, 76.85; H, 5.33.

4-Methoxy-1-methylphenanthrene (VII).—Attempts to decarboxylate the free phenolic acid VI or the acetate (which are described below) were not successful, because these substances were too sensitive. The more stable methoxy derivative VIc, however, was quite suitable.

The decarboxylation of 1.20 g. of VIc was effected by heating in 5 cc. of quinoline with 0.60 g. of copper powder at 205–210° for one-half hour, then at 215–220° for twenty minutes. On working up the mixture 0.03 g. of unchanged acid was recovered. The neutral fraction was recrystallized from methanol (Norit) to give 0.71 g. of colorless needles, m. p. 76.5–78°. From the mother liquor was obtained an additional 0.09 g., m. p. 74–76°, making the total yield 80%. A sample of the methoxymethylphenanthrene VII after further recrystallizations from methanol melted at 78–79° (reported[6] 78.5–79°). The picrate was prepared in the customary way. It crystallized from the reaction mixture in the form of orange, microscopic crystals, m. p. 183–184° (reported[6] 182–183°).

4-Hydroxy-1-methylphenanthrene-2-carboxylic acid (VI) was obtained by the hydrolysis of VIa (3.00 g.) with 60 cc. of 5% alcoholic potassium hydroxide. The yield of material obtained after three hours of refluxing and recrystallization from dilute acetic acid was 2.25 g. (86%); slightly yellow rods, m. p. 249–251° (dec.) (uncor.). Material having the same appearance and melting at 253–254° (dec.) (uncor.) was obtained after several recrystallizations.

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80. Found: C, 76.02; H, 5.01.

4-Acetoxy-1-methylphenanthrene-2-carboxylic acid was obtained in 94% yield by acetylation of the phenolic acid

(13) Zelinsky and Turowa-Pollak, *Ber.*, **58**, 1295 (1925).

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VI with acetic anhydride and sulfuric acid. The best material formed almost colorless needles, m. p. 227.5–229°, from ethyl acetate.

Anal. Calcd. for $C_{18}H_{14}O_4$: C, 73.46; H, 4.79. Found: C, 73.48; H, 5.06.

Cyclization of Ethyl 3-Carboxy-4-(2-naphthyl)-*trans*-3-pentenoate (IIb).—The half-ester (0.530 g.) was treated with 0.14 g. of sodium acetate in 5 cc. each of acetic acid and acetic anhydride according to procedures described above. Only a trace of acidic material was recovered. The neutral fraction was crystallized from chloroform–petroleum ether.[9] The first crop amounted to 0.211 g., m. p. 112–115°; and the second 0.078 g., m. p. 108–112°. Both fractions were identified (by mixed m. p.) as the anhydride of II described above. The oily residue was almost all converted to bicarbonate-soluble material after treatment with 5 cc. of ethanol containing a drop of sulfuric acid. This indicated that little, if any, of the phenanthrol derivative VIa could have been present.

Cyclization of 3-Carboxy-4-(2-naphthyl)-*cis*-3-pentenoic Acid (I).—A solution of 0.710 g. of the dibasic acid (I) in about 20 g. of anhydrous hydrogen fluoride was allowed to stand in a platinum vessel in an ice–salt bath for one and one-half hours. The reagent was evaporated in a current of air, and the residue taken up in ether and extracted with 5% sodium bicarbonate solution. Acidification of the latter gave 0.220 g. of crude **3-methyl-6,7-benz-1-indone-2-acetic acid (III)**, m. p. 198–211°. The best sample, obtained as flat, red rods after two recrystallizations from benzene–alcohol, melted at 215.5–219.5°. Attempts to prepare this acid by saponification of the ester IIIa failed.

Anal. Calcd. for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80. Found: C, 75.87; H, 4.88.

The material which remained in the original ether layer amounted to 0.271 g., m. p. 164–166°. It was identified (by mixed m. p.) as the lactone (IV) of 3-methyl-3-hydroxy-6,7-benz-1-hydrindone-2-acetic acid described above.

Cyclization of 3-Carboxy-4-(2-naphthyl)-*trans*-3-pentenoic Acid (II).—The dibasic acid (0.321 g., m. p. 165–166°) was treated with hydrogen fluoride according to the procedure described for the stereoisomer I. The yield of material once recrystallized from ethyl acetate–petroleum ether[9] was 0.246 g. (82%), m. p. 251–253° (dec.) (uncor.). The mixed m. p. with 4-hydroxy-1-methylphenanthrene-2-carboxylic acid (VI) was not depressed.

Analysis of Original Reaction Mixture.—This is a continuation of the procedure described at the beginning of the experimental part for the condensation of diethyl succinate with 2-acetylnaphthalene (part b). The combined residues from the crystallization of the half-ester Ia were dissolved in 400 cc. of alcohol, and a concentrated aqueous solution of barium hydroxide was added with stirring until the mixture was basic to litmus. The crude insoluble barium salt of dibasic acid was filtered, washed with water, alcohol and finally with ether, and was then decomposed with dilute hydrochloric acid. After extraction and drying the crude oily acidic material amounted to 6.9 g. This could not be crystallized. With acetyl chloride at room temperature all but 0.8 g. was converted to neutral material, which also could not be crystallized readily and was not further investigated.

The solution and washings containing the barium salt of the half-ester mixture were combined, acidified with dilute hydrochloric acid, and the organic solvents removed under reduced pressure. The oily residue was extracted with ether and dried over anhydrous sodium sulfate. The ether was removed, and the residue was treated with 11 g. of sodium acetate in 100 cc. each of acetic acid and acetic anhydride. After refluxing for three hours the solvent was removed under reduced pressure and the residue was taken up in ethyl acetate where it was washed with sodium bicarbonate solution. Acidification gave 6.0 g. of crude half-ester. Crystallization from ether–petroleum ether[9] gave 2.2 g. of half-ester Ia, m. p. 116–117°. An additional 1.5 g. of good material was accounted for in the filtrate making the yield of Ia in this fraction 5%. If it is assumed that this represents three-fifths of the amount of Ia which was present before cyclization—the remaining two-fifths presumably having been converted to the anhydride as observed in the experiment described above with pure Ia—an additional 3% of Ia may be accounted for. The neutral fraction in the ethyl acetate solution was concentrated and crystallized by the addition of petroleum ether.[9] In this way 24.1 g. (30% yield) of ethyl 4-acetoxy-1-methylphenanthrene-2-carboxylate (VIa), m. p. 126.5–127.5°, was obtained. No more crystals could be obtained from the oily residue (12.1 g.) which was submitted to acid-catalyzed alcoholysis in order to convert any anhydride of I into the bicarbonate soluble half-ester Ib, and thus to separate any remaining phenanthrene derivative either in the neutral fraction as VIa or in the sodium hydroxide-soluble fraction as VIb. In this way a trace (0.2 g.) of additional VIa was obtained, and the presence of Ib was verified by cyclization of the crude acidic fraction to give the indoneacetic ester IIIa; a small yield of red needles, m. p. 94–96.5°, was obtained. The various oily residues have not been investigated further.

Mixture of Itaconic Di-esters.—The acidic portion of a condensation reaction in which 85 g. (0.5 mole) of 2-acetylnaphthalene was employed was exhaustively esterified with ethanol and hydrogen chloride. Only 2.5 g. of dark, oily acid material was recovered. The distilled yellow mixture of di-esters amounted to 106.7 g. (65% yield) boiling over a 10° range. The main fraction boiled at 203–206° (2–3 mm.).

Anal. Calcd. for $C_{20}H_{22}O_4$: C, 73.60; H, 6.80. Found: C, 73.66; H, 6.75.

The balance of material was accounted for as decomposed residue from the distillation. Since the itaconic di-esters are perfectly stable to distillation, the residue (which may correspond to the uncrystallizable fractions of the preceding experiment) probably contained little, if any, of the itaconic di-esters. The undistillable fraction may contain higher molecular weight substances possibly of the type produced by the condensation of two moles of ketone with one of succinic ester.[14]

Mixture of Itaconic Half-esters.—The partial saponification of 10.17 g. of the above di-ester mixture was effected with 5.10 g. of barium hydroxide octahydrate in 250 cc. of ethanol and 200 cc. of water. After refluxing for seven hours the dibasic acid fraction (1.38 g.) was obtained in the usual way via the insoluble barium salt. An equivalent amount (1.71 g.) of unchanged di-ester fraction was found in the neutral portion. The crude mixture of half-esters amounted to 6.64 g. of brown semi-crystalline material.

Analysis of Mixture of Half-esters.—Crystallization of the above half-ester fraction gave 2.66 g. (40% yield) of colorless half-ester Ia, m. p. 116.5–118.5°. The residues were cyclized with 1.5 g. of sodium acetate in 10 cc. each of acetic acid and anhydride. An additional 4% yield of Ia was accounted for in the small acidic portion which remained. The neutral fraction amounted to 2.97 g. (41% yield) of crude phenanthrene derivative VIa presumably containing about a 3% yield of anhydride of I estimated from the 4% of Ia accounted for above. Purification by distillation under reduced pressure gave 2.06 g. of VIa, m. p. 124–127°. The identity of all crystalline products isolated in the above analyses of mixtures was checked by mixed m. ps. with authentic samples.

Summary

1. The condensation of 2-acetylnaphthalene with diethyl succinate in the presence of sodium ethoxide has been studied.

2. Structures and configurations have been assigned to the resulting itaconic acid derivatives, in the course of which some interesting phenanthrene and 6,7-benzindone cyclization products were encountered.

(14) Stobbe, *Ann.*, **380**, 1–120 (1911).

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3. A method has been described for the rough estimation of the itaconic acid derivatives present in the original reaction mixture.

MADISON 6, WISCONSIN RECEIVED MARCH 9, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

The Carbonation and Carbethoxylation of Certain Esters Using Sodium Triphenylmethide Reagent[1,2,3]

BY ERWIN BAUMGARTEN AND CHARLES R. HAUSER

In the present paper, the synthesis of certain malonic acid derivatives by means of the carbonation or carbethoxylation of the anions of esters (prepared by the action of sodium triphenylmethide) is reported.

Carbonations.—The carbonation of esters to form half malonic acid esters has previously been carried out apparently only with methyl diphenylacetate,[4] the reaction being effected by means of sodium triphenylmethide. In the present investigation, four aliphatic esters have been carbonated using this reagent.

The carbonation of *t*-butyl acetate gave mono-*t*-butyl malonate as a slightly impure oil in 57% yield, while the carbonation of *t*-butyl isobutyrate gave mono-*t*-butyl dimethylmalonate as a crystalline solid in 81% yield. Such half *t*-butyl esters of malonic acids have apparently not been reported previously. The general reaction may be represented as

$$\mathrm{HCCOOC(CH_3)_3} \xrightarrow[\text{by } CO_2 \text{ and acid}]{(C_6H_5)_3CNa \text{ followed}} \mathrm{HOOCCCOOC(CH_3)_3}$$

In contrast to malonic acids and their ethyl esters (which undergo decarboxylation when heated),[5] mono-*t*-butyl malonate and mono-*t*-butyl dimethylmalonate undergo mainly the elimination reaction to form isobutene and the corresponding malonic acid on pyrolysis.

$$\mathrm{HOOCCCOOC(CH_3)_3} \longrightarrow \mathrm{HOOCCCOOH} + \mathrm{CH_2{=}C(CH_3)_2}$$

The ease with which this elimination reaction occurs is probably due to an acid catalysis, since ordinary *t*-butyl esters, such as *t*-butyl cinnamate and *t*-butyl isovalerate, are stable at these temperatures.[6] It should be pointed out, however, that *t*-butyl esters undergo the elimination reaction more readily[7] than the corresponding ethyl esters.

The carbonation of ethyl acetate and ethyl isobutyrate formed presumably the half-ethyl esters of the corresponding malonic acids (in the form of their sodium salts). In the present study, these intermediates were allowed to hydrolyze to the corresponding malonic acids; this reaction occurred readily. There were obtained from ethyl acetate, a 34% yield of malonic acid and from ethyl isobutyrate, a 73% yield of dimethylmalonic acid.

$$\mathrm{HCCOOC_2H_5} \xrightarrow[\text{by } CO_2]{(C_6H_5)_3CNa \text{ followed}} \mathrm{NaOOCCCOOC_2H_5} \xrightarrow[\text{and acid}]{\text{hydrolysis}} \mathrm{C(COOH)_2}$$

The mechanism of the carbonation of esters by means of sodium triphenylmethide reagent is analogous to that for the carbonation of ketones reported in the preceding paper.[1]

Carbethoxylations.—The carbethoxylation of ethyl acetate with diethyl carbonate to form diethyl malonate has previously been effected with sodium ethoxide.[8] This reaction has now been effected by sodium triphenylmethide. The carbethoxylation of ethyl isobutyrate to form diethyl dimethylmalonate, which has been effected previously with ethyl chlorocarbonate[9] in high yield using sodium triphenylmethide, has now been effected in even higher yield with ethyl 4-phenylphenyl carbonate using the same base.

The carbethoxylation of *t*-butyl acetate with diethyl carbonate using sodium triphenylmethide, which has been carried out previously[10] and confirmed in the present investigation, gives ethyl *t*-butyl malonate in more than 50% yield. It has been found, however, that when ethyl 4-phenylphenyl carbonate is used instead of diethyl carbonate, the yield of ethyl *t*-butylmalonate is only 23% after one and one-half hours, and negligible after twelve hours. Apparently, in the presence of the reactive diphenyl ester, the ethyl *t*-butylmalonate first formed undergoes further carbethoxylation to give the di-carbethoxylation

(1) Paper XXV on "Condensations"; paper XXIV, THIS JOURNAL, 66, 862 (1944).

(2) Presented at the Pittsburgh meeting of the A. C. S., Sept., 1943.

(3) Supported in part by a grant of the Duke University Research Council.

(4) Schlenk, Hillemann and Rodloff, *Ann.*, **487**, 135 (1931).

(5) Marguery, *Bull. Soc. Chim.*, [3] **33**, 541 (1905).

(6) Abramovitch, Shivers, Hudson and Hauser, THIS JOURNAL, **65**, 986 (1943).

(7) See for example, Norris and Rigby, *ibid.*, **54**, 2097 (1932).

(8) Wallingford, Homeyer and Jones, *ibid.*, **63**, 2056 (1941).

(9) Hudson and Hauser, *ibid.*, **63**, 3156 (1941).

(10) Hauser, Abramovitch and Adams, *ibid.*, **66**, 2714 (1942).

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product. Analogous reactions have been observed previously.[8,9]

Experimental[11]

General Procedure.—Ester anions were prepared from equivalents (0.2 mole) of ester and sodium triphenylmethide reagent essentially as described for the preparation of ketone anions.[12] When formation of the anion was indicated by the disappearance of the characteristic color of the reagent, the anions were carbonated or carbethoxylated as described for these reactions with ketones.[12]

Dimethylmalonic Acid.—The anion of ethyl isobutyrate prepared at room temperature from 23.2 g. (0.2 mole) of ethyl isobutyrate was carbonated after fifteen minutes. After the Dry-Ice had evaporated, 400 ml. of water and 200 ml. of ether were added and the resulting ether phase extracted with 50 ml. of 10% sodium hydroxide solution. The combined aqueous phases (washed with ether) were left for twenty-four hours at room temperature (to permit hydrolysis of the half ester) prior to neutralization with dilute sulfuric acid. Extraction of the acidic solution with ether followed by evaporation of the solvent gave 19 g. (73%) of dimethylmalonic acid, m. p. 193–194° (dec.) (reported,[13] 192–193°).

Malonic Acid.—The anion of ethyl acetate prepared at 0° from 10.55 g. (0.12 mole) of ethyl acetate was carbonated immediately and the mixture worked up as in the preceding experiment. The aqueous solution of malonic acid was saturated with sodium chloride prior to the final ether extractions. There was obtained 4.3 g. (34%) of malonic acid, m. p. 131–133°. Recrystallization gave 3.4 g. of pure product, m. p. 133.5–134.5° (dec.) (reported,[14] 134.8–134.9°).

Mono-*t*-butyl Dimethylmalonate.—The anion of *t*-butyl isobutyrate prepared at room temperature from 28.8 g. (0.2 mole) of *t*-butyl isobutyrate[6] was carbonated after five hours. The alkaline solution of the reaction product, obtained as described above, was immediately acidified with iced sulfuric acid. Evaporation of the ether extract of the acidic solution yielded 30 g. (81%) of mono-*t*-butyl dimethylmalonate, m. p. 78–81°; from petroleum ether (b. p. 30–60°), m. p. 80.0–80.9°.

Anal. Calcd. for $C_9H_{16}O_4$: C, 57.43; H, 8.57; neut. eq., 188.2. Found: C, 57.64; H, 8.26; neut. eq., 188.5.

Mono-*t*-butyl Malonate.—The anion of *t*-butyl acetate prepared at 0° from 23.2 g. (0.2 mole) of *t*-butyl acetate[6] was carbonated immediately. After removal of low boiling impurities from the crude acidic material, 18 g. (57%) of slightly impure mono-*t*-butyl malonate was obtained. Neutral equivalent: calcd. for $C_6H_{12}O_4$: 160.2. Found: 154. The compound could not be distilled at a pressure below 1 mm.

Pyrolysis of Mono-*t*-butyl Malonates.—Pyrolysis of mono-*t*-butyl dimethylmalonate at 140–150° for two hours gave dimethylmalonic acid, m. p. 180–182.5°; from ether–petroleum ether, m. p. 190–192°.[13] The characteristic odor of isobutyric acid, arising from decarboxylation of dimethylmalonic acid, was observed after pyrolysis. A gas evolved during the pyrolysis and condensed in a Dry-Ice trap absorbed bromine in carbon tetrachloride solution. The gas was presumably isobutene.

The pyrolysis of mono-*t*-butyl malonate at 120° proceeded with the evolution of a gas. The residue was malonic acid, m. p. 133.5–134.5° (dec.).[14]

Diethyl Malonate.—The anion of ethyl acetate was prepared from 17.2 g. (0.2 mole) of ethyl acetate and carbethoxylated immediately with 23.6 g. (0.2 mole) of diethyl carbonate. A precipitate formed and after four hours 20 ml. of glacial acetic acid in 80 ml. of ice-water was added to the reaction mixture. The ether phase (extracted with iced sodium hydroxide solution) was dried (sodium sulfate followed by "Drierite") and distilled. The material, b. p. 40° (atm.) to 150° (15 mm.), was redistilled, yielding 6.6 g. (41%, based on sodium triphenylmethide) of diethyl malonate, b. p. 94–97° (19 mm.). From the alkaline extract of the original reaction mixture, 1.5 g. (12%) of ethyl acetoacetate, b. p. 76–79° (19 mm.), was isolated.

Diethyl Dimethylmalonate.—The anion of ethyl isobutyrate was prepared from 23.2 g. (0.2 mole) of ethyl isobutyrate and carbethoxylated with 36.3 g. (0.15 mole) of ethyl 4-phenylphenyl carbonate.[15] The mixture was worked up after one and one-half hours as in the preceding experiment (omitting alkali extraction of the ether phase), yielding 23 g. (83%, based on ethyl 4-phenylphenylcarbonate) of diethyl dimethylmalonate, b. p. 87–88° (15.5 mm.[9]). Diethyl dimethylmalonate did not absorb bromine in carbon tetrachloride solution and was hydrolyzed in 90% yield to dimethylmalonic acid, m. p. 193–194°.[13]

Ethyl *t*-Butyl Malonate.—The carbethoxylation of 0.2 mole of *t*-butyl acetate[6] with ethyl *p*-diphenylcarbonate[15] gave 4.4 g. (23%, based on sodium triphenylmethide) of ethyl *t*-butyl malonate, b. p. 100–101° (18.5 mm.[10]), after one and one-half hours. No ethyl *t*-butyl malonate could be isolated after twelve hours reaction time.

Summary

1. The carbonation of certain *t*-butyl esters has been effected by means of sodium triphenylmethide to form the corresponding mono-*t*-butyl esters of malonic acids. The carbonation of certain ethyl esters, followed by hydrolysis, has given the corresponding malonic acids.

2. The carbethoxylation of certain esters with diethyl carbonate has been effected using sodium triphenylmethide to form the corresponding malonic esters. Carbethoxylation with ethyl 4-phenylphenylcarbonate appears to give partly the dicarbethoxylation product.

3. Half *t*-butyl malonates on heating were found to undergo mainly the elimination reaction instead of the more common decarboxylation reaction.

DURHAM, N. C. RECEIVED FEBRUARY 29, 1944

(11) Micro analyses by Dr. T. S. Ma, University of Chicago, Chicago, Illinois.

(12) Baumgarten, Levine and Hauser, THIS JOURNAL, **66**, 862 (1944).

(13) Koenigs and Hoerlin, *Ber.*, **26**, 2049 (1893).

(14) Serwy, *Bull. soc. chim. Belg.*, **42**, 483 (1933).

(15) Baumgarten, Walker and Hauser, THIS JOURNAL, **66**, 303 (1944).

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NOTES

t-Butyl Trichloroacetate

By Warner E. Scovill, Robert E. Burk and Herman P. Lankelma

Of the four butyl esters of trichloroacetic acid only the tertiary isomer has not been described. We find that it is readily prepared in 95% yield from trichloroacetyl chloride in the presence of pyridine, following the method used by Bryant and Smith[1] in the preparation of the corresponding acetate. No solvent was added, however, and heating was unnecessary. It was purified by distillation at 1 mm. pressure.

It may also be prepared from trichloroacetic acid and isobutylene, following the method used by Timofeev and Andreasov[2] for the preparation of the corresponding amyl ester. The isobutylene is rapidly absorbed in the trichloroacetic acid at 60°, the absorption being complete in three hours. The resulting brown, oily liquid crystallized on cooling with ice. It recrystallized well from both pentane and methanol at 0°, a yield of 80% being obtained from the former.

The following physical properties were determined: m. p. 25.5°; b. p. 37° at 1 mm. pressure; d^{25}_4 1.2363; n^{25} 1.4398.

Anal. Calcd. for $C_6H_9O_2Cl_3$: C, 32.83; H, 4.13; Cl, 48.46. Found: C, 32.50; H, 4.05; Cl, 48.65.

(1) Bryant and Smith, This Journal, **58**, 1014 (1936).
(2) Timofeev and Andreasov, *Chem. Zentr.*, **96**, II, 1652 (1925).

Morley Chemical Laboratory
Western Reserve University
Cleveland, Ohio
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An Apparatus for the Manipulation of Sodium Triphenylmethide Reagent

By Erwin Baumgarten and Charles R. Hauser

Sodium triphenylmethide in ether solution is a useful reagent to bring about certain condensation reactions.[1] The present note describes a simple apparatus[2] for the manipulation of the reagent permitting the withdrawal of analyzed aliquots from a single large scale preparation of the reagent so that a series of relatively small scale experiments may be carried out conveniently.

The analyzed solution of sodium triphenylmethide, prepared[3] in a two-liter bottle from one mole of triphenylchloromethane,[4] is divided into desired aliquots by means of the buret assembly illustrated in Diagram I, the essential features of which are a mercury-filled pressure release and a three-way stopcock, connected as shown. The system is swept with nitrogen[5] before use. In operation, a constant pressure of nitrogen is maintained in the system sufficient to push the reagent from the storage bottle to the buret. Transfer of the reagent from the storage bottle to the buret is effected by adjusting stopcock A to position (a), applying a positive pressure on the storage bottle while the buret communicates with the atmosphere. Transfer is stopped by adjusting stopcock (A) to position (b), equalizing the pressure between the storage bottle and the buret. The buret may now be drained into the receiver, previously filled with nitrogen.

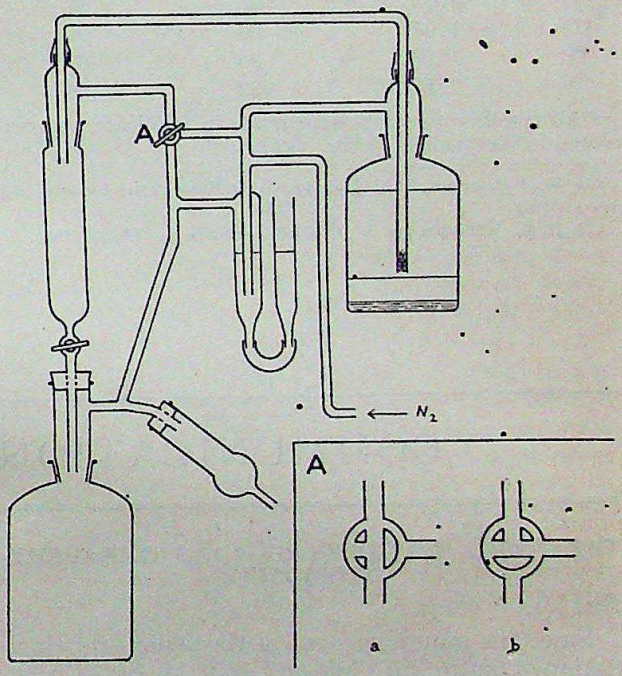

Fig. 1.

It should be noted that this apparatus maintains the reagent at all times under a small positive pressure of nitrogen preventing contact with moisture or oxygen.

(1) See especially, Hauser and Hudson, "Organic Reactions," John Wiley and Sons, New York, N. Y., 1942, Chapter 9.
(2) An apparatus for analytical purposes has been described by Corwin and Ellington, This Journal, **64**, 2098 (1942).
(3) Hauser and Hudson, "Organic Syntheses," John Wiley and Sons, New York, N. Y., 1943, Second Coll. Vol., 609 (Note 3).
(4) Hauser and Hudson, "Organic Syntheses," John Wiley and Sons, New York, N. Y., 1943, Vol. 23, p. 102.
(5) Commercial nitrogen was used without purification with the sodium triphenylmethide reagent; see Morton and Richardson, This Journal, **62**, 123 (1940).

Department of Chemistry
Duke University
Durham, North Carolina
Received February 29, 1944

Photochemical Destruction of Vitamin B_2 in Milk

By John A. Ziegler

The results of experiments carried out [illegible] March, 1944, on the destruction of riboflavin with

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milk independently confirm those recently reported by Peterson, Haig and Shaw.[1] Preliminary experiments have also indicated that the destruction by radiation increases with temperature, as previously reported by Williams and Cheldelin.[2]

Samples of so-called "raw" milk (I), homogenized raw milk (II), pasteurized milk (III), homogenized pasteurized milk (IV), and irradiated vitamin D-containing milk (V), were freshly obtained. All samples were stored in the dark in the usual capped quart bottles and were refrigerated until the experiment was begun. Exposures were made within twenty-four hours of bottling to direct mid-morning spring sunshine in the open air for periods up to two hours during which the atmospheric temperature was 16.7 to 20.6°.

TABLE I

Sample	Riboflavin concentration,[a] γ/ml.	Destruction of riboflavin after 1 hr. exposure,[a] %	2 hr. exposure[a] %
I	2.07	36	59
II	2.05	27	54
III	1.97	26	54
IV	1.86	39	68
V	1.89	32	66

[a] All riboflavin assays were made in triplicate and corrected for the values of the blank.

Riboflavin assays were made by the microbiological method of Snell and Strong[3] and frequent recovery experiments were made by adding known amounts of the pure crystalline vitamin to samples of milk to check the accuracy of the method. Recoveries amounted to 94–102%. In addition, samples of milk were withdrawn at the same time as those for assay, made alkaline to *p*H 10 with 1 *N* sodium hydroxide, and exposed to the light from a 750-watt bulb at 50 cm. for twenty-four hours in order to destroy all riboflavin present. The photolyzed milk was then neutralized to *p*H 6.8 and added separately to the basal medium in identical amount to the samples being assayed. The results of these blanks were subtracted from the values of the actual assays to give the riboflavin concentrations reported in Table I.

Since milk after delivery to the consumer frequently remains on an open porch in direct sunlight, it is apparent that during this period from one-third to two-thirds of the riboflavin may be destroyed.

DEPARTMENT OF PATHOLOGICAL CHEMISTRY
BANTING INSTITUTE
UNIVERSITY OF TORONTO
TORONTO, CANADA

RECEIVED APRIL 24, 1944

(1) W. J. Peterson, F. M. Haig and A. O. Shaw, THIS JOURNAL, **66**, 662 (1944).

(2) R. R. Williams and V. H. Cheldelin, *Science*, **96**, 22 (1942).

(3) E. E. Snell and F. M. Strong, *Ind. Eng. Chem., Anal. Ed.*, **11**, 346 (1939).

COMMUNICATIONS TO THE EDITOR

THE TOTAL SYNTHESIS OF 2,3,4,5-TETRADEHYDROBIOTIN

Sir:

Since the announcement of the structural elucidation of biotin [du Vigneaud, *et al.*, *J. Biol. Chem.*, **146**, 475, 487 (1942)], the quest for a practical synthesis of the vitamin in this Laboratory has led to the development of a seventeen-step synthesis of 2′-keto-3,4-imidazolido-2-thiophenevaleric acid, the aromatic analog of biotin. Experiments are now in progress on the nuclear reduction of this compound to biotin.

The starting materials were trimethylene chlorobromide and ethyl malonate, from which was obtained ethyl 3-chloropropylmalonate by the method of Fischer and Bergmann [*Ann.*, **398**, 120 (1913)]. Hydrolysis and decarboxylation followed by esterification gave ethyl 5-chlorovalerate, described by Mellor [*J. Chem. Soc.*, **79**, 132 (1901)]. This compound reacted with ethyl malonate to duce ethyl pentane-1,1,5-tricarboxylate (b. p. –170° (4 mm.), for $C_{14}H_{24}O_6$—Calcd.: C, 58.32; H, 8.37. Found: C, 58.49; H, 8.54). Hydrolysis yielded pentane-1,1,5-tricarboxylic acid (m. p. 82°, for $C_8H_{12}O_6$—Calcd.: C, 47.05; H, 5.92. Found: C, 47.11; H, 5.88). Treatment with sulfuryl chloride followed by decarboxylation gave 2-chloropimelic acid (m. p. 89–90°, for $C_7H_{11}O_4Cl$—Calcd.: C, 43.25; H, 5.70. Found: C, 43.27; H, 5.78) which after reaction with β-mercaptopropionic acid and esterification yielded 2-carbethoxyethyl 1,5-dicarbethoxyamyl sulfide (b. p. 210–213° (3 mm.), for $C_{16}H_{28}O_6S$—Calcd.: C, 55.14; H, 8.10. Found: C, 55.14; H, 8.15). Cyclization by the Dieckmann reaction gave ethyl 4-carbethoxy-3-keto-2-tetrahydrothiophenevalerate (for $C_{14}H_{22}O_5S$—Calcd.: C, 55.60; H, 7.33. Found: C, 55.53; H, 7.36). The oxime of this keto ester was converted to ethyl 3-amino-4-carbethoxy-2-thiophenevalerate (m. p. 43–44°) by means of dry hydrogen chloride followed by decomposition of the resulting amine hydrochloride with a suitable base. Selective hydrolysis produced 3-amino-4-carbethoxy-2-thiopheneval-

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eric acid (m. p. 97–97.5°, for $C_{12}H_{17}O_4NS$—Calcd.: C, 53.12; H, 6.32. Found: C, 53.14; H, 6.32) which was converted to the N-benzoyl derivative (m. p. 126.5–127.5°, for $C_{19}H_{21}O_5NS$—Calcd.: C, 60.77; H, 5.63. Found: C, 60.70; H, 5.53). The Curtius degradation through the hydrazide (m. p. 140–141°, for $C_{17}H_{19}O_4N_3S$—Calcd.: C, 56.49; H, 5.30. Found: C, 56.40; H, 5.57), and the azide (dec. 99–100°, for $C_{17}H_{16}O_4N_4S$—Calcd.: C, 54.83; H, 4.33. Found: C, 55.11; H, 4.53) gave 3-benzoylamino-4-carbethoxyamino-2-thiophenevaleric acid (m. p. 156.5–157.5°, for $C_{19}H_{22}O_5N_2S$—Calcd.: C, 58.44; H, 5.68. Found: C, 58.88; H, 5.72) when the azide was refluxed with absolute alcohol. The final product, 2′-keto-3,4-imidazolido-2-thiophenevaleric acid (m. p. 253–254° with decomposition, for $C_{10}H_{12}O_3N_2S$—Calcd.: C, 49.98; H, 5.03. Found: C, 50.33; H, 5.25) was prepared from the urethan by hydrolysis to the diamine and immediate treatment with phosgene.

Ultraviolet absorption curves prepared by Dr. J. M. Vandenbelt show that the compound has strong absorption in the region 250 to 270 mμ, with the peak value at 260 mμ having a molar extinction coefficient of approximately 17×10^{-3}. The curve closely corresponds with the curves for 2′-keto-3,4-imidazolido-2-γ-phenoxypropylthiophene (m. p. 174–174.5°), 2′-keto-3,4-imidazolido-2-γ-benzyloxypropylthiophene (m. p. 127–127.5°) and 2′-keto-3,4-imidazolido-2-γ-hydroxypropylthiophene (m. p. 138–139°), all of which have been prepared and characterized during this work.

The authors gratefully acknowledge the assistance of A. W. Spang who did the microanalyses. Details for the preparation of all compounds and the results of biological tests for biotin and antibiotin activity will be forthcoming.

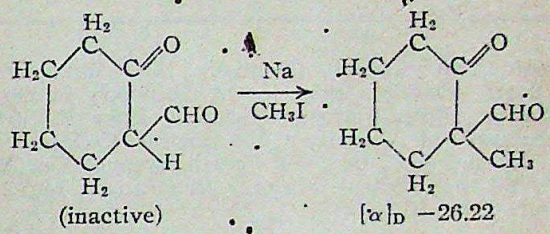
Research Laboratories
Parke, Davis and Co. Lee C. Cheney
Detroit 32, Michigan J. Robert Piening

Received May 20, 1944

ATTEMPTED REPETITION OF A REPORTED TOTAL ASYMMETRIC SYNTHESIS

Sir:

In a recent letter to the editors of *Nature*, Paranjape, Phalnikar, Bhide and Nargund[1] report the synthesis of several optically active substances from inactive starting materials without the use of any asymmetric reagents or catalysts. They report that the asymmetric synthesis occurred at the following step in their series of reactions



(inactive) $[\alpha]_D$ −26.22

The reported activity was determined on the crude material, since the methylated-formylcyclohexanone was reported to be an unstable liquid, impossible to purify by distillation.

An attempt has been made in these Laboratories to repeat this extraordinary result, which would not be predicted on the basis of any known theory of optical activity.

Inactive formylcyclohexanone was prepared according to the method of Rupe and Klemm,[2] and the methylation was carried out using two different techniques.

In the first trial, formylcyclohexanone was added to a 10% ethanolic solution of sodium ethylate and refluxed with methyl iodide. This yielded, after evaporation of the solvent and washing with water, a reddish liquid, a portion of which darkened and resinified when an attempt was made to distill it. The crude material had a specific rotation of zero, with an error of ±0.7° due to the difficulty of taking readings on such a comparatively strongly colored material.

In the second synthesis, the sodium salt of the formylcyclohexanone was suspended in toluene and allowed to react with methyl iodide. This procedure yielded a much clearer product after removal of the solvent, and it was possible to determine that the material was totally inactive within the 0.01° accuracy of the Zeiss polarimeter. Readings were taken on the material itself as well as on chloroform solutions of it as reported by the Indian authors.

Considerable speculation on possible sources of their reported results has yielded no reasonable explanation.

Contribution No. 970 from the
Gates and Crellin Laboratories of Chemistry
California Institute of Technology
Pasadena 4, California John Michael O'Gorman

Received May 17, 1944

(1) K. D. Paranjape, N. L. Phalnikar, B. V. Bhide and K. S. Nargund, *Nature*, **153**, 141 (1944).

(2) H. Rupe and Otto Klemm, *Helv. Chim. Acta*, **21**, 1539 (1938).

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NEW BOOKS

Second Year College Chemistry. By WILLIAM H. CHAPIN, Emeritus Professor of Chemistry in Oberlin College. Fifth edition, revised, by Luke E. Steiner, Professor of Chemistry in Oberlin College. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y., 1943. viii + 575 pp. Illustrated. 14.5 × 22 cm. Price, $3.75.

The passage of five years has brought the fifth edition of this popular and old reliable text, steadily changing in content to better serve its original purpose of extending the frontiers of elementary chemistry. Unfortunately, there is no place in many college programs for the lessons it could teach. In the Preface, Dr. Steiner writes: ". . . Liquids and solutions are discussed more fully and more exactly. A new chapter on crystalline solids relates the dimensions of atoms, ions and molecules to the structure of crystals and chemical behavior, and serves as an introduction to crystal chemistry and to structural chemistry. Similarly, the chapters on liquids and solutions correlate their properties more closely, with chemical behavior. . . . Early chapters place greater emphasis on mathematics, . . . but the kinetic point of view is maintained."

The revision has been extensive, thirteen of the twenty chapters showing an increase of three pages or more, and two chapters only having been shortened. The net increase in pages is 168, including a block of miscellaneous problems at the end. The typography is unchanged, but in keeping with war-time necessity the paper is thinner and the margins are narrower, giving a book no larger than the previous edition.

ALLEN D. BLISS

Laboratory Manual of Explosive Chemistry. By ALLEN L. OLSEN AND JOHN W. GREENE, Kansas State College. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y., 1943. vi + 106 pp. Illustrated. 14 × 22 cm. Price, $1.75.

This laboratory manual is designed for a short course on explosives such as that set up by the Engineering, Science and Management War Training Program, the purpose of which is to provide training in the chemistry of explosives for persons planning to work in explosives and loading plants as (1) inspectors for the Ordnance Department and (2) operators for the manufacturers having contracts in this field. It consists almost entirely of directions for testing, which are taken directly from the War Department Technical Manual 9-2900 (August 29, 1940). Suitable acknowledgment is made to the Technical Manual and no pretense of originality is made.

From the standpoint of a course such as that mentioned above, limitation to the specification procedures of the Ordnance Department is well advised. In evaluating this book, it should be emphasized that the procedures, as given, represent the standard procedures of the Ordnance Department and not the best possible procedures which might be worked out for the various tests. The authors have exerted commendable restraint in avoiding the temptation to devise more elaborate and perhaps more accurate tests.

Since it is mostly a duplication of Technical Manual 9-2900, it may, perhaps, be useful to compare the scope of the Technical Manual with this book. In the latter the details of the manufacture of explosives are omitted, but the methods are illustrated by small-scale laboratory directions. The chief contribution of the Laboratory Manual over the information available in the Technical Manual is the inclusion of a number of explanatory notes summarizing the reasons for various operations and mentioning additional precautions. Another useful feature is a chapter on "Safety," which would answer many of the questions occurring in the minds of people inexperienced in this field who might be given the responsibility for organizing a course on the testing of explosives. The substances for which methods of testing are given are the same as those included in Technical Manual 9-2900. No classified information is included in this book.

The book contains a few errors, but these are not serious and would generally be fairly obvious to the user. The book is not intended to cover the entire field of explosives but is intended, primarily, for those interested in the routine testing of products in current manufacture. It will be of interest and helpful to those participating in courses of this type.

RALPH CONNOR

Quantum Chemistry. By HENRY EYRING, Frick Chemical Laboratory, Princeton University, JOHN WALTER, Palmer Physical Laboratory, Princeton University, and GEORGE E. KIMBALL, Department of Chemistry, Columbia University. John Wiley and Sons, Inc., 440 Fourth Avenue, New York 16, N. Y., 1944. vi + 394 pp. Illustrated. 14.5 × 22 cm. Price, $5.00.

Into this book, just over an inch between the covers, the authors have packed a large amount of basic theoretical material, much of it not elsewhere available except in special monographs and reviews. In addition to the standard contents of an elementary text on quantum mechanics there are chapters on group theory, statistics reaction rates, and other applications of interest to the modern theoretical chemist. The presentation is of necessity condensed in style, but is skilfull and accurate (except for an occasional misplaced index or average sign), and no essentials have been omitted. The work will be valuable as a convenient general reference book for the student, and for this purpose has the merit that each chapter can be read by itself, sufficient back references being supplied to indicate where the necessary preliminary material may be found. As an aid to further study, a good bibliography is appended.

A. S. COOLIDGE

Enzyme Technology. HENRY TAUBER. John Wiley and Sons, Inc., New York, N. Y.; Chapman and Hall Ltd., London, 1943. vii + 275 pp. 46 figures. Price, $3.50.

The purpose of this book, according to the author, is to present practical information concerning the role and use of enzymes in industry, their preparation, and their use in medicine. These objectives are achieved, although many of the subjects are not discussed in great detail. Fortunately, there is a generous bibliography included at the end of each chapter, enabling one to refer to the original material. In some cases the author has not followed his original objective. This is true in the discussion on the use of yeast in medicine.

There are sixteen chapters covering the following material:

Yeast: Production and Utilization and the Enzyme Systems
Production of Ethyl Alcohol by Fermentation
The Role of Enzymes in Brewing
Mold Fermentations
Bacterial Fermentations
The Production of Enzymes and Methods of Their Estimation
Enzymes for Medical Use
Enzymes of Grains and Malt and the Role of Enzymes in Bread Making

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Enzymes in Dairy Products
Enzymes in the Meat, Egg, Vegetable, and Fruit Industries
Pectin-Decomposing Enzymes and Their Use in the Fruit Juice, Wine, and Jelly Industries
Vitamin-Destroying Enzymes
Enzymes in Textile, Paper, and Related Industries
The Use of Enzymes in the Manufacture of Leather
Enzymes in Other Industries
Microbiological Methods for the Estimation of Vitamins

The individual chapter headings do not always give a reliable index of the contents within the chapter. For example, Chapter VI: "The Production of Enzymes and Methods of Their Estimation," contains methods for the preparation of diastatic enzymes from molds, bacteria and pancreas, and also proteolytic enzymes, whereas the preparation of yeast enzymes, malt diastase, and some other preparations are described in other chapters. The only methods included in this chapter are those covering proteolytic activity, lipolytic activity, and one method for saccharogenic amylase activity. Some of the other methods are given in the respective chapters describing specific enzymes in more detail.

It is believed that it would have been preferable to group the chapters containing material on the amylases together, thereby enabling the author to make possible a more unified treatment of the subject.

The author has confused the starch liquefying property of α-amylase and the as yet unverified amylophosphatase of Waldschmidt-Leitz and Mayer. It is also unfortunate that the models of Hanes for the structure of the starch molecule are given, since it is quite well-established that starch consists of straight-chain amylose and branched-chain amylopectin and the simple Haworth structure is no longer tenable.

The last chapter contains a description of the microbiological assay methods for the six B vitamins.

There are relatively few errors and the binding and printing are quite good. The book is a useful contribution to the growing field of enzyme technology. It covers a broad scope, possibly too broad, but the reader can cover the field more thoroughly with the help of the excellent collection of references given after each chapter.

CHARLES N. FREY
SUTTON REDFERN

General Chemistry. A First Course. By L. E. YOUNG, Professor of Chemistry, Mills College, and C. W. PORTER, Professor of Chemistry, University of California. Revised edition. Prentice-Hall, Inc., 70 Fifth Avenue, New York, N. Y., 1943. xi + 527 pp. Illustrated. 15.5 × 23.5 cm. Price, $3.75.

This book is, in many ways, better than most texts that have been written lately for beginners. Many glaring faults to be found in texts much used in High Schools and Academies have been corrected. Thus *nascent* hydrogen is not mentioned and a correct explanation is given of the electrolysis of brine. Equation balancing, solving of problems, oxidation–reduction, etc., are explained intelligently and the student is not encouraged to follow the German practice of expressing all chemical arithmetic in terms of ratio and proportion. The book is intended to be used in colleges but it is well suited for use in High Schools although no attempt is made to satisfy the requirements of College Entrance Boards, and it is not a reference book.

As stated in the preface, "The attempt is made to explain the fundamental principles of chemistry in simple language and illustrative matter is drawn from the experiences of daily life." In teaching beginners, the chief difficulty is the approach to the subject because no single element, except perhaps the rare gases, can be studied adequately without reference to other elements. For this reason, the first quarter of the book is rather conversational in style and easy to understand although the reader is expected to swallow considerable dosage about as one takes a pill. Thus on page 3 it is shown that a single molecule of sodium chloride would weigh so little that it would have to be a gas and after stating that matter cannot be created or destroyed a foot-note is inserted which states that the "escape or absorption of heat results in a corresponding loss or gain in matter" and a little later the student is taught that when 20 million tons of coal are burned one pound of it is converted into heat and light. This will almost lead some beginners to think that heat and light can be weighed, which agrees pretty well with conceptions that prevailed in the Middle Ages. In this connection, it may be stated that Physicists often have claimed that Chemists don't understand the difference between *mass* and *weight*.

Subjects such as *isotopes*, *deuterium*, *electrons*, *neutrons* and the *Periodic Table* are discussed early in the book when hydrogen is the only element that has been studied. This rather pleases the reviewer although some may think that this leads to over-emphasis of theory. The elements of crystallography are given on pages 20–22, which leads to the discussion of *space lattice* and the crystal lattice of sodium chloride is shown on page 24.

In general, the descriptive matter concerning the elements and their compounds is adequate for a course given beginners, but some modern ideas concerning acids, bases, salts and the hydronium ion are not mentioned, which will probably displease some good chemists. The law of chemical mass action and the reversibility of most reactions is not discussed adequately and the chapter on the *Electromotive Series* is unsatisfactory because no attention is paid to the concentrations of the ions in solution. In fact, a table of twenty oxidation-potential potentials is given in the Appendix and is stated to pertain to "infinite dilution" although the values given are identical with those usually given for molar concentrations. It is quite likely that the authors themselves do not entirely understand the application of the *Nernst rule* to oxidation–reduction potentials.

The sections on *Organic Chemistry* are excellent and the reviewer is greatly pleased to find the conception that the carbon is negative in CH_4 but positive in CCl_4.

In examining a book for review, one is inclined to overemphasize the things he does *not* like and in reading a text is more likely to underline false statements and misprints than to note excellent points. This book is well-published, is well-written and contains very few false statements or misprints. It might be better if, in the *Table of Contents*, the reference to the *Metric System* were given as page 511 instead of 504, that the definition of *amphoteric* substances be restricted to oxides and hydroxides and that *amorphous* substances be recognized as being in a state of extreme fineness of the particles rather than due to lack of any crystalline form, but enumeration of such things is more or less captious and the reviewer hopes he has made it clear that he likes the book.

WILLIAM T. HALL

The Physical Chemistry of Electrolytic Solutions. By HERBERT S. HARNED, Professor of Chemistry, and BENTON B. OWEN, Associate Professor of Chemistry, Yale University. (American Chemical Society Monograph Series.) Reinhold Publishing Corporation, 330 West 42nd Street, New York, N. Y., 1943. xi + 611 pp. Illustrated. 15.5 × 23.5 cm. Price, $10.00.

Appearing twenty years after the publication of both Debye and Hückel's first papers on the interionic attraction theory and Lewis and Randall's "Thermodynamics," "The Physical Chemistry of Electrolytic Solutions" rounds out one period in the development of solution theory. This is the period in which the physical chemists have been taught to use exact thermodynamics in the treatment of solutions and to use the Debye theory for extrapolation to solutions too dilute for accurate experimental measurements. The authors consider the Debye theory sufficiently established so that they take the first five chapters to develop the theory before making any comparison with experiment to check its validity. The second group of fi-

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chapters discusses experimental methods beginning with the irreversible effects and ending with electromotive force measurements, which make a smooth transition to the last group of five chapters which discuss the equilibrium properties of various types of solutions, particularly those studied in the Yale laboratories.

During this period it has been necessary to make a large number of measurements upon simple systems to verify the theory, to discover the nature of the transition from solutions so dilute that the theory is exact and measurements are impossible to those so concentrated that the theory becomes too complicated but measurements are relatively easy, and to obtain a body of correlated data for the study of concentrated solutions. Most of the more accurate results are presented in the last ten chapters.

Theoretical studies are much less well presented than experimental work. So much of the book is based upon the Debye theory that one might expect a thorough discussion of its derivation. However, the investigations of the statistical basis are limited to a footnote citation, and there is no discussion at all of the fact that the Debye equations are derived for a very special model with all the ion spheres of the same size, and no mention of the attempts to determine the deviations to be expected when these conditions are not fulfilled.

The book is weak in a few places where we might expect it to be strongest. The equation which is the basis of the treatment of the thermodynamics of "The Reversible Galvanic Cell," equation 1-5-1, cannot be derived from equation 1-2-6 by any method known to me. Equation 1-5-5, which is called "the equation for concentration cells," is not used as such either in this book or elsewhere as far as I know. In the "General Statement of the Interionic Attraction Theory" (Chapter 2) an outline of the complicated mathematical framework of the Onsager–Fuoss treatment of irreversible processes is followed by a simplified derivation of the Debye potential, neglecting the ionic diameter. The mathematics of the proper derivation, which has to be given in the next chapter, is so much simpler than that of the preceding sections that there seems no excuse for an approximate derivation here. The case is aggravated by two errors in the derivation. From the fact that κA is not a function of r, it does not follow that κA must vanish as κ approaches zero; even if this were true, it would not follow that A is not a function of κ.

The authors have a difficult problem in the treatment of non-reversible processes. The mathematics is so complex that it cannot be presented completely, yet there should be enough to illustrate the methods. How much should be presented? Although my own taste would have been for more space devoted to a physical picture and less to the mathematics, I think the compromise chosen by the authors is a good one.

Their treatment of numerical results involves another problem which is not so wisely handled. The data from the Yale laboratories are computed with the Lewis and Randall "International Critical Tables" values of fundamental physical constants, like most data in the literature, and with values for the fundamental hydrochloric acid concentration cell based on smoothing less skillful than the present practice. These values are given in the book with the explicit excuse for the incorrect constants that the errors "are generally less than the errors in the physicochemical data with which they are combined." Hanging on to erroneous quantities is much like drug addiction. Each paper published with the old values makes it more difficult to give them up for the new. The better the paper, the worse is its effect. A book like the present makes the recovery of the authors almost impossible, and the publication of many convenient tables in chapter 5 tempt others to the same bad habits. This chapter should not have been allowed to appear without a poison label. For freezing point measurements the discrepancy is greater though not used so much. Attention should be called to the fact that the most probable value of the constant for water is 1.860 and not 1.858.

The most valuable part of the book is the bringing together of experimental work. Chapter 6 presents and discusses data on the conductance, transference, viscosity and diffusion. Chapter 7 treats the relation of conductance to the electrostatic formation of ion pairs and higher complexes and to the association of weak electrolytes, the effect of frequency on conductance and dielectric constant, and the effect of field strength on the former. In Chapter 8 are presented thermochemical quantities, partial molal volumes and coefficients of expansion and compressibility. Chapter 9 discusses freezing points, boiling points and vapor pressures. Chapter 11 treats hydrochloric acid; chapter 12 covers other strong 1-1 electrolytes in aqueous solution, including their effect on non-electrolytes. Chapter 13 is devoted to polyvalent electrolytes in aqueous solution. Mixtures of strong electrolytes are discussed in Chapter 14, and weak electrolytes in Chapter 15. The appendix collects tables which would have spread out the text too much if included earlier. These later chapters are, quite properly, built around the electromotive force measurements in the Yale laboratories and emphasize those electrolytes which can be studied by this method. The only chemical reaction discussed is the acid-base equilibrium. Every worker in the field will be grateful to the authors for the labor they have spent collecting and coördinating this material, and will need to have a copy easily accessible.

A glossary of symbols at the beginning is very helpful. The convenience as a reference book could have been increased greatly by having the chapter and section numbers at the top of each page. Trivial slips like typographical errors, split infinitives, and stabilization energy from proton resonance have been kept infrequent, though they have not been entirely eliminated.

GEORGE SCATCHARD

BOOKS RECEIVED

April 10, 1944—May 10, 1944

ROGER ADAMS, Editor-in-Chief. "Organic Reactions." Volume II. John Wiley and Sons, Inc., 440 Fourth Avenue, New York, N. Y. 461 pp. $4.50.

R. BOWLING BARNES, ROBERT C. GORE, URNER LIDDEL AND VAN ZANDT WILLIAMS. "Infrared Spectroscopy. Industrial Applications and Bibliography." Reinhold Publishing Corporation, 330 West 42nd Street, New York, N. Y. 236 pp. $2.25.

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